56 Published Papers on Electroencephalography

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The results of previous workers with very small numbers of subjects have shown that there is a great individual variation in the electroencephalographic pattern. The present study deals with quantitative changes in blood sugar level, respiratory volume, electroencephalographic rhythm, and their intercorrelations in a series of 45 normal subjects. Repeated electroencephalographic tracings were obtained on each subject during a 3-minute period of normal breathing, followed by a 3-minute period of controlled and measured hyperventilation. Blood sugar determinations were made after each test.

The following results were obtained:

1. Normal ventilation.
   (a) No delta activity was observed during normal breathing at any blood sugar level.

2. Hyperventilation.
   (a) In 22 per cent of the subjects, no delta wave activity at fasting blood sugar levels was observed. Delta wave activity could be elicited after the administration of insulin.
   (b) Fifty-three per cent of the subjects showed delta waves at fasting blood sugar levels, but not after the ingestion of glucose.
   (c) The remaining 25 per cent showed the presence of delta activity at all blood sugar levels, even after the ingestion of glucose.

3. In some subjects, low blood sugar levels produce a slowing of the alpha rhythm during normal breathing.

4. In subjects in whom the ingestion of glucose inhibits the production of delta activity on hyperventilation for 3 minutes, the critical blood sugar level is approximately 130 mgm. per 100 cc.

5. In tests in which the blood sugar level was the same, the depth of respiration was the deciding factor in determining the amount of delta activity present.

6. Since the frequency of alpha rhythm and the presence of delta waves are now used in assessing normal electroencephalographic records, it is essential that all tests be carried out at non-fasting blood sugar levels.
CONCEPTS OF MUSCLE DYSFUNCTION IN POLIOMYELITIS
BASED ON ELECTROMYOGRAPHIC STUDIES

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The importance of muscle "spasm" as a symptom of acute poliomyelitis has received emphasis since the Kenny concepts of the symptomatology and treatment of this disease have come into prominence. Muscular pain, tenderness and shortening have been recognized for many years as characteristic features of acute poliomyelitis and have been described by different authors, particularly by Lovett and by Ober, who have advocated treatment with local heat in the form of hot fomentations and by gentle passive movements followed by active muscle reeducation. In recent studies of "spasm," Schwartz and his associates have recorded electrical potentials from muscles in cases of acute poliomyelitis with a cathode ray oscillograph and found widespread hyperirritability to stretching, not only in
completely the musculature of an extremity by comfortable positioning and support, no action potentials are recorded. Hoefer's technics were similar to those used in our investigations. The occurrence then of spontaneous discharges from relaxed muscles examined by this technic indicates some abnormality and forms a point of study in cases of poliomyelitis.

Electromyograms were therefore recorded from muscles which were tender and painful on palpation or stretching (clinically in "spasm") and also from weak muscles not showing "spasm." In some instances the antagonists of the muscles exhibiting clinical evidence of "spasm" were the weaker muscles, although this was not uniformly true.

In the acute stage of the disease some low voltage discharges were found at rest, but only from the most weakened muscles and frequently not at all from the posterior muscles of the trunk and lower extremities, although clinically these muscles were quite tender and painful on stretching (fig. 1 A).
In the later stages of the disease, particularly beginning about the third month, in cases with considerable paresis, we have noted in the resting muscles the onset of spontaneous electrical discharges of a more striking character (fig. 1B). These potentials were of higher voltage and were somewhat suggestive of motor unit activity as described by Weddell, Feinstein and Pattle. The muscles which clinically showed the most loss of power gave rise to these discharges more frequently than did their antagonists, which usually showed clinical “spasm.” This electrical activity appeared to be an index of weakness and could not be correlated with clinical “spasm.” Similar spontaneous discharges have been found to persist for many months particularly in muscles with continuous improvement in function. In one case, followed for a year and a half, with good restoration of muscle power (as indicated by ergographic studies and manual tests of strength), the discharges were still present on the final examination although there was no pain, tenderness or other evidence of “spasm” clinically (fig. 2). In other cases, with only slight restoration of function, electrical discharges gradually lessened in incidence (fig. 1C) and finally disappeared when the improvement ceased.

From these observations we conclude that the foregoing examples of electrical discharge are manifestations

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of a recovery process. This hypothesis is further substantiated by muscle studies during regeneration of traumatized peripheral nerves. From these muscles we have recorded similar electrical discharges. They appeared as an early sign of regeneration and persisted throughout the period of improving function (fig. 3).

Response of Muscles to Passive Stretching.—The response of muscles to passive stretching, during the early and late stages of poliomyelitis, was studied by electromyography. In these tests the muscles were stretched through the full arc of motion by a quick passive movement. During the acute stage this frequent brought out electrical discharges of a voltage higher than any which can be elicited from normal muscle by such a manipulation (fig. 4). Moreover, these discharges would persist for some time after the passive stretching had been released. In many instances a similar response was obtained by placing muscles under a slight increase of tension through adjusting the position of the limb. The appearance of these discharges was similar to those which we have recorded in patients with muscle spasm associated with painful joint motion following a recent fracture (fig. 5).

Although the voltage of the discharges gave an indication of the degree of irritability to passive stretching,
we found that this abnormality occurred primarily in the partially paralyzed muscles, and only minimally in unparalyzed muscles which showed clinical "spasm." When there was equal degree of weakness in a pair of antagonistic muscles we found equal irritability on stretching as recorded electrically, even though clinically one muscle showed more "spasm." We conclude, therefore, that when one muscle is functionally weaker than its antagonist the weaker muscle will show the greater abnormality electromyographically. That this weakness is not due to "alienation," as suggested by Kenny, but to greater involvement by the disease process was further substantiated by loss of electrical excitability in

![Fig. 6.—Action potentials during ergographic tests. Recordings from biceps. A, four months after onset of poliomyelitis; B, seven months; C, fifteen months.](image)

the weak muscles as measured by voltage-capacity curves.

In the later stages, during improvement of motor power, passive stretching accentuated the spontaneous discharges present in the weak muscles at rest. Again, the irritability was correlated with the degree of weakness and not with the degree of shortening, tenderness or other clinical sign of "spasm."

In the long-standing cases, several years after the onset, no abnormal response to stretching was obtained in paralyzed muscles or in those which were shortened by contracture but still functioning.

Electromyograms During Voluntary Contractions.—Action potentials were studied during voluntary contractions such as are required in an ergographic test.
The voltage of these discharges was found to be proportional to the degree of strength and gave indication of the rate of restoration of function (fig. 6). There was, however, no constant correlation between the voltage of spontaneous discharges at rest and that of the action potentials.

Observations were made during active movement, with simultaneous recording from antagonist and protagonist. By reciprocal innervation, inhibition of antagonists occurs during coordinated voluntary movements. Studying pairs of muscles, such as the anterior tibialis and gastrocnemius, or the quadriceps and hamstrings,

we found in our patients with poliomyelitis that, on flexion or extension of the knee or ankle, the two opposing muscles were activated simultaneously (fig. 7). This phenomenon occurred in patients who were receiving muscle reeducation and were being specifically trained to avoid such "incoordination." In these cases simultaneous contraction of opposing muscles could be detected electrically, although not suspected on observation of the muscles in action.

In addition to the simultaneous action of opposing muscles we have observed in many instances that individual diphasic spikes were discharged synchronously in the pair of opposing muscles. This synchrony was
apparent in the spontaneous discharges from resting muscles at times but was not consistently present. During a single examination, periods of synchronous discharges would come and go, being most frequently elicited by voluntary contractions (fig. 8). These synchronous action potentials have been found in patients whose poliomyelitis had occurred ten or fifteen years previously, as well as in patients in the early convalescent stage, and seem unrelated to the presence or absence of "spasm" in one or both of the muscles tested (fig. 9).

In studies of muscles during regeneration following traumatic peripheral nerve lesions we have observed similar synchrony of electrical discharges. The large diphasic spikes recorded from resting muscles have been
found to occur synchronously in separate muscles at times and also asynchronously during the same recording period. This was illustrated in the case of a brachial plexus injury in which discharges occurred synchronously in two opposing muscles of the lower arm, whereas the discharges from the upper arm were asynchronous (fig. 10). In the same patient, on voluntary flexion of the elbow there were simultaneous action potentials from the biceps, triceps and deltoid without definite synchrony of individual spikes (fig. 11).

This synchronization of individual discharges was such an unexpected finding that we took every precaution to rule out the possibility of artefact. Since this synchronization was not continuous but intermittent, it seemed unlikely that it could be due to the picking up by one amplifier of currents from its neighbor in the examining room. Furthermore, it was never found in normal controls. Careful efforts were made, however, to eliminate any possibility of such extraneous effects. Two different electrode systems were used: the surface electrodes were replaced by coaxial needles and the recording was run first on the push-pull circuit and then on the grounded circuit. Shifting of the electrodes from one position on the muscle to another was also tried. All these experiments led us to the same conclusion: that this type of synchronous discharge is a neuromuscular phenomenon.

These observations indicate that an important feature of poliomyelitis is a disorganization of normal reciprocal innervation. The similarity of findings in peripheral nerve injuries suggests that this disorganization is a manifestation of regeneration in the lower motor neuron.

**COMMENT**

Relatively little electrical activity was found in affected muscles during the acute stage of poliomyelitis as compared with that observed two or three months after the onset. These patients promptly received hot fomentations of the type described by Kenny,1 with consequent reduction in muscle sensitivity.

The electrical response of muscles to passive stretching in our poliomyelitis patients resembled that seen in other conditions in which muscle spasm acted as a protective mechanism in response to pain, as in acute back strain, or painful joints associated with arthritis or with trauma. This similarity may indicate that the
response is nonspecific as far as a neurologic disease is concerned being a reflex phenomenon stimulated by pain.

The spontaneous electrical discharges at rest, however, appeared to be unrelated to pain or other clinical evidence of muscle spasm. The correlation in this instance was with the degree of muscle weakness and consequently was an index of involvement of the neuromuscular system by the disease process. In completely paralyzed muscles, however, or in muscles much weakened in which there was no evidence of improving function, these spontaneous discharges were not obtained.

Because of the limitations in the speed of recording by ink-writing oscillographs, fibrillations of denervation are of too short duration to be recordable (1-2 milliseconds). The cathode ray oscillograph provides a more suitable recording speed for this purpose. Needle electrodes are unsatisfactory for detection of the fibrillations of denervation since they frequently act as an irritant to the muscle, causing discharges which should be regarded as artefacts; these confuse the records of spontaneous activity in resting muscle.

In our work with an ink-writing oscillograph, therefore, no fibrillations of denervation were recorded. The speed was, however, entirely suitable for registering motor unit activity, the spikes being usually of 5 to 10 milliseconds in duration.

In muscles showing such evidence of improving function as an increase in electrical excitability and in strength there were spontaneous electrical discharges which persisted at least as long as one and a half years. As this same type of electrical activity is also found in muscles supplied by regenerating peripheral nerves following suture, it seems reasonable to conclude that the discharges from the muscles in poliomyelitis are manifestations of a regenerative process. When present in the acute stage it may, of course, represent the occurrence of degeneration rather than regeneration. The pattern of electrical discharges differs, however, in regard to frequency and voltage from that seen in progressive muscular atrophy, presumably an entirely degenerative disease. In the latter disease increased electrical activity is usually associated with loss of power and atrophy, whereas in poliomyelitis it has been correlated with clinical improvement, the discharges disappearing when this ceased. These discharges may
depend on the presence of a combination of functioning and nonfunctioning fibers in a muscle, with a resultant hyperirritability on some chemical basis such as sensitivity to acetylcholine, or they may represent motor neuron activity. Further experiments, such as peripheral nerve blocks, might throw more light on this point. In any case the conclusion seems warranted that this electrical evidence of hyperirritability is not correlated with clinical signs of muscle “spasm” and is probably an indication of neuromuscular regeneration.

The term muscle “spasm” is inadequate to describe the abnormalities revealed by electromyography and may even be misleading. Instead of a single condition, we find that three types of abnormality are observable. The first is hyperirritability of the affected muscles to stretching as indicated objectively by electrical discharges and subjectively by pain during the acute stage of the disease. This may be a nonspecific reflex tension initiated by a painful stimulus. The cause of the pain is obscure. The hyperirritability may be due to invasion by the virus of the posterior roots, meninges or peripheral nerves and muscles.

Secondly, during the period of improving motor function muscle irritability, as evidenced by spontaneous discharges, is not correlated clinically with pain, tenderness or shortening but with weakness and with electrical indication of regeneration.

Thirdly, the shortening or contracture of muscles, which may persist for months or years after the onset, is not associated with hyperirritability electrically and may be due to changes intrinsic to the muscle rather than to spinal cord disease.

The term “mental alienation” seems unnecessary, for weakness or actual paralysis of muscles is probably due to specific lesions in the anterior horn cells. Loss of volitional control of muscles does occur without such anatomic lesions, particularly after immobilization as for fractures, and in association with painful movements. In our cases of poliomyelitis, however, weakness was always accompanied by objective signs of neuromuscular disease such as loss of electrical excitability or abnormal electromyograms. Whenever there was imbalance about a joint, such as results in an equinus or calcaneus deformity, we have observed a corresponding imbalance of involvement, the weaker muscle showing the greater
electrical abnormalities. If paralyses unrelated to the cord lesion occur in poliomyelitis they would seem, therefore, to result from treatment such as immobilization, or from failure to relieve pain, rather than from "alienation" or some other speculative neuromuscular dysfunction specific to the disease process.

We have found objective evidence, however, of "incoordination" in poliomyelitis. The simultaneous activation of protagonists and antagonists was a striking feature of our electrical recordings. This does not necessarily prove an abnormality of the nervous system as it is well recognized that individuals with weak muscles from any cause may contract all the muscles together in attempting movements beyond their strength. This is common clinical experience in the muscles of an extremity immobilized for treatment of a simple fracture. In our cases, however, the attempted movements were only minimal and specific muscle reeducation had been given to eliminate, if possible, the simultaneous contraction of opposing muscles. Furthermore, those movements were painless. The actual synchrony of individual spikes in opposing muscles both at rest and during motion is a most unusual finding. This cannot be produced in normal muscles by voluntary attempts and indicates striking disorganization of the neuromuscular mechanism. The fact that this synchrony of muscle discharges was observed also during regeneration of peripheral nerves after injury leads us to believe that it is a phenomenon associated with a regenerative process. It is known that peripheral nerves do not function entirely normally after regeneration if the lesion has been severe enough to cause wallerian degeneration. For example, in many cases of facial paralysis of the common Bell's type coordinated individual muscle action is never regained and the muscles of the eye and mouth consequently function simultaneously with all voluntary movements. The so-called "incoordination" in patients with poliomyelitis may also be an example of abnormal function following regeneration. Although these studies do not rule out involvement of higher levels in the central nervous system, all the results obtained are explainable on a basis of a disordered peripheral neuromuscular mechanism.

SUMMARY

1. In poliomyelitis the term "muscle spasm" is inadequate to describe the complexity of dysfunction which is revealed by electromyography.

2. In the acute stage, only muscles with some degree of paralysis discharge electrical potentials at rest; these electrical abnormalities are not correlated with the presence of clinical "spasm."

3. Partially paralyzed muscles are hyperirritable to passive stretching, as indicated by electrical discharges and pain; the muscle tension thus developed appears to be a reflex protective mechanism.

4. The electrical activity in paretic muscles at rest increases during the period of improving motor power, and the pattern of discharges corresponds with that seen in muscles during regeneration of peripheral nerves. When improvement in motor power ceases, spontaneous electrical discharges disappear.

5. No abnormal electrical activity is associated with the muscle contractures of the late stage of poliomyelitis, nor are any discharges present in completely paralyzed muscles.

6. The concept of "mental alienation" does not contribute to the explanation of paresis in our cases, since objective signs of a disease process were always present in the paretic antagonists of muscles in "spasm."

7. Increase of voltage of action potentials during successive ergographic tests is an index of recovery of motor power.

8. Of the three concepts of Kenny, the only one upheld by our objective measurements is that of "incoordination," although the term is misleading. We demonstrated not only simultaneous activation of protagonists and antagonists but also intermittent synchrony of individual discharges from opposing muscles, such as is found in peripheral nerve injuries during regeneration of axons. Disordered reciprocal innervation seems to be a more descriptive term for this type of dysfunction.
QUANTITATION OF MUSCULAR FUNCTION IN CASES OF POLIOMYELITIS AND OTHER MOTOR NERVE LESIONS

ELECTRICAL EXCITABILITY TESTS AND ELECTROMYOGRAPHIC AND ERGOGRAPHIC STUDIES

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Accurate evaluation of muscular function is of clinical importance as an aid to diagnosis and prognosis in a number of neurologic conditions. It is essential for determination of the site and extent of injuries to peripheral nerves and is useful in establishment of the prognosis, particularly by early detection of signs of regeneration. In cases of poliomyelitis, tests of muscular function are of particular value when one is charting the degree of involvement and as a guide to muscle reeducation and evaluation of progress in response to therapy. The recent work of Kenny has brought fresh interest to the problem of behavior of muscle in the acute stage of this disease and has introduced new concepts of the symptoms and treatment. In order to assess the merits of her contribution, it is important to use objective and quantitative methods for measuring the performance of muscles.

At present the most generally used tests of muscular function in this disease are similar to the method described by Lovett. In this method of examination the strength of individual muscles is graded according to their ability to overcome gravitational and manual resistances in prescribed positions. There is, inevitably, a large subjective element in such evaluations, with disagreement between observers. Although tests of this type are often of clinical value, they are not satisfactory as quantitative measurements, nor do they take into consideration the presence of "spasm." This symptom of poliomyelitis is assuming great importance since the advent of the Kenny theories. Clinical methods for detection of its presence are the means in most common use, but it is difficult to estimate the extent and severity of spasm without some accurate method, such as the recording of electrical potentials from the muscles.

Another method of examination frequently used is an assay of the electrical excitability of muscles to the make and break stimulus of a direct current, since the resultant contraction is qualitatively different in normal and in denervated muscles.

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muscles. A tetanizing current, such as the faradic or the 60 cycle alternating current, may also be used to test for the reaction of degeneration, as described by Erb. A direct current with a slow rate of increase in potential further helps to indicate a change in irritability, since a normal muscle is able to accommodate such a slow increase in current with no resultant contraction, whereas a denervated muscle has lost this power of accommodation and responds with a slow, wavelike contraction. These methods have many limitations and at best give only an approximate idea of the excitability of the muscle, since small variations escape all but the most experienced and skilled observers and objective recordings are impossible.

These qualitative evidences of impaired electrical excitability may be quantitated by determination of the threshold of contraction for currents of measured intensity and duration. Chronaximetry is the familiar means employed for this purpose. According to Lapicque’s conception of a universal time factor, the duration threshold of response to a current of arbitrarily set intensity (twice the rheobase) is the important factor to be determined. It has been shown, however, that many factors, such as the type, position and size of the electrodes, greatly influence the results and that the concept of a universal time factor applies only under certain arbitrary or empiric conditions. Furthermore, Rosenblueth and Dempsey have shown that when the whole voltage-capacity curve is constructed, changes become apparent in the voltage parameter in degenerating nerves without alterations in the time parameter or the chronaxia. Since a change in either the voltage or the time parameter indicates a change in excitability, it seems that measurement of the strength-duration relationship over the entire curve is a superior method and avoids introduction of the arbitrary concept of chronaxia.

Since the clinical tests outlined here for evaluation of muscular function do not meet the requirements of objective measurement, a number of methods have been devised in this laboratory for quantitation of electrical excitability, work performance and electrical discharges of affected muscles in cases of poliomyelitis and other lesions of motor nerves.

**TECHNIC OF MEASUREMENT OF ELECTRICAL EXCITABILITY BY VOLTAGE-CAPACITY CURVES**

The stimulating current used for this purpose is that of condenser discharges of measured capacity and voltage, varying from 0.0001 to 10 microfarads and 1 to 400 volts. The discharges are automatically controlled at a frequency of 12 per minute. The negative pole is used for the stimulating electrode, which usually consists of a small gage hypodermic needle inserted into the muscle at a recorded site. Sometimes a surface electrode is employed. This is either a thin disk of metal approximately 1 cm. in diameter, held in place by electrode paste and transparent adhesive tape, or a metal round tip electrode, held manually at a constant pressure, as measured by a spring balance incorporated in the handle. The positive pole is a large, dispersive electrode, placed in a neutral position on the patient.

The end point used is a threshold contraction as indicated by the just perceptible movement of the needle electrode or, in the case of the surface electrode, by the visible movement of the skin overlying the contracting muscle. From eight to sixteen determinations are made in both ascending and descending order. Voltage-capacity curves are plotted logarithmically,

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as suggested by Hill, but do not fit his theoretic curves, as the shape is altered when stigmatic electrodes are used. Differences in cutaneous resistance are made negligible as compared with the total resistance obtained by 20,000 ohm shunt and series resistances being coupled in the circuit.

The results of a series of such tests are shown in figure 1. Voltage-capacity curves in these determinations were constructed for the extensor carpi radialis muscle in a study of the regenerative process in a patient whose injured radial nerve had been sutured. The improvement in excitability, as indicated by the results of these measurements, appeared before any clinical signs of regeneration were apparent. Other cases in which these methods were used have previously been described.

Another method of objective evaluation of muscular function which is applicable to muscles activating the extremities is measurement of the amount of work of which the muscle is capable. For this purpose an ergograph has been designed in this laboratory which not only records each contraction of the muscle but measures the sum of the work done in any given period. This provides for an

![Diagram](image.png)

Fig. 1.—Voltage-capacity curves of the extensor carpi radialis muscle before and after suture of the radial nerve. Ordinate, log voltage; abscissa, log capacity.

... objective, and much more accurate, measurement of the strength of the muscle than does the Lovett method of assessing the power exerted against manual and gravitational resistance.

**TECHNIC FOR MEASUREMENT OF WORK PERFORMANCE OF MUSCLES**

The principle of the ergograph, a photograph of which is seen in figure 2, has a mechanical basis. That part of the limb which is activated by the affected muscle is attached to a weight by a string passed over a pulley, so that each contraction of the muscle lifts the weight. A pen writing on a revolving drum is actuated by the pulley through the same excursion as the weight. This drum is driven by a synchronous motor and has two speeds, 7 and 14 cm. per minute. The weight can be set to any value that is comparable to the amount of muscular force being tested.


An additional device attached to this apparatus enables the operator to quantitate the amount of work done per minute; this consists of a ticker tape on a revolving wheel, the tape being pulled through a ratchet each time the weight is lifted. In this manner, the total elevation of the weight, expressed in centimeters, can be measured by the length of the tape which passes through the ratchet. This length of tape, expressed in centimeters, multiplied by the weight lifted, expressed in grams, gives the amount of work done. An additional check on the amount of work done is given by the sum of the upward excursions of the pen on the drum. The tracing of the pen on the drum also gives a fatigue curve for the muscle under examination. Ergograms of muscular strength can be made at various stages of a disease process, or throughout the whole period of regeneration in the case of a recovering nerve lesion.

The results of a series of such ergographic determinations are shown in figure 3. These measurements were made in the same case of suture of an injured radial nerve as that shown in figure 1. Figure 3 shows clearly the steady increase in muscular strength as recovery progresses.

Fig. 2.—The ergograph used for recording and measuring the amount of work done by the contraction of a muscle.

Fig. 3.—Ergograms recording the amount of work done by the arm in extension of the wrist at various stages of the regenerative process following suture of an injured radial nerve in the same case as that for which records appear in figure 1.
in the amount of work which the extensor carpi radialis muscle could accomplish in extension of the wrist as regeneration of the nerve progressed. Each contraction was recorded, the height of the excursion being proportional to the movement made; the average work done per contraction was calculated and entered in the right hand column. This method of measurement has been applied to the study of many types of injury to peripheral nerves and to studies of muscle in cases of poliomyelitis and infectious polyneuritis.

At the same time that an ergogram is being recorded from a working muscle, another property can be measured which gives material useful in both diagnosis and prognosis, that is, the electrical action potentials released by the muscle during contraction.

TECHNIC FOR RECORDING OF ELECTROMYOGRAMS

Technics employing two types of electrodes were used in this study: 1. Surface electrodes made from solder disks, approximately 1 cm. in diameter, applied to the skin over the belly of the muscle with electrode paste and adhesive tape. A third electrode is placed on a neutral point to act as a ground. 2. Coaxial needle electrodes made by inserting an insulated core into a 24 gage hypodermic needle. These electrodes are placed in the muscle, and the outside of the needle is grounded. In some of the experiments synchronous recordings were made from the same muscle with both types of electrodes for comparison. Insulated copper wire from the electrodes leads the current into the preamplifier stage of a standard Grass electroencephalographic apparatus.

In the second stage of the apparatus the filters are arranged so that they may pass high frequency potential changes, and the degree of amplification is varied according to the amount of electrical discharge. Calibrations with a standard input are made with every recording, so that at any moment an exact assessment of the actual voltage elicited from the muscle can be made.

The final recording is made with a Grass ink-writing oscillograph on paper which is usually run through at a speed of 6 cm. per second; this speed has been found to give a satisfactory record of the range of frequencies found in muscular activity.

A further measurement of voltage is also made. The calibration already referred to gives a measure of the voltage of each individual deflection, but a summation of these voltages is also recorded by the use of an integrator. This instrument works on the principle of a condenser discharge: The incoming potentials are led through a condenser, which discharges each time it reaches its maximum load, and in discharging operates an electric signal on the same record on which the pattern of the muscle potentials is being traced.

An example of the application of this technic to the study of nerve regeneration is shown in figure 4. This figure illustrates the electrical action potentials from the extensor carpi radialis muscle during contraction in the subject whose strength-duration curves and ergograms are illustrated in figures 1 and 3. In figure 4 the amount of electrical energy released per second is computed on the right side of the chart. A steady increase is noticeable as regeneration progresses.

The electromyogram can be of considerable prognostic value, since traces of low voltage action potentials may be recorded on attempted contraction before any visible sign of movement can be detected.

Another application of electromyography is the recording of spontaneous electrical activity in resting muscles, such as is encountered with various types of nerve lesions. This is of especial interest in cases of poliomyelitis in view of Kenny’s theory of “spasm” and has been intensively studied in this laboratory. The effects of the position of the limb and of passive and of voluntary movement on these discharges have also been studied and form the subject of another report.

COMMENT

A threefold technic has been described for quantitative measurement of regeneration of injured peripheral nerves. This has been designed as a clinical laboratory procedure in our attempt to study the behavior of muscles in cases of poliomyelitis by more accurate methods than were heretofore available. It is not suggested that this battery of tests should be a part of the routine procedure or in any way a substitute for clinical observation. In many cases, however, such tests serve as a valuable adjunct to the usual methods of examination although for the trunk musculature, for example, it is obvious that this type of ergographic recording is not suitable. Nor is it always satisfactorily applicable to individual muscles serving joint movements which are activated by a complex of accessory muscles.

Study of muscular function in poliomyelitis was the primary object of these tests, but only a few new cases of the disease have been available to date (June 1943); consequently, injuries of peripheral nerves were the chief subject of investigation. We have had an opportunity to apply these methods of quantitation of regeneration in 21 cases, including instances of lesions of the brachial plexus and the median, ulnar and radial nerves, and in 6 cases of infectious polyneuritis.

In the problem of diagnosis these tests have proved of aid in determination of such questions as the degree and location of injury to a nerve and in the detection of hysterical components in cases of peripheral paralyses. A large number of the cases in which these technics have been applied have been those of service personnel suffering from war wounds in whom the degree of injury to the nerve was measurable by the tests for electrical excitability. The retention of good response to a tetanizing current, after the lapse of an adequate period to allow for the appearance of degenerative changes, is of course of great significance, as it indicates an incomplete lesion and, consequently, a relatively early return of function.

A difficult problem in war casualties is the localization of the level of nerve injury in cases of multiple wounds from gunshot or flying fragments. In these
instances tests for electrical excitability of the individual muscles reveal the distribution of involvement of the nerve, which might otherwise be obscured by limitation of movement due to lesions of bone, tendon or skin. As a case in which these objective tests were useful in detection of hysterical symptoms, we may cite that of a sailor who received an injury to his elbow resulting in apparently complete paralysis of the radial, median and ulnar nerves. Tests for electrical excitability showed that the injury was restricted to the radial nerve alone, with no involvement of the median and ulnar nerves at any time; even with evidence of progressive improvement in function of the radial nerve the patient retained his apparent paralysis.

These methods have also been used as prognostic leads. Since nerve regeneration after severe injury is necessarily a slow process, any test which will give early evidence of returning function is of value. As is known, the response to tetanic stimulation usually reappears only after return of voluntary motion, whereas improvement in electrical excitability as measured by voltage-capacity curves has been noted before clinical evidence of regeneration.

Returning activity in the muscle can also be detected by the electromyogram during volitional efforts before any motion can be demonstrated either by observation or by the ergograph. A feature of the electromyogram, other than action potentials, which is of clinical significance is the appearance of spontaneous discharges in resting muscles. It may here be noted that ink-writing oscillographs are incapable of recording the fibrillation of denervation, since the speed of the pens is a limiting factor. This method, however, is satisfactory for the recording of motor unit activity. It had been planned to use a Dumont cathode ray oscilloscope and camera in these studies in order to obtain a faster speed of recording, but war conditions made it impossible to obtain the necessary short persistence, blue screen cathode ray tube.

In cases of lesions of peripheral nerves, before any clinical signs of regeneration could be detected, spontaneous discharges were recorded from the paralyzed muscles which were characteristic of motor unit activity; the appearance of these discharges was suggestive of nerve regeneration and, in fact, preceded other evidence of returning function (fig. 5).

The laboratory technics described in this paper not only have been of use in the study of injuries of peripheral nerves but have yielded material of interest in the
investigation of poliomyelitis and polyneuritis. In cases of the latter diseases the objective data are of aid in the evaluation of the newer types of therapeutic procedures and in elucidation of the more recent theories of their pathology.

Detailed reports dealing with the results of study in cases of poliomyelitis and polyneuritis have been made elsewhere.9

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ELECTROMYOGRAPHIC STUDIES OF MUSCLE DYSFUNCTION IN INFECTIONOUS POLYNEURITIS AND POLIOMYELITIS*

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T he similarity of clinical findings in acute infectious polyneuritis and in poliomyelitis and the difficulties in differential diagnosis have recently been emphasized by several authors. The outstanding symptoms that are common to both diseases are motor weakness or paralysis and varying degrees of tenderness and pain in the muscles of the back and extremities. The distribution of the involvement is an important point in differentiation, for in poliomyelitis the typical weakness is segmental and asymmetrical in distribution, whereas in polyneuritis the extremities are usually symmetrically weakened, the most severe involvement occurring proximally. Minor sensory changes can usually be detected in cases of polyneuritis and the cerebrospinal-fluid findings with albuminocytologic dissociation are characteristic of this disease. The prognosis in poliomyelitis in the acute stage is uncertain, residual paralyses being frequent, whereas in polyneuritis residual palsies are rare. The progression of paralysis is also different in these diseases, for in poliomyelitis the weakness is maximal during the acute phase, whereas in polyneuritis there may be a gradual increase in the degree of involvement and a spread to new muscles late in the course of the disease. Further details of the clinical picture and pathologic lesions have been discussed in recent reviews.

In view of the similarity of symptoms in these diseases, we have treated patients with polyneuritis with hot packs and have observed as effective relief of muscle pain and tenderness as we have in poliomyelitis. To elucidate further the similarities in the behavior of muscles, we have studied by electromyography the patterns of electrical activity in the affected muscles of a series of patients with polyneuritis. Comparisons have been made with similar recordings from muscles in poliomyelitis in an attempt to throw light on the problem of muscle spasm and other dysfunctions in these diseases. In some cases comparisons have also been made with the recordings from cases with traumatic lesions of peripheral nerve, since these give direct evidence of the electrical behavior of muscle during regenerative changes in nerve.

METHODS OF STUDY

Ten cases of infectious polyneuritis from the Neurological Service of the Massachusetts General Hospital have been studied during the acute and convalescent stages of the disease. These had the characteristic symptomatology already described, including albuminocytologic dissociation in the cerebrospinal fluid.

The affected muscles were examined for clinical evidence of tenderness or pain on stretching, and their functional strength was assessed by the usual manual tests. The electrical discharges from these muscles at rest and during active and passive motion were recorded by means of an ink-writing oscillograph. Surface electrodes were usually employed, but in some cases these were supplemented by coaxial needle electrodes inserted in the belly of the muscle. The details of the technic have been fully described. Comparisons have been made with similar studies on 10 patients with poliomyelitis and on others with traumatic nerve lesions.

RESULTS

Resting Muscles

The first series of electromyograms were recorded from resting muscles in positions of complete relaxation. No electrical discharges are recordable from normal controls by this technic under such conditions. In patients with polyneuritis, although the muscles were tender to pressure and stretching, spontaneous discharges were found only in the pres-
ence of motor weakness. In poliomyelitis, also, electrical activity at rest was correlated with muscular weakness and not with clinical signs of sensitivity, except in complete paralysis, when no discharges were observed. The electromyographic patterns were similar in these two diseases (Fig. 1). The discharges persisted in both conditions so long as improvement continued or until recovery was complete. This suggests that spontaneous electrical activity is a sign of a recovery process. Our studies on peripheral-nerve injuries corroborate this, for diphasic spikes of a similar appearance were found as an early indication of regeneration and are probably due to motor-unit activity, as suggested by Weddell, Feinstein and Pattle. These spikes do not resemble the fibrillations of denervation, which are of much lower voltage and of too short a duration to be recordable by an ink-writing oscillograph.

A study of Figure 1 also reveals the striking similarity between the spontaneous electrical activity found in polyneuritis and poliomyelitis and the characteristic discharges present in muscles supplied by a regenerating motor nerve after traumatic lesion. This similarity is not surprising, since the electrical discharges from resting muscles in polyneuritis and in poliomyelitis are correlated with paresis and not with clinical spasm. They may well be associated with recovery of function in lower motor neurones.

In both polyneuritis and poliomyelitis, if the degree of paresis was unequal in a pair of opposing muscles, the greater electrical activity was found in the weaker muscle regardless of the degree of muscle tenderness (Fig. 2).

As a check on the type of recording obtained by surface electrodes in registering the spontaneous discharges of resting muscles, we have from time to time substituted coaxial needle electrodes. One example of such a comparison is given in Figure 3. It will be seen that the records are of essentially the same character.

**Passive Stretching**

The response of weakened muscles to quick, passive stretching consistently gave evidence of their hyperirritability in acute polyneuritis, as in poliomyelitis (Fig. 4). Instead of a few discrete spikes, as seen normally in controls, there were prolonged bursts of fairly high voltage discharges that persisted after the stimulus had ceased. These movements caused the patients some discomfort, and the muscle tension developed was similar to that seen in a pain reflex. Hyperirritability did not appear unless there was some appreciable weakness in the muscle tested, and when spontaneous discharges were present at rest these were increased by stretching. As clinical signs of muscle sensitivity lessened, the electrical activity in response to this stimulus also diminished.

**Voluntary Contraction**

The electromyograms of voluntary movements in polyneuritis revealed that protagonists and antagonists frequently contract simultaneously (Fig. 5), although this is not true of normal controls. This disruption of normal reciprocal innervation has also been demonstrated in poliomyelitis, and is of interest in relation to Kenny's conception of "inco-ordination." If the movements were painful, the electromyogram usually showed evidence of disordered reciprocal innervation. The inference from this observation is that the tension in the antagonistic muscles is a protective reflex serving to guard against excessive painful movement. Furthermore, this type of mass activation ceased with the decrease in muscle sensitivity.

In previous electromyographic analyses of this phenomenon in poliomyelitis, we showed that in addition to simultaneous activation of opposing muscles there was synchrony between components of the discharge. This was also observed in cases of recovery from injuries to peripheral nerves, which suggested that the abnormality was that of the regenerative process. In the cases of polyneuritis, although simultaneous discharges were seen there were no clearly marked instances of synchrony of individual action potentials. In poliomyelitis this synchrony occurred only after severe paresis and only after complete paralysis in nerve injuries. In these cases dysfunction accompanying regeneration could be anticipated. In polyneuritis, however, the paresis was never so severe and the recovery was more...
rapid; the absence of synchrony may therefore be explained by the lesser degree of neuronal damage.

**Discussion**

The similar distribution of muscle tenderness in polyneuritis and poliomyelitis is striking. Characteristically, in both diseases the muscles of the posterior neck, trunk and lower extremities are painful to stretching and deep pressure. It is also of interest that in both diseases hot fomentations are effective in relieving this symptom. In polyneuritis this might be explained by a sedative effect on hyperirritable sensory nerves, but in poliomyelitis no similar lesions are known. There are, however, definite pathologic changes occurring in the posterior-horn cells or nerve roots in both diseases that may be the basis of the similar response to heat. The pattern of electrical discharges obtained from affected muscles on passive stretching is also essentially the same in polyneuritis and in poliomyelitis, and is further evidence of a similar mechanism in both diseases.

Flexion contractures of the extremities are rarely seen as residual deformities in patients with polyneuritis, whereas these are not infrequent in poliomyelitis. Asymmetrical weakening of antagonistic muscles together with permanent paralyses may be responsible for these deformities in poliomyelitis. The possibility still remains that most of the residual limitation of joint movement is due to early immobilization with plaster and braces as commonly employed in poliomyelitis, whereas patients with polyneuritis rarely receive this orthopedic attention, being allowed to move freely in bed, and are usually given some form of heat for relief of sensitivity. It has been demonstrated by numerous observers that without splinting and with intensive hot fomentations and therapeutic exercises in the acute stages, as recommended by Kenny, these deformities do not occur in poliomyelitis. The residual paralyses...
from destruction of the anterior-horn cells cannot, of course, be influenced by any treatment applied

erative process, since the electrical patterns are indistinguishable and these discharges are correlated

PASSIVE PLANTAR FLEXION

POLYNEURITIS

A

B

POLIOMYELITIS

A

B

Figure 4. Hyperirritability Elicited by Passively Stretching a Partially Paralyzed Muscle. The A tracings are from the anterior tibialis muscle, and the B tracings from the gastrocnemius.

to the muscles, although the function of remaining motor units can be brought to the maximum by physical therapy.

It has been suggested that spontaneous discharges

Figure 5. Simultaneous Activation of Opposing Muscles on Voluntary Dorsiflexion. The A tracings are from the anterior tibialis muscle, and the B tracings from the gastrocnemius. Simultaneous activation occurs in polyneuritis and poliomyelitis, but not in a normal control.

from resting muscles in polyneuritis, poliomyelitis and traumatic nerve lesions are a sign of a regen-

with improving motor power. The histologic features of regenerating axons after traumatic nerve lesions are well known. The degenerative changes in peripheral nerves in polyneuritis have been described, and to account for recovery it is natural to assume that regeneration of axons takes place. In poliomyelitis no primary lesions in the peripheral nerves are generally recognized, although the virus may enter the cord by passage up an axon after experimental injection. Axonal regeneration is, therefore, not thought to account for the improvement in motor strength that usually occurs. We have noted, however, that paretic muscles have diminished electrical excitability as measured by strength-duration curves, and that as power returns the excitability improves. This indicates that there are relatively severe although reversible lesions, presumably in the anterior-horn cells, and that secondary axonal changes may also occur. The electrical discharges probably represent returning function in motor units, but, of course, reveal no evidence of the types of histologic change that are taking place. The microscopical appearance of the axons is probably quite different in all three conditions under discussion, so that the term "regeneration" when used to describe our observations implies only a recovery process.

The simultaneous activation of opposing muscles observed in polyneuritis and poliomyelitis might be thought of as a type of "inco-ordination," as described by Kenny. This is not, of course, incoordination in its usual meaning of abnormal muscular control in cerebellar disease. We prefer to interpret it as disruption of reciprocal innervation. In some
cases this disorder is apparently related to pain, the antagonistic muscle involuntarily contracting to prevent excessive movement. In poliomyelitis and in regenerating peripheral nerves after injury, we observed synchrony of action potentials, indicating severer disorganization of reciprocal innervation. In traumatic nerve lesions this probably represents abnormal axonal regeneration. There may also be similar abnormalities in the regenerative processes in poliomyelitis, although histologic evidence of this is lacking.

**Summary and Conclusions**

Electromyographic studies revealed the following similarities of muscle dysfunction in infectious polyneuritis and poliomyelitis: muscle tenderness and paresis are characteristic of both diseases, and the electrical abnormalities in both cases are correlated with weakness rather than with sensitivity; partially paralyzed muscles on stretching show hyperirritability, which can be relieved by hot fomentations; even at rest, paretic muscles are hyperirritable, discharging electrical potentials characteristic of regenerating motor units; and reciprocal innervation is frequently disrupted in polyneuritis and poliomyelitis, with resulting simultaneous activation of opposing muscles—this abnormality is probably secondary to painful motion.

The disorganization of reciprocal innervation is not so severe in polyneuritis as in poliomyelitis, for the simultaneous activation of opposing muscles in the former disease is not characterized by synchrony of component discharges.

**References**

The whole subject of geriatrics is relatively new. It can be compared to pediatrics, which was a blossoming subject when I was in medical school, but has now come to full fruition. The situation of the elderly has changed a great deal, because whereas a few years ago the average age of death was in the forties, a child born in the year 1943 may be expected to live to at least sixty-four years of age. The interesting thing is that the advances of medicine and public health have been directed almost entirely toward the early age group—that is, the age in which there has been improvement in mortality and morbidity statistics.

The man of forty to sixty-five lives no longer than he did fifty years ago, and there is a certain amount of evidence that he is no healthier. In other words, the present program of preventive medicine is enabling a great many people to live to sixty-five years but is not promising them anything when they do. It seems only fair that if they are to live as long as this, life ought to be made happier and healthier for them than it now is. Old age has been what one might call tolerated by the medical profession and by the public in general. No one is enthusiastic about old age. Certainly elderly people themselves are not particularly enthusiastic about it. In general, society has taken a negative and an entirely defeatist attitude toward old age. When the elderly are dead, society decrees a costly funeral and flowers.

As long as this negative, defeatist attitude continues, nothing is going to happen. Of course, part of this situation has been due to the fact that many of those who were looking for the alleviation of old age were not doing it from a medical or scientific point of view. All the folklore, all the tales about those who were interested in the elixirs of youth—Ponce de Leon, in trying to find the Fountain of Youth, Ulysses, Sinbad the Sailor—show that these people were interested in only one thing, the re-creation of their sexual capacities, and not in the health of old age. This attitude has, of course, damaged the whole movement of geriatrics, when men are interested only in sex rejuvenation, and women only in keeping their charm, and, it will be noted, not usually their fertility.

I have no intention of discussing the damaging diseases of older people,—by which term is meant all those older than fifty-five and certainly those older than sixty,—such as advanced cancer, apoplexy, degenerative heart disease or what not may bear fruit in the long-distant future. A few simple diseases, however, are particularly frequent in old age. Gallstones, for example, increase in frequency with advancing birthdays, and it is likely that if people lived to be one hundred and twenty all would have gallstones. Certainly, autopsies performed on people of eighty or over show almost uniformly the presence of gallstones. This may have some effect on the present attitude toward the diet of older people, which is discussed below.

Another illustration of the diseases of old age is diverticulosis, which is increasingly frequent with advancing age. X-ray studies show that nearly all people over sixty have a few diverticulums. This condition may lead to an inflammation of one of the diverticulums—the clinical entity known as diverticulitis.

Inflammation of the intestines also seems to be on the increase in the elderly. Appendicitis is usually thought of as a disease of young people, and it is certainly extremely common in that age group, but it again becomes frequent after the age of sixty. Since gallstones occur in elderly people, it is often taken for granted that a stomachache is due to them or to diverticulitis, but a passing plea must be made for the consideration of appendicitis, which often takes the dangerous form in people over sixty.

As the aging process, like the growing process, has been studied, it has been found that to keep the machine running, just the same as to keep the machine growing, there must be food and nourishment. Probably one of the greatest mistakes, by and large, has been to let the aged select their own diet, the latter depending on the condition of their teeth, whether they could chew it or not, depending perhaps on their pocketbooks and on the convenience of getting the food. It is certain that whereas in the family circle great attention is paid to the food for growing children, little attention is paid to the food for elderly people, even though they need it to continue their somewhat waning energies. To repeat, probably the most important thing in elderly people is the administration of the proper food in adequate quantity and quality. Here may be seen par excellence the necessity of giving vitamins.
CHARACTERISTICS OF THE NORMAL ELECTROENCEPHALOGRAM.
I. A STUDY OF THE OCCIPITAL CORTICAL POTENTIALS
IN 500 NORMAL ADULTS

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This study represents an attempt to codify the main characteristics of the electroencephalogram in the normal adult. This attempt was inspired by the recent interest in the use of the electroencephalogram as a possible method of grading normals in the selection of air pilots.

The chief characteristics of the normal electroencephalogram may be studied by considering the following components:

(1) Dominant frequency . . . which is here defined as the frequency in cycles per second of the majority of the waves present. The degree of fluctuation in the dominant frequency of an individual in repeated recordings has also been studied.

(2) Percentage time alpha . . . the percentage of the record occupied by waves of 8.0 to 13.0 cycles per second, whether occurring singly or in chains.

(3) Percentage time intermediate frequencies . . . the percentage of the record occupied by waves in the intermediate band (13.5 to 17.5 per second).

(4) Percentage time beta . . . the percentage of the record occupied by cortical potentials of frequencies above 17.5 per second, and of voltages so low as to make them individually uncountable.

(5) Percentage time slow activity . . . i.e., waves slower than 8.0 cycles per second.

(6) Voltage . . . In this study, the voltage characteristic studied was the maximum voltage of the potentials from the bipolar occipital leads.

The characteristics listed above will be found to vary in the same person, according to the part of the head examined. Throughout the present study, all analyses were made from bipolar recordings from the occiput.

METHOD OF ANALYZING THE RECORDS

After many attempts at easier and more rapid methods of analysis, the method finally chosen for this research, because it gave more information than any other, was the frequency distribution of the waves, compiled by counting the percentage time covered by waves of each different number of cycles per second.

In order to compile a frequency distribution curve, a 2-minute record, taken when the subject was lying quietly and breathing normally, is first inspected for the presence of artifacts. Any portion showing artifacts due to eye-blanks, muscle movements, etc., is omitted from the sample for analysis. The remainder is measured for total length of time, and this figure becomes the total on which all percentages are calculated.

A transparent grating (designed by Davis), marked off in intervals equivalent to each of the frequencies, is then laid on the record, and the frequency of any chains of waves is thus easily determined. The time covered by waves of each frequency is then totalled, the results being expressed as percentages of the whole period measured.

This process can be shortened by measuring only chains in which at least 3 waves of the same frequency occur together; in the majority of normal records, this arbitrary rule gives an adequately representative picture of the record, although its only specific merit is as a time saver.

When these figures have been compiled, they can be presented either in tabular form, or in diagrammatic form (Figure 1). On the whole, the diagram is to be preferred, because it gives an immediate representation of the most characteristic features of the electroencephalogram.

The characteristics listed in the introduction were studied in detail in a series of 500 young normal adults and the records of these subjects form the basis for the major portion of this paper. Most of these subjects received only one test, but in order to study the consistency of various of the properties of the electroencephalogram, 45 of the series were given 4 to 5 tests each; in all, 176 tests were made on this smaller series of 45.

RESULTS

(1) Dominant frequency

(a) Types of dominant frequency. On first inspection, the most outstanding feature of an electroencephalogram is the dominant rhythm,
The dominant frequency is defined as the one present in the greatest amount, i.e., at the mode of the curve. (In this case, it is 9.5 cycles per second.) i.e., the frequency in cycles per second which is present in greater amounts than any other frequency. This frequency is usually apparent on rough inspection and most electroencephalographers have adopted the classification into two groups, as first suggested by Berger, namely, the alpha and the beta types. These have usually been defined as the frequencies between 8.0 and 13.0 cycles per second for the alpha group, and frequencies faster than 18.0 cycles for the beta group. This classification is not satisfactory since, in fact, all electroencephalograms consist of a mixture of these rhythms in some degree, and no record consists wholly of either alpha or beta waves. Hence, if this classification is to be used, some criterion must be defined as to the percentage of beta activity which must be present in a record before that record should be classified as a beta type. For the purposes of the present study, records are classed as beta type only if there is present less than 20 per cent of other activity, i.e., of waves slower than 18 cycles per second.

Also, in the present work, a third classification is used, since it has been found in this series of 500 normal adults that there is evidence for regarding the dominant frequencies in the intermediate band (13.5 to 17.5 cycles per second) between the alpha and the beta ranges as a separate entity (Figure 2).

A detailed statistical analysis was made of the activity slower than beta (i.e., slower than 18.0 cycles) in the records of 500 normal adults. The mean for all the dominant frequencies in this range was 10.5 cycles per second, with a standard deviation of 0.9. Thus, any dominant frequency slower than 8.0 or faster than 13.0 cycles is outside 3 times standard deviation for normals, and is therefore, by definition, excluded from the alpha range. Further reason for regarding records with a dominant frequency in the intermediate range as a separate group is found in a study of the distribution curve of the dominant frequencies of 500 normal adults (Figure 3).

In this graph, there appears to be a normal distribution curve dominating the picture but with some outlying stragglers in the faster frequencies. The main curve consists of 474

**Fig. 1. Graph Compiled from the Electroencephalogram of One Normal Adult, Showing the Percentages of Each Frequency Present, Omitting the Beta Range**

The upright line to the right of each tracing is the calibration for 100 mV.
subjects whose dominant frequencies give a normal distribution around a mode of 10.0 cycles per second, with 26 subjects outside the normal distribution curve. Hence, it is felt that those frequencies in the range 13.5 to 17.5 should not be included in the alpha group. Frequencies falling within this range are referred to as intermediate rhythms.

In this group of 500 normal adults, examined in this laboratory, the following distribution of the three types (alpha, intermediate, and beta) was found:

<table>
<thead>
<tr>
<th>Type of Frequency</th>
<th>Number of Subjects</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha (8 to 13.0 cycles)</td>
<td>474</td>
<td>94.8</td>
</tr>
<tr>
<td>Intermediate (13.5 to 17.5)</td>
<td>18</td>
<td>3.6</td>
</tr>
<tr>
<td>Beta (18.0 and over)</td>
<td>8</td>
<td>1.6</td>
</tr>
</tbody>
</table>

(b) Consistency of the dominant frequency. That the dominant frequency remains constant within narrow limits for the same individual over long periods of time can be demonstrated by repeated observations on the same person. A discussion of some factors which may, in certain circumstances, alter the dominant frequency will be reported in a subsequent paper.

Electroencephalograms repeated on the same subjects over a period of a few years revealed only small fluctuations in the dominant frequency from one test to the next:

| Subject | Age | Gender | Tests | Dominant Frequency
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>35</td>
<td>Female</td>
<td>1</td>
<td>9.5, 9.5, 9.5, 10.0, 9.5</td>
</tr>
<tr>
<td>2</td>
<td>24</td>
<td>Female</td>
<td>3</td>
<td>9.5, 9.5, 10.0, 10.0, 9.5</td>
</tr>
<tr>
<td>3</td>
<td>36</td>
<td>Female</td>
<td>4</td>
<td>20.0, 20.0, 18.0, 20.0, 20.0</td>
</tr>
</tbody>
</table>

This degree of fluctuation is of the same order as that reported by other workers (Loomis, Harvey, and Hobart (1), Jasper and Cruikshank (2), and Jasper and Andrews (3)).

That there is also only a small fluctuation in the dominant frequency of an individual when examined several times during the same day, has been established on a larger group.

One hundred and seventy-six observations were made on 45 normal subjects, all of whom were examined at non-fasting blood sugar levels (above 70 mgm per 100 cc.), i.e., 4 to 5 tests were made on the same individual at intervals during the same day.

Ten of the 45 subjects showed no variation in their dominant frequency. In 1 subject only did the dominant frequency vary from his own mean value by more than 7 per cent. The mean variation for the whole series of 45 subjects was under 1 per cent (176 observations).

(c) Relation between consistency of the dominant frequency and age. If the consistency of a person's dominant frequency be studied, it is found that age is a factor in the degree of variability found in the electroencephalogram at non-fasting blood sugar levels (above 70 mgm).

This degree of variability is determined by finding the coefficient of variation for the dominant frequency of each individual. (The coefficient of variation = $100 \times \frac{\text{standard deviation}}{\text{mean}}$)

A group of 45 young adults between the ages of 17 and 38 were thus examined for consistency of dominant frequency at normal blood sugar levels. By rough observation, it appeared as though the dominant frequency in records of those subjects over the age of 20 was less stable than of those under that age, and for this reason the division into two groups was made at this age level. In the series examined, there were
13 subjects under the age of 20, and 32 were aged 20 or over. Calculations of the coefficient of variation gave the following result:

<table>
<thead>
<tr>
<th></th>
<th>Under 20</th>
<th>20 and over</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean of coefficient of variation</td>
<td>1.2</td>
<td>3.2</td>
</tr>
<tr>
<td>Standard deviation of coefficient of variation</td>
<td>1.3</td>
<td>2.4</td>
</tr>
</tbody>
</table>

The difference between these two means was tested for reliability by determining the standard error of the difference:

\[
\frac{D}{\sigma D} = 3.52,
\]

where \(D\) equals the difference between the two means, and \(\sigma D\), the standard error of that difference.

The result is indicative of a significant difference between these two groups, i.e., the chances of this being a true difference are over 1000 to 1.

It would appear therefore that the dominant cortical frequency becomes less stable with increasing age, and this is demonstrable even in a series which contains no one over the age of 38.

(d) Dominant frequency and the age factor.
The total group of 500 young adults, between the ages of 17 and 47, was studied for correlation between their age and the actual frequency of their dominant rhythm at non-fasting blood sugar levels (in contrast to the consistency of this dominant frequency which has just been examined).

There have been several studies of this kind in relation to age in children (Berger (4), Loomis (5), Lindsley (6), Smith (7), and Weinbach (8)); but the age factor in adults has not received much attention. Bernhard and Skoglund (9, 10) demonstrated a difference of over half a cycle in the mean dominant frequency between two age groups of 15 to 18 and 19 to 30, respectively.

In the present series of 500 adults between the ages of 17 and 47, with a mean age of 24, the following results were obtained:

<table>
<thead>
<tr>
<th></th>
<th>Under 24 years</th>
<th>24 years old and over</th>
</tr>
</thead>
<tbody>
<tr>
<td>270 alphas</td>
<td>mean dominant frequency 10.5</td>
<td>mean dominant frequency 10.4</td>
</tr>
<tr>
<td>7 intermediates</td>
<td>4 betas</td>
<td>17 intermediates</td>
</tr>
<tr>
<td>4 betas</td>
<td></td>
<td>4 betas</td>
</tr>
</tbody>
</table>

Thus, it would appear that age has no influence on the dominant frequency of the electroencephalogram of adults up to the age of 47. We have no data on normal individuals over this age.

(e) Dominant frequency and its relation to other physiological factors. The dominant frequencies in this group were examined for any possible correlation with sex, weight, height, or height-weight ratio, but no relation was found with any of these factors.

(2) Percentage time alpha

This is defined as the percentage time occupied by waves of 8.0 to 13.0 cycles per second, occurring either singly or in chains; i.e., it is the gross alpha count.

In 500 subjects who were examined at non-fasting blood sugar levels, the percentage time alpha varied in the group from 9 to 93 per cent, with a mean of 61 per cent. There was some alpha activity present in all records, even those which were predominantly beta in type.

The distribution among this group of the amount of alpha activity present at non-fasting blood sugar levels is given in the following distribution diagram (Figure 4).

![Graph Illustrating 500 Normal Subjects (Expressed as Percentages) Grouped According to the Amount of Alpha Activity Present in Their Records](image-url)
Of the 24 subjects with less than 25 per cent alpha activity, 16 had a predominantly intermediate rhythm, and 8 had dominant frequencies in the beta range.

(a) Consistency of percentage time alpha. The variability in percentage time alpha for an individual was not so marked in this series as has been described by Rubin (11) in bipolar recordings, the mean standard deviation for repeated tests on an individual being 7.1. It should be pointed out that in this work the percentage time alpha quoted includes all alpha activity present, whether occurring in single waves or in chains, whereas Rubin's observations are based on a criterion of 3 waves of alpha frequency occurring together; and in Rubin's experiments, the blood sugar was not controlled.

The relation between variability of percentage time alpha and high or low alpha percentage, as described by Rubin (12), did not hold in this series.

(b) Relation between percentage time alpha and dominant frequency. There was found to be an inverse relationship between percentage time alpha and the dominant frequency of that alpha; in other words, individuals whose percentage time alpha values were high showed dominant frequencies in the slower alpha range.

In the total series of 500 subjects, the records were examined for the relation between the dominant frequency of any alpha present and the percentage time occupied by this alpha activity. The following results were obtained:

<table>
<thead>
<tr>
<th>Alpha frequency</th>
<th>Number of subjects</th>
<th>Mean percentage time alpha</th>
<th>Standard deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slower than 10.5 cycles</td>
<td>236</td>
<td>68.5</td>
<td>14.1</td>
</tr>
<tr>
<td>10.5 cycles and faster</td>
<td>264</td>
<td>54.7</td>
<td>20.1</td>
</tr>
</tbody>
</table>

The difference between these 2 means was tested for reliability by determining the standard error of the difference which was found to be 8.90. Such a high standard error of the difference is beyond the possibility of chance.

It is therefore concluded that an inverse relationship exists between the dominant frequency of the alpha present and the amount of total alpha present.

(c) Relation between percentage time alpha and other physiological factors. No correlation was found in this series between the percentage time alpha and age, sex, height, weight, or the height-weight ratio.

(3) Percentage time intermediate rhythm

Frequencies of 13.5 to 17.5 cycles per second, i.e., those which lie between the alpha and beta ranges, are not commonly found in more than negligible quantities in the records of normal adults, and are only rarely found as the dominant frequency of the record. In this series of 500 subjects, there were 18 with a dominant frequency in this range, or 3.6 per cent.

Rhythms in this range, however, normally occur in bursts during the lighter stages of sleep (13), and it would not be surprising to find that they have a different physiological origin from the alpha waves. They do not appear to be merely accelerated alpha waves, since observations on sleep show that they appear abruptly and do not emerge by gradual transition from the higher alpha frequencies. These facts suggest that one is here dealing with a dichotomy.

As has already been noted, the electroencephalogram in normal adults contains very little activity in this intermediate frequency band. What little there is might be expected to appear in those records with the faster alpha frequencies as an extreme variation of their predominantly 12.5 to 13.0 cycle rhythms, but an examination of this series failed to establish any such correlation. There were no more waves of the intermediate frequencies in those records with dominant frequencies in the faster alpha range than in those with predominantly 9.0 and 9.5 cycle activity.

Unlike the so-called alpha and beta rhythms which are present to some extent in all records, the intermediate band of 13.5 to 17.5 cycle activity is sometimes totally absent, a fact which contributes to the impression, previously mentioned, that one is here dealing with a dichotomy.

(4) Percentage time beta

Beta activity (i.e., 18.0 cycles per second and over) was found, to a greater or less extent, in every record in this series at non-fasting blood sugar levels. As has already been remarked, all
electroencephalograms are a mixture of rhythms, and, in this series, the 8 cases which have been classified as beta type, all contained some alpha; their percentages of beta activity varied from 51 to 80 per cent. The distribution of beta activity in this series is given in Figure 5.

Figures 4 and 5 taken together do not, of course, give the total picture for the group, since the time occupied by intermediate frequencies and by slow activity is not represented. The amount of beta activity in an individual's record was found to be remarkably constant in repeated runs, and is characteristic for the individual. It did not vary with the degree of relaxation achieved by the subject.

Although in this series there was a tendency to more beta activity in the records of the older subjects, no statistical relation between it and age could be established. The amount of beta activity present did not correlate with sex, height, or weight.

(5) Activity slower than 8.0 cycles per second
Waves of a frequency slower than 8.0 cycles per second are here referred to as slow activity. Traces of 7.0 to 7.5 per second frequencies were found in the records of 125 out of the series of 500 subjects, but only in 4 individuals was there more than 5 per cent of such slow activity in the 2-minute recording; of these 4 individuals, 1 had 19 per cent slow activity, 2 had 9 per cent, and 1 had 6 per cent.

Six-cycle waves were found in the occipital leads in 41 (8 per cent) of the 500 records at non-fasting blood sugar levels, but waves slower than 6 cycles per second were found in only 4 subjects, or less than 1 per cent.

Were an investigation of the potentials from the temporal regions to be made in a way similar to the present detailed study of the occipital potentials, it seems likely that there would be a higher incidence of 6- and 7-cycle waves in normal records, this being our experience and that of other electroencephalographers (14).

No wave in the range commonly called delta activity (i.e., 4 cycles or slower) was found.

(6) Voltage
This was measured by a pair of calipers, adjusted to the calibration made for voltage at the beginning of each record.

The maximum voltage was measured in every case and classified as to whether it was under 25 mV, over 25 mV but under 50 mV, over 50 mV but under 100 mV, or over 100 mV. In the latter case, a further breakdown in classification was made between those who had less than 20 waves which reached 100 mV in amplitude and those which had more than this number in a 2-minute run.

The distribution of voltage in this series of 500 normal subjects at non-fasting blood sugar levels was as follows:

<table>
<thead>
<tr>
<th>Voltage Range</th>
<th>Number of Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Under 25 mV</td>
<td>16</td>
</tr>
<tr>
<td>Over 25 mV but under 50 mV</td>
<td>109</td>
</tr>
<tr>
<td>Over 50 mV but under 75 mV</td>
<td>151</td>
</tr>
<tr>
<td>Over 75 mV but under 100 mV</td>
<td>128</td>
</tr>
<tr>
<td>Over 100 mV</td>
<td>96</td>
</tr>
</tbody>
</table>

(a) Voltage and dominant frequency. The faster frequencies tend to be of low voltage; no record with a dominant frequency faster than 11.5 had any potentials which reached as much as 100 mV.

In the alpha range, the records with the slower alpha frequencies were of higher voltage than
the faster ones, thus following the usual character of oscillations in which the amplitude is inversely proportional to the frequency. In the following table, 474 normal subjects, whose dominant frequencies were in the 8.0 to 13.0 cycle band, are listed according to their voltage.

<table>
<thead>
<tr>
<th>Voltage Range</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum voltage under 50 mV</td>
<td>11.0</td>
</tr>
<tr>
<td>Maximum voltage over 50 mV</td>
<td>10.4</td>
</tr>
<tr>
<td>but under 100 mV</td>
<td></td>
</tr>
<tr>
<td>Maximum voltage over 100 mV</td>
<td>10.0</td>
</tr>
</tbody>
</table>

(b) Voltage and percentage time alpha. The maximum voltage of the potentials in a record vary directly with the percentage time alpha activity present; i.e., those records which have a large amount of 8.0 to 13.0 cycle waves reach a higher maximum potential.

In the following table, voltage is related to the mean percentage time alpha found in the same series of 474 normal subjects whose dominant frequencies were in the 8.0 to 13.0 cycle band.

<table>
<thead>
<tr>
<th>Voltage Range</th>
<th>Mean percentage time alpha</th>
</tr>
</thead>
<tbody>
<tr>
<td>Under 25 mV</td>
<td>40.3 (10 subjects)</td>
</tr>
<tr>
<td>Over 25 mV, under 50 mV</td>
<td>48.4 (95 subjects)</td>
</tr>
<tr>
<td>Over 50 mV, under 100 mV</td>
<td>65.4 (274 subjects)</td>
</tr>
<tr>
<td>Over 100 mV</td>
<td>73.6 (95 subjects)</td>
</tr>
</tbody>
</table>

DISCUSSION

Since the first development of electroencephalography, interest has been centered mainly on its application to clinical problems, and it is only recently that there has been a shift of interest to the study of the normal adult. For many reasons, it would have been preferable had the reverse taken place, for the development of this test to have proceeded from a basic study of the normal to a comparison of clinical records with a norm already well established.

The desirability is patent for the establishment of a yardstick for the normal population against which may be measured the variables found in pathological records. It is equally desirable in attempting to assess the electroencephalograms of normal subjects (as, for example, is being done in air-pilot selection) to have a quantitative basis from which one may calculate the chances of any observed phenomenon being a normal finding.

In this paper, a beginning has been made in an attempt to find what range of variation can be found for some of the characteristics of the electroencephalogram of normal adults. At the present stage, this study has been limited to an analysis of the cortical potentials from the occipital lobes, and it cannot be too strongly emphasized that a different set of data would undoubtedly be obtained from the frontal lobes, and different again from the temporal and parietal regions.

This study is also limited to analysis of electroencephalograms during normal breathing. A report of an investigation during hyperventilation will follow this, with special reference to the role of blood sugar and depth of hyperventilation.

In the past, the bulk of the work on both normal and clinical electroencephalograms has been done by the method of appraisal. The experienced electroencephalographer has looked at the record, compared it in his mind with his impression of those records which have previously come into his laboratory, and assessed it from this mental comparison. Where gross differences are present, such as are found in patients with epilepsy or with neoplasms, this method has in the main sufficed, but when finer shades of difference are being searched for, a more finely differentiated set of standards is necessary.

Such standards can only be set up on a basis of actual measurement, a method which is time absorbing, but essential in any research project designed to establish normal control standards. Were such a set of standards established on a large enough group of individuals, it would then be possible to estimate the chances of normality when any fine differences occur in the record, as for example, 7 cycle waves occurring singly in the occipital leads, or trains of 14 cycle waves. The percentage of normal records in which such waves occur would be known and the importance of the finding could thus be assessed.

A development in the measuring of electroencephalograms has been made by Gibbs and Grass (15) in the form of a spectrum analyzer. This apparatus gives a compilation of the amount of energy present at each frequency. At the present stage of our experience, we have found more meaning in the frequency of waves than
in their voltage in normal records, and we therefore look for a method where the number of waves present at any frequency is not obscured by the voltage. An instrument for this purpose has recently been designed by Walter (16), but is not yet on the market.

It is obvious that the current differentiation of electrical potentials into alpha, beta, and delta rhythms is arbitrary and, in some respects, unfortunate. The classification of records into alpha and beta rhythms tends to obscure the fact that many so-called alpha records contain potentials of faster frequencies and that many beta records contain percentages of the slower alpha frequencies. A more accurate and more complete assessment could be made by describing the frequency distribution on the potentials. It would seem much wiser to describe rhythms in terms of the incidence of actually measured frequencies until some physiological or statistical reason can be found for grouping frequencies into certain rhythms.

The fact that significant contributions to clinical diagnosis in epilepsy and the localization of neoplasms have been made by the crude methods of gross inspection of records would by no means invalidate the need for studies based upon careful measurements. However, once the data on a sufficiently large number of cases are collected, it might well be possible to develop simpler methods of analysis, based upon the known verifiable distributions of frequencies. This would seem a more logical approach and could give more precise information in the study of problems in which fine differentiations occur in the records.

**SUMMARY**

The occipital cortical potentials have been analyzed under conditions of controlled blood sugar in 500 subjects. Of these, the majority received but one test, but in 45, repeated observations were obtained.

The following characteristics were found in these electroencephalograms.

1. The dominant frequency of an individual is comparatively stable, but becomes less so with increasing age. There is a statistically significant correlation between age and stability of dominant frequency (45 subjects).

2. Waves of 8.0 to 13.0 cycles per second ("alpha") were present in all records examined. The percentage time occupied by alpha waves varied inversely with the frequency of the dominant frequency. This inverse relationship has been established statistically in 500 subjects.

3. Waves of 13.5 to 17.5 cycles per second ("intermediate") are rarely found in any quantity in normal records, and constitute the dominant frequency in only 3.6 per cent of all normals examined (500).

4. Waves of 18.0 cycles per second and faster ("beta") were present in all records examined (500). The percentage time occupied by waves in this range is nearly constant for an individual in repeated runs (45 subjects).

5. Waves slower than 8.0 cycles per second are found in occipital potentials of 25 per cent of normal subjects. Waves as slow as 6.0 cycles were found in only 41 out of 500 subjects.

6. No waves of 4.0 cycles per second or slower ("delta") were found in the occipital recordings of any normal subject while breathing normally (500 subjects).

7. Maximum voltages are higher in those records which contain the most alpha activity, and in those records whose dominant frequencies fall in the slower alpha frequencies (500 subjects).

8. The physiological factors of sex, height, weight, or the height-weight ratio did not correlate with any characteristic in the brain wave record.

All the electroencephalographic tracings for this research were recorded in the Brain Wave Laboratory of the Massachusetts General Hospital with the cooperation of the director, Dr. Robert S. Schwab.

The authors are indebted to Mrs. Frances Cooperstein and Miss Margaret Gray for technical help, and to Mrs. Mary Newell for analysis of the records.

**BIBLIOGRAPHY**


CHARACTERISTICS OF THE NORMAL ELECTROENCEPHALOGRAM.

II. THE EFFECT OF VARYING BLOOD SUGAR LEVELS ON THE OCCIPITAL CORTICAL POTENTIALS IN ADULTS DURING QUIET BREATHING

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(Received for publication August 2, 1943)

Although the rôle of blood sugar level in the slowing of cortical rhythms during hyperventilation is now very generally recognized, its effect on the electroencephalogram during quiet breathing has not been fully studied in the normal human subject.

Gibbs, Williams, and Gibbs (1), using the spectrum analyzer, concluded from a series of 4 adult normals that between extreme limits, alterations of blood sugar level have no effect on the frequency of the brain waves at normal depths of ventilation. Lennox, Gibbs, and Gibbs (2) found an upper limit of 50 mgm. for the blood sugar level to affect the electroencephalogram during normal breathing.

Davis (3) made a more extensive study on 30 normals to whom injections of insulin were given in order to lower the blood sugar below fasting levels. She found that, within 20 minutes of the injection, there was a reduction in the alpha rhythm with the appearance of 8 cycle waves. Within 30 minutes of the injection, delta waves dominated the picture. Her study was made while the subjects were breathing normally. Hoagland (4, 5) and his co-workers made a study of the alpha rhythm in schizophrenics at blood sugars so low as to induce loss of consciousness.

The present study is an attempt to establish the influence of blood sugar level upon the electroencephalogram at stages of unimpaired consciousness in the normal subject.

METHOD

The subjects for these experiments were all young adults, mostly college students (29 males, 16 females), between the ages of 17 and 38. A brief medical history was taken and, in most cases, a brief physical examination was made before the experiment. Only those whose history indicated the absence of medical, neurological, and psychiatric disease, and whose physical examinations were within normal limits were included in the series. As a result of these brief preliminary examinations, the data on 15 individuals out of the 60 who volunteered were discarded from the series.

The routine procedure was as follows: The subject reported to the laboratory in the morning, fasting. He was asked to lie down for a period of at least 30 minutes during which time the history was taken, a brief physical examination made, and the scalp electrodes attached. A sample of blood was drawn for the microdetermination of capillary blood sugar, and the subject was attached, by a mouth mask fitted with flutter valves, to a large spirometer with an open circuit for a period of approximately 8 minutes. He breathed outside air from the spirometer at the normal rate and depth of ventilation for a period of 2 minutes, and was then told to breathe as deeply as he could, inhaling and exhaling to the rhythm of a metronome clicking 30 times a minute. The depth of ventilation could be followed on the spirometer scale, and if the subject was not reaching the required depth for his body weight, he was urged to breathe deeper. (A study of the effects of the hyperventilation period will appear in a later paper in this series.)

After the 3-minute period of hyperventilation, the subject was told to breathe naturally, and another sample of blood was taken for the blood sugar determination, one minute after the hyperventilation period. Normal breathing was then continued for a period varying from 2 to 6 minutes, until the minute-respiratory volume was back to its base-line level.

The subject was disconnected from the spirometer and was asked to describe his subjective sensations during the test; he was then given a brief questionnaire designed to review the subjective sensations systematically.

This whole procedure was repeated within approximately 30 minutes, with the subject still in the fasting state. After another similar interval, an intravenous injection of saline was given as a control on the insulin injection to follow; this was identical in quantity and appearance with the insulin injection, and the subject was ignorant as to its nature and purpose. This control injection was to
check on any possible rise in blood sugar, such as is sometimes found in normal persons when excited.

If, at fasting blood sugar levels, the electroencephalogram had shown no slowing of rhythm, an injection of insulin was given intravenously, the dose being calculated to give 1/10 unit per kgm. ideal body weight. Two complete experiments were then run through, one immediately after the injection, and one approximately 25 minutes after it, this being the time for the maximum effect of insulin.

After this second run under the influence of insulin, the subject was given glucose by mouth, the usual amount being 100 grams of glucose in 100 cc. of water with lemon added to make it palatable. Three further experiments were then carried through, one immediately after ingestion of glucose, one 30 minutes after, and one approximately an hour later; if the electroencephalogram did not appear normal after the second of these runs after sugar, a second dose of glucose would be given. At the end of the hyperventilation period of each and every electroencephalogram recording, a blood sample was taken for blood sugar determination.

In all these experiments, the technique used for recording the electroencephalogram was standardized as follows:

Six scalp electrodes were applied in the usual manner to the right and left frontal, right and left occipital, and left parietal regions, respectively. In left-handed subjects, the parietal lead was put on the right parietal region. A reference electrode was placed on one mastoid process.

For the recording, a Grass electroencephalographic apparatus was used; in all the recordings, the paper speed was 3 cm. per second, and the pen excursion was calibrated for a sensitivity of 1 cm. for 100 mV. All recordings were made by remote control, the subject being in a darkened room at some distance from the laboratory where the electroencephalogram was recorded.

Electroencephalographic recordings were taken throughout the whole period of each experiment, except for the minute during which the subject was being pricked for the blood sample. These blood samples were analyzed for sugar content by a modification of the Folin-Wu micro method.

RESULTS

The first characteristic of the electroencephalogram to be examined for the effect of low sugar was the dominant frequency, which is here defined as the frequency in cycles per second of the majority of the waves present.

This was determined by compiling a distribution curve of the frequencies found in the record from the occipital bipolar leads and was made by counting the percentage time occupied by waves of each frequency during the preliminary 2-minute run when the subject was breathing normally. A sample of one of these distribution curves is shown in Figure 1. The full technique, compiling these distribution curves of frequency, has been described in a previous paper (6).

The frequency at the mode of the curve, i.e., the one present in the highest amount, is the one defined as the dominant frequency. This peak may fall in the alpha range (8.0 to 13.0 cycles), in the intermediate range (13.5 to 17.5), or in the beta range (18.0 or over).

Sixteen subjects with dominant frequencies in the alpha range received insulin injections, and these were examined for change in this frequency at low blood sugar levels. There were 2 to 3 recordings for each of these subjects at normal blood sugar levels (70 to 130 mgm. per
BLOOD SUGAR LEVEL AND E.E.G. DURING NORMAL BREATHING

When these 16 individuals are examined as a group, it is found that the mean dominant frequency after insulin is slower than at ordinary sugar levels.

The mean dominant frequency after insulin injection differs from that at normal levels by more than 4 times the standard deviation at normal levels, and this may thus be regarded as a significant difference, and it can therefore be concluded that lowering the blood sugar below 100 cc.), so that a mean could be established as a base-line for each individual.

100 mgm. per 100 cc. causes a slowing of the alpha rhythm during normal breathing. Blood sugar levels as low as 60 mgm. per 100 cc. are often found in fasting individuals who have received no insulin.

An example of the distribution curve for one individual in the series (a male aged 21) is shown in Figure 2. This diagram gives the distribution of the various frequencies found at two different blood sugar levels in the same person while breathing at a normal depth.

The plain line is the curve for the blood sugar level of 45 mgm. and the crossed line is at 85 mgm. This is a chart of the alpha and intermediate ranges of activity, and does not represent the beta frequencies.

**The effect of low blood sugar on the amount of slow activity during normal breathing**

Waves of a rhythm slower than the alpha range (i.e., slower than 8.0 cycles) are infrequently found in the potentials from the occiput

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</thead>
<tbody>
<tr>
<td>Mean dominant rhythm at normal sugar levels (70 to 130 mgm.)</td>
<td>Mean dominant rhythm 20 min. after insulin (under 70 mgm. blood sugar)</td>
<td>Difference between the two means</td>
<td></td>
</tr>
<tr>
<td>10.56</td>
<td>10.00</td>
<td>0.56</td>
<td></td>
</tr>
</tbody>
</table>

**Sixteen subjects**

(53 recordings)
in the normal subject at ordinary blood sugar levels. In this series of 45 subjects, no one had as much as 1 per cent of slow activity, and 35 had none at all. In no case in this series were any waves slower than 6 cycles found.

Slow activity does appear in the records of some normal subjects if the blood sugar is lowered by insulin injection. Of 18 subjects who received insulin injections, 2 developed 6 cycle waves in occipital leads while breathing normally, and 2 others showed some 7.5 cycle. The maximum percentage time slow activity (i.e., slower than 8.0 cycles) induced by insulin in any one in this series was 13.8 per cent at a blood sugar level of 45 mgm. per 100 cc.

The effect of high blood sugar (above 130 mgm.) on the dominant frequency

In this series of subjects, of those who were given glucose there were 31 (with alpha rhythms) whose blood sugars rose above 130 mgm. per 100 cc. Their mean dominant frequency was 10.31 which does not differ from the mean dominant frequency (i.e., 10.33) found at ordinary blood sugar levels.

The practical outcome of this finding, coupled with that of the slowing of the rhythm at low blood sugar levels, is that in any assessment of an electroencephalogram on a basis of frequency, one can insure against changes due to low sugar by giving the subject glucose before the test, without any fear that changes may accrue from too high blood sugar.

Effect of high blood sugar on the percentage time alpha, intermediate, and beta rhythm

At blood sugar levels above 130 mgm. per 100 cc., as induced by glucose ingestion, there is no change in the electroencephalogram from the rhythms and patterns found at normal blood sugar levels.

DISCUSSION

This quantitative study of the frequencies of cortical potentials has shown that they may be slowed in the normal adult by moderate lowering of the blood sugar level without impairment of consciousness. Since the alpha rhythm has been shown, by Hoagland's (7) experiments with pyrexia, to be directly determined by the local respiration of the cells of the cortex, any deprivation of the oxygen supply to these cells would be expected to slow the rhythm. Dextrose being the principal substrate in cerebral metabolism, hypoglycemia results in a lowering of the oxygen utilization of the brain with consequent slowing of the potentials; in animals, this has been studied by Maddock, Hawkins, and Holmes (8), and in man, by Himwich (9) who have demonstrated that on insulin injection, the progression of clinical symptoms follows the increase in cerebral arterio-venous oxygen difference and this depression of cerebral metabolism is paralleled by a decrease in alpha frequency.

A similar correlation between brain metabolism and brain potentials has been found in cretins in whom the arterial-venous oxygen differences were reduced by thyroid administration (Himwich (10)). Lindsley and Rubenstein (11) and Ross and Schwab (12) have demonstrated a direct relationship in man between the frequency of alpha waves and the total calories per hour.

Further evidence for this theory is provided by the experiments on animals of Gellhorn and Kessler (13). These authors demonstrated that the action of hypoglycemia on the brain potentials can be offset by the inhalation of pure oxygen (provided that the hypoglycemia is not so severe as to induce convulsions). Conversely, the effect of anoxia on brain potentials is greatly aggravated during insulin hypoglycemia.

SUMMARY

Blood sugar levels below 70 mgm., but insufficiently low to impair consciousness, may have the following effects on the occipital potentials of the normal electroencephalogram during quiet breathing:

- Slowing of the dominant frequency.
- Development of activity slower than alpha.

No change has been observed in the following characteristics:

- Percentage time alpha,
- Percentage time beta,
- Percentage time intermediate.

High blood sugar levels, induced by the inges-
tion of glucose (i.e., above 130 mgm. per 100 cc.), do not affect the electroencephalogram.

CONCLUSION

In the assessment of the electroencephalogram for normality, the subject should take some glucose (50 to 100 grams) by mouth, 30 minutes before the test, to ensure a blood sugar level above 70 mgm. per 100 cc. In this way, changes in the electroencephalogram due to low blood sugar will be avoided; raising the blood sugar above 130 mgm. per 100 cc. does not alter the electroencephalogram pattern from that at ordinary blood sugar levels.

For technical assistance in this work the authors are indebted to Miss Margaret Gray and Mrs. Frances Cooperstein.

BIBLIOGRAPHY


CHARACTERISTICS OF THE NORMAL ELECTROENCEPHALOGRAM.

III. THE EFFECT OF VARYING BLOOD SUGAR LEVELS ON THE OCCIPITAL CORTICAL POTENTIALS IN ADULTS DURING HYPERVENTILATION

BY MARY A. B. BRAZIER, JACOB E. FINESINGER, AND ROBERT S. SCHWAB

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(Received for publication August 2, 1943)

Delta activity, i.e., waves of a frequency slower than 5 per second, is not a normal finding in the electroencephalograms of adults when they are fully awake and breathing quietly (1). This type of slow activity is found in some pathological states, but there are certain physiological factors which will cause it to appear in the record of the normal adult. The purpose of the present study was to investigate the effect of hyperventilation upon the occipital cortical potentials in a series of 45 normal subjects (29 males, 16 females), at varying blood sugar levels. The technique for the following experiments has been fully described in a previous paper (2).

If the blood sugar is lowered in normal sub-
jects, delta waves will appear in the third minute of hyperventilation in nearly all cases. An example of one such case (female, age 21) is shown in Figure 1. This figure demonstrates clearly that in this subject, the brain wave pattern is a typical alpha type, stable at fasting blood sugar levels, where it is, in fact, identical with the tracing obtained at the higher level after the ingestion of glucose. Only at the artificially low blood sugar level of 50 mgm. per 100 cc. is the brain wave abnormal with trains of high voltage delta waves. All the tracings in this illustration (Figure 1) were taken during the third minute of hyperventilation.

Great individual variation was found within the group of 45 normals as to the level at which delta waves could be made to appear by hyper-

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This study was aided by a grant from the Harrington Fund.

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**Fig. 1. Delta Activity in a Normal Adult, Produced by Hyperventilation at Low Blood Sugar Levels**

Three tracings from the same individual during hyperventilation at different blood sugar levels.
ventilation. In some (13 per cent of this series), they could not be elicited, even by lowering the blood sugar to 40 mgm. with insulin, whereas in a few (4 per cent), they were present at all levels, even after the ingestion of glucose.

The arbitrary criterion taken was the appearance of delta waves during at least 5 per cent of the third minute of hyperventilation (i.e., for at least 3 seconds). At blood sugar levels higher than 70 mgm. per 100 cc., 31 subjects (69 per cent of the total series) were found to give at least this amount of delta activity.

Of these 31 subjects, 17 (38 per cent of the total series) still gave delta waves when the blood sugar level was raised to 100 mgm.; 5 subjects (11 per cent of the total) gave this amount of delta waves when the blood sugar level was as high as 130 mgm.

The clinical importance of these findings is their demonstration of the fact that, in the interpretation of brain wave records, delta waves in the third minute of hyperventilation cannot be regarded as an abnormal finding, since they occur in 38 per cent of normal adults at non-fasting blood sugar levels (100 mgm. or over). The importance of controlling the blood sugar level has also been stressed by Davis and Wallace (3, 4) as a result of their experiments on controlled hyperventilation of normals.

If the subject is given glucose by mouth before the test, or is examined within one-half hour of a meal in order to ensure a blood sugar of over 130 mgm., the number of normals giving delta waves falls to 11 per cent, but is still appreciable.

The records were then examined to determine whether the delta activity found in the second minute of overbreathing would be a better differentiating criterion. Seventeen (38 per cent) gave delta waves in the second minute for at least 5 per cent of the time when the blood sugar was kept at or above 70 mgm. Of these 17 subjects, 3 (7 per cent of the total series) still gave this amount of delta waves in the second minute when the blood sugar was raised to above 100 mgm. No one gave delta waves in the second minute when the blood sugar was kept at or above 130 mgm.

The same criterion, that is, regarding anything less than 5 per cent delta as negligible, was used in compiling the above figures; they are therefore strictly comparable with the figures for the third minute of overbreathing, and suggest that the differentiating threshold for delta activity should be the second minute of hyperventilation at blood sugar levels of 130 mgm. or over. Delta waves appearing for 5 per cent of the time in these circumstances may be regarded as an abnormal finding.

The percentage time delta in the third minute of hyperventilation at various blood sugar levels

This report has so far dealt with the number of individuals giving delta activity under certain experimental conditions. The next point to be examined is the amount of delta activity induced by the various factors, i.e., the percentage time delta.

One hundred and sixty-one observations on 45 normal subjects were made at different blood sugar levels, and the mean percentage time delta.

The above chart shows the percentage time delta activity in the second minute of hyperventilation (black columns), and in the third minute (white columns), in 45 normal adults. Where more than one observation at the same blood sugar level was made for one individual, the maximum amount of delta at this level is the one recorded. The number at the top of each column is the arithmetical mean for the group. The number of observations from which each column was computed were, reading from left to right: 11, 28, 39, 24, 31, 23, and 5.
in the third minute of hyperventilation was calculated at the various levels. The results are seen in the white columns of Figure 2. These are to be compared with the figures obtained on the same persons in the second minute of overbreathing, which are shown in the blackened portion of the columns in Figure 2. It is clear from this figure that there is a negligible amount of delta activity in the second minute of hyperventilation at non-fasting blood sugar levels.

**Dominant frequency and tendency to delta activity on hyperventilation**

The dominant frequency of the majority of waves in the occipital recordings was determined in this series by the distribution curve method, described in a previous paper (1). It was thought that possibly the slower the original rhythm, the more delta activity could be expected, but no significant difference in the amount of delta activity in the third minute of hyperventilation was found between the group with dominant frequencies slower than 10.5 and those with 10.5 cycles and faster. The figures are:

- 25 normals with dominant frequencies slower than 10.5 mean percentage time delta = 44.9 ± 27.8
- 19 normals with dominant frequencies of 10.5 and faster mean percentage time delta = 36.4 ± 19.7

The standard deviations of these means are so large that the difference between the 2 means is not significant. Thus, in this series, the lack of stability of the electroencephalogram to lowered blood sugar and increased ventilation shows no statistically significant relationship with the basic rhythm of the subject.

**Depth of hyperventilation and its effect on delta activity**

In addition to blood sugar level, there is another factor at work in determining the amount of delta activity which will occur, and this is the depth of hyperventilation. If the blood sugar level is kept constant, the amount of delta activity appearing in the third minute of hyperventilation will be significantly greater if the average respiratory volume during each of the 3 minutes of overbreathing is over 600 cc. per kgm. body weight, than if it is below this figure. Taking, as an example, the blood sugar range 80 to 99 mgm., there were 31 readings on subjects who breathed under 600 cc. per kilogram body weight in each of the 3 minutes of hyperventilation, and 18 readings on subjects who breathed over this amount. The mean percentage time delta in the third minute of hyperventilation for each of the two groups is shown below:

- Under 600 cc. per kgm. body weight per minute 
  Mean percentage time delta 10 per cent
- Over 600 cc. per kgm. body weight per minute
  Mean percentage time delta 20 per cent

These figures reveal that there is an average of twice as much delta activity with the deeper level of breathing when the blood sugar is kept constant.

In 13 subjects, more than one observation was obtained at a blood sugar level between 80 and 99 mgm., but at different depths of hyperventilation. The results are given in Table I as the percentage time delta in the third minute of hyperventilation. The figures show clearly the influence of the greater depth of breathing upon delta activity, for the percentage time delta in the third minute is greater when the mean ventilation for the 3 minutes is increased.

**The effect of age on the stability of the electroencephalogram during hyperventilation**

A study of age relations was made in this series, although the age range was a very narrow one (17 to 38). It revealed that the breakdown into delta activity in the third minute of hyperventilation occurred more readily, i.e., at higher blood sugar levels, in the younger members of the group. Examining once again the different groups which gave delta at widely different blood sugar levels, the following mean age for each group was found: (The results are given in order of decreasing stability)

- 2 subjects gave no delta at any level mean age 30
<table>
<thead>
<tr>
<th>Subject</th>
<th>Under 500 cc.</th>
<th>500 cc.</th>
<th>Between 500 and 600</th>
<th>600 cc.</th>
<th>Between 600 and 700</th>
<th>700 cc. and over</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>18</td>
<td>41</td>
<td>10</td>
<td>16</td>
<td>30</td>
<td>13</td>
</tr>
<tr>
<td>10</td>
<td>16</td>
<td>30</td>
<td>10</td>
<td>2</td>
<td>11</td>
<td>13</td>
</tr>
<tr>
<td>13</td>
<td>6</td>
<td>11</td>
<td>4</td>
<td>18</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>18</td>
<td>1</td>
<td>2</td>
<td>4</td>
<td>30</td>
<td>10</td>
<td>35</td>
</tr>
<tr>
<td>26</td>
<td>24</td>
<td>13</td>
<td>8</td>
<td>73</td>
<td>40</td>
<td>24</td>
</tr>
<tr>
<td>27</td>
<td>10</td>
<td>22</td>
<td>10</td>
<td>84</td>
<td>40</td>
<td>22</td>
</tr>
<tr>
<td>35</td>
<td>30</td>
<td>15</td>
<td>0</td>
<td>61</td>
<td>49</td>
<td>61</td>
</tr>
<tr>
<td>40</td>
<td>43</td>
<td>2</td>
<td>10</td>
<td>80</td>
<td>40</td>
<td>22</td>
</tr>
<tr>
<td>43</td>
<td>35</td>
<td>0</td>
<td>0</td>
<td>84</td>
<td>40</td>
<td>22</td>
</tr>
<tr>
<td>44</td>
<td>7</td>
<td>10</td>
<td>0</td>
<td>31</td>
<td>40</td>
<td>22</td>
</tr>
</tbody>
</table>

14 subjects gave delta only when the blood sugar was below 70 mgm. mean age 25
17 subjects still gave delta when the blood sugar was above 100 mgm. mean age 22

These groups are too small, and the age range too narrow for a statistical presentation of the age effect, but it would appear that the stability of the cortical potentials to hyperventilation increases with increasing age.

**DISCUSSION**

The appearance of high voltage slow waves as a result of voluntary hyperventilation is well known. This has been shown by Lennox and Gibbs (5, 6) to be due to increase in the carbon dioxide tension of the arterial blood reaching the brain, and not to anoxia, secondary to vasocostriction. Berger (7) showed that slow waves can also be elicited by anoxia induced by rebreathing respired air from which the carbon dioxide has been removed; this has been confirmed by Gibbs and Davis (8) in human subjects breathing pure nitrogen, but the anoxemia has to be severe before any significant slowing takes place (Gibbs (9)). Himwich (10) has demonstrated an inverse relationship between oxygen utilization by the brain and delta frequency.

In the present paper, a study has been made of the interplay of the two factors: the influence of decreased carbon dioxide tension of the blood produced by varying depths of ventilation, and the anoxic effect on the cortex of lowering the sugar content of the blood.

**SUMMARY**

1. Delta activity in the third minute of hyperventilation is not diagnostic of abnormality, since it occurs in 38 per cent of normals at non-fasting blood sugar levels. If the blood sugar level be raised above 130 mgm., 11 per cent of normals still give delta activity in the third minute.
2. A better differentiation is given by the second minute of hyperventilation, since only 7 per cent of normals give delta activity at non-fasting blood sugar levels, and none above 130 mgm.
3. The percentage time delta in normals varies inversely with the blood sugar level, in both the second and third minutes of hyperventilation.
4. The tendency of an individual to produce delta activity on hyperventilation is not related to the basic dominant frequency of his resting record.
5. When the blood sugar level is kept constant, the deciding factor in determining the amount of delta activity induced by hyperventilation is the depth of breathing during the 3-minute period.
6. There is some evidence that at lower age levels in the adult, the electroencephalogram is
less stable to change in blood sugar and ventilation level.

For technical assistance in this work, the authors are indebted to Miss Margaret Gray and Mrs. Frances Cooperstein.

BIBLIOGRAPHY
The incidence of psychoneuroses in the armed services in the present war is so great as to make it one of the major problems brought to the attention of the psychiatrist. These disturbances are found under war conditions among the civilian population, selectees, draftees, and soldiers and sailors on active duty. The variation in the intensity of the psychoneurotic symptoms and of maladjusted behavior has already resulted in the introduction of such new terms as "battle reaction" and "combat fatigue." It is possible in most instances to differentiate between patients whose symptoms are precipitated by unusual conditions, such as battle or shipwreck, in which the patient is exposed to unusually powerful stimuli occurring in dramatic sequence and those who develop symptoms without exposure to combat. The former group is usually referred to as "traumatic" or "combat" neuroses. It is this group of patients that is the major concern of this paper.

The purpose of this study was to ascertain whether patients with persistent psychoneurotic symptoms which were precipitated in combat, had a past history of similar or other psychoneurotic complaints. In addition, an attempt was made to study various physiologic functions under laboratory conditions of rest and stimulus, in order to compare the results with those obtained from psychoneurotic patients who had not been exposed to combat experience, and from a series of normal control subjects.

In a previous survey undertaken for neuropsychiatric data on the survivors of shipwreck, two groups of individuals were studied. The first was a group of 25 psychoneurotic patients who were survivors of shipwreck or sinking by enemy action, and the second was a control group of 41 survivors from shipwreck or sinking who had no neuropsychiatric symptoms. These studies included an investigation of the past history and an appraisal of the current symptoms in an interview lasting one-half hour.

It was found that 72 percent of the psychoneurotic patients gave a history of having had psychoneurotic symptoms in civil life prior to entering the Navy. In contrast to this, only 11 percent of the control group of 41 survivors, when studied by the same method gave a history
of psychoneurotic symptoms prior to enlistment. Of the patient group, 23 (91 percent) were troubled with disturbing dreams and difficulty in sleeping, and 18 (72 percent) had poor appetite and weight loss. In the control group only 2 (5 percent) were troubled with disturbing dreams or complained of poor appetite and showed loss of weight.

It was interesting to note further that 8 of the psychoneurotic group (32 percent) had suffered physical injury as against 23 of the control subjects (56 percent).

In order to check and evaluate the results of this survey another study was made of 26 patients with psychoneuroses precipitated by combat conditions. These were patients whose symptoms did not respond to the usual therapeutic measures available aboard ship or in the combat zone but were sufficiently serious and incapacitating to necessitate transfer to a base hospital in this country. The symptoms had been present in most cases for over 3 months and in some cases for as long as 1 year after the initial combat experience. At the time of the examination most of these patients were not suffering from other illness or injury and in most instances the physical and neurologic examinations were within normal limits.

As a control series for these patients with combat or traumatic neuroses, a second group was selected of 23 subjects who were not ostensibly suffering from any neuropsychiatric complaints or disorders and who had not come to the attention of the medical staff. These men were of the same age distribution as those with combat neuroses and had been through similar combat experiences. These subjects are referred to in this paper as the control series. In addition, a third group of 25 psychoneurotic subjects was studied who had not been exposed to combat, and whose symptoms developed while in military service at a shore station within the limits of the continental United States. This group is referred to as noncombat neuroses.

All three series of subjects were selected at random and were studied in essentially the same way. The nature of the procedure was described to the man and no one was examined against his will. It was explained that this clinical study would not appear in the health record and that they, therefore, need have no apprehension about its influence on any medical decisions as far as the Navy was concerned. In addition an electroencephalographic examination was made and the men were all subjected to an auditory stimulus, during which records of respiration, heart rate, and muscle tension were made. The data obtained from these various measurements are presented as follows.

INTERVIEW.

The interview was conducted by a civilian psychiatrist and was modeled after a "controlled" interview which had been used in a pre-
vious study of 150 normal college students now training in the Navy. The interview which lasted 30 to 45 minutes was held in a closed room and arranged so that it could be taken down in its entirety by a stenographer in an adjoining room without the subject’s being aware of the procedure. An attempt was made to keep the interview in the form of a free conversation, yet essentially the same topics were discussed with all of the subjects. The following topics were dealt with:

1. The present illness, with special emphasis on a description of the symptoms.
2. School and job history, with emphasis on psychoneurotic symptoms and social adjustment.
3. A brief family history, with emphasis on psychoneurotic symptoms and medical illnesses present in the other members of the family, and on the subject’s adjustment to his family.
4. Early childhood history with emphasis on the presence of psychoneurotic symptoms and neurotic traits.

The stenographic records of the interviews were studied and the subjects were divided into four groups on the basis of the following criteria:

1. Severe psychoneurosis. These were individuals who complained of definite psychoneurotic symptoms which had been present for long periods of time and which were severe enough to be disabling. These patients had a history of many neurotic traits in childhood, and a diagnosis of a specific psychoneurosis could be made on the basis of symptoms present before the patient had enlisted.
2. Moderate psychoneurosis. These subjects complained of psychoneurotic symptoms present occasionally for only short periods of time, and which on the whole were not disabling. In this group, however, a diagnosis of a specific psychoneurosis could be made on the basis of symptoms present before the subject had enlisted.
3. Minimal psychoneurosis. In these subjects the history revealed psychoneurotic symptoms which were only very occasionally present, and not in any way disabling or severe. There was no history of neurotic traits in childhood. On the basis of the history, as obtained during the interview, it was not possible to make a diagnosis of a typical psychoneurotic syndrome.
4. No psychoneurosis. In these patients there was no history of psychoneurotic symptoms and no neurotic traits in childhood were reported.

RESULTS.

The incidence of symptoms reported in the group of patients with combat neurosis is presented in figure 1. The striking finding was the large percentage of gastro-intestinal symptoms (85 percent). The patients described feelings of shakiness, jitteriness of the stom-
ach, feelings of turning and jumping inside. The symptoms peculiar to this group were the severe reaction to loud or even ordinary noises, and the presence of repetitive anxiety dreams, depicting in most cases some aspect of the combat experience. The other symptoms of headache, trembling hands, palpitation or precordial pain found in most cases were typical of anxiety neurosis. The most common diagnosis was anxiety neurosis, which occurred in approximately 80 percent. Most of the other cases were diagnosed as hysteria.

**Symptoms of Traumatic Neurosis (26 Cases)**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>80%</td>
</tr>
<tr>
<td>Trembling Hands</td>
<td></td>
</tr>
<tr>
<td>Startle Reaction</td>
<td></td>
</tr>
<tr>
<td>&quot;Nervous&quot; Stomach</td>
<td></td>
</tr>
<tr>
<td>Upsetting Dreams</td>
<td></td>
</tr>
<tr>
<td>Palpitation</td>
<td></td>
</tr>
<tr>
<td>Disturbed Sleep</td>
<td></td>
</tr>
<tr>
<td>Breathing Difficulty</td>
<td></td>
</tr>
<tr>
<td>Precordial or Chest Pain</td>
<td></td>
</tr>
</tbody>
</table>

Figure 1.

From the history obtained during the interview, 80 percent of the combat neuroses group could be classified as having severe or moderate psychoneurosis and a further 12 percent had minimal symptoms. Only 8 percent were diagnosed as having no psychoneurosis. Of the 10 patients with noncombat neuroses, 9 had a past history of either severe, moderate or minimal symptoms. The same incidence of psychoneurotic symptoms was found in an additional group of 15 noncombat neuroses by study of their clinical histories. A review of the histories of 25 unselected civilian patients with psychoneuroses studied in the same laboratory, showed that all of these patients had psychoneurotic symptoms previous to the hospital admission (fig. 2).

Of the control subjects exposed to combat without apparent psychoneurotic symptoms, only 17 percent gave a previous history of psychoneurotic symptoms. This compares rather strikingly with the findings in a series of 150 college normals studied previously. In this group a past history of symptoms was elicited in 15 percent of the subjects (fig. 2).
It is of interest to compare these data with the findings in the naval health records of these patients and in their examinations by naval personnel. A study of the health records of the 26 patients with combat neurosis revealed that a statement describing the existence of psychoneurotic symptoms prior to admission to a naval hospital was found in only four of these records (fig. 3). Only three of these subjects were diagnosed by psychiatrists at those stations as having pre-existing psychoneurosis, i.e., before admission to the naval hospital.
In the routine neuropsychiatric investigation during a stay of approximately 2 weeks before diagnosis and disposal, it was found that 21 patients or 80 percent showed some history of psychoneurotic symptoms prior to enlistment. Of this group 65 percent had moderate or severe symptoms and 15 percent mild or minimal. A comparison of the percentage of subjects with previous neurotic symptoms, as described in the health record prior to the base hospital admission, in the routine hospital examination, and in the specially controlled interviews is shown in figure 3.

The principal groups of symptoms which brought these patients to the hospital are shown in figure 4. A number of them had more than one complaint, but their most obvious difficulty was the inability to perform their routine duties.

### Principal Symptom Groups Which Brought Patients to Hospital

<table>
<thead>
<tr>
<th>Symptom Group</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inability to work</td>
<td>26</td>
</tr>
<tr>
<td>Irritability with sensitivity to noise</td>
<td></td>
</tr>
<tr>
<td>Sleep disturbances with nightmares</td>
<td></td>
</tr>
<tr>
<td>Stomach complaints—Anorexia—Weight loss</td>
<td></td>
</tr>
<tr>
<td>Headache—Dizzy spells</td>
<td></td>
</tr>
</tbody>
</table>

Laboratory Findings.

**Electroencephalogram.**—A standard recording was made from 6 scalp electrodes, one-half hour after the subject had ingested 100 cc. of 50-percent glucose in water to ensure a normal blood sugar level. The necessity for this procedure in the control conditions for recording EEG's has been described elsewhere.

The tracings from all these subjects were, on gross inspection, apparently normal and they were therefore subjected to a detailed method of analysis which has been developed in this laboratory for the grading of normal electroencephalograms. For this purpose, the recording of the bipolar occipital potentials during normal breathing is accurately measured for frequencies of component waves and also for voltage. From such measurements many characteristics of the electroencephalogram can be analyzed and studied.
In the present work the characteristic receiving special study was the distribution of dominant frequencies. By dominant frequency is meant the frequency in cycles per second of the majority of the waves present. It has been found in previous research on civilian psychoneuroses that the distribution of dominant frequencies differed from that of normal controls (which centers around 10 cycles), in that the most prevalent dominant frequency was at 9 cycles with subsidiary peaks in the faster frequencies at 11 and 12.5 cycles.

The EEG's of the group with combat neuroses were therefore compared with those of 31 civilian psychoneurotic patients and 115 college students considered normal. The results are shown in figure 5.

![Distribution of the Dominant Alpha Frequency in 3 Groups](image)

It will be seen that the distribution curve for the group of combat neuroses is very close to that of the college student normals excepting for the fact that the two peaks in the fast frequency range found in the civilian psychoneuroses are again present in this series. The interpretation of these findings is a matter for future investigation.

**Auditory stimulus test.**—The purpose of this test was to record the reaction of the subject to a disturbing auditory stimulus. This consisted of an extremely high-pitched whistle of mixed frequencies and of great intensity, blown for a period of 3 minutes. During this stimulus period, for 3 minutes preceding it and for a 3-minute recovery period following it, recordings were made of the heart rate, muscle tension and respiration.

The heart rate was recorded from standard electrocardiographic leads by an ink-written oscillograph; the same instrument recorded simultaneously the electromyogram from surface electrodes attached to
the flexor carpi muscle of the subject. Thus any gripping movement or tensing of the hand resulted in an increase of potentials from the muscle. These potentials were not only recorded on the electromyogram but were also led through an integrator working on the principle of a condenser which discharged every time a certain amount of electricity collected. Each discharge of the condenser was automatically recorded on the same tracing as the electromyogram, and this record gave a measurement of the tension of the muscle. The ventilation was recorded by having the subject breathe into a Benedict-Roth type of metabolism apparatus equipped with a ventilometer. The ventilation was measured directly from the breathing record and corrected for surface area, which was determined by means of the Boothby-Sandiford nomograph.

In figure 6 a summary is given of the reactions of the three groups of subjects to this auditory stimulus. It is very striking that in all 3 types of response, i.e., heart rate, muscle tension and ventilation, the control group was the most stable and reacted least to the sound of the whistle. The greatest reaction to the stimulus was observed in the patients with noncombat neuroses. This is brought out most clearly in the muscle tension response.

DISCUSSION

This report indicates that a past history of psychoneurotic symptoms was found in approximately 90 percent of naval personnel who were diagnosed as having a persistent combat neurosis. In the control
series, a history of psychoneurotic symptoms was found in less than 20 percent of the subjects. As a rule the symptoms present in the control group prior to enlistment were less severe and in most cases less incapacitating. It is to be noted that of the patients with combat neurosis about 25 percent have been in service for over 2 years. This fact would indicate that some patients who in combat develop severe psychoneurotic symptoms may, in the absence of combat conditions, adjust sufficiently well to do their duties with a reasonable degree of efficiency. Of men new to the service, in spite of the history of neurotic symptoms before enlistment, those with combat neurosis had, for the most part, been able to get along in civilian life without hospitalization or treatment for their symptoms.

It is difficult at present to determine exactly the degree of psychoneurotic symptoms which should keep a man out of the service. This study indicates that, were all individuals in whom was elicited a history of psychoneurotic symptoms to be excluded from the armed forces, we would be rejecting almost 20 percent of men who were able to carry out their duties under combat conditions without coming to the attention of the naval neuropsychiatrists. On the other hand, we would also be excluding over 80 percent of the individuals who subsequently developed combat neurosis. From the statistical point of view it would seem that a greater efficiency in selection would be achieved by excluding all men in whom a past history of psychoneurosis exists. This would be especially wise if there were an abundance of manpower.

Patients who develop symptoms without actual exposure to combat situations are more vulnerable than those who develop combat neurosis. It would seem that in these patients the psychoneurotic reaction is elicited by stimuli of much smaller intensity than is the case in the patients with combat neurosis. The auditory stimulus test corroborates this impression by showing that, when exposed to the stimulus, these patients (noncombat neurosis had a greater reaction in respect to measurements of muscle tension, ventilation and heart rate than did the patients with combat neurosis.

Our data revealed that almost every subject exposed to combat conditions reacts to the overwhelming stimuli with subjective feelings of fear and with palpitation, shortness of breath, chest pain, gastric symptoms and tremors. In many, the reactions are of short duration and rarely recur when the individual is removed from the stimuli. In other individuals the reaction persists for a prolonged time. In some patients the reaction, after a slow period of extinction, readily returns in relation to combat stimuli or associated stimuli. Symptoms which last 4 to 5 weeks after exposure to combat conditions, and which are sufficiently aggravating for admission to a base hospital are
found in patients usually giving a past history of psychoneurotic symptoms. These symptoms can be readily elicited when neuro-psychiatric studies can be made by qualified personnel.

**SUMMARY**

Three groups of naval personnel were examined in this study; 26 cases of combat neurosis, 25 cases of neurosis in individuals not exposed to combat, and 23 control cases exposed to combat without development of neurosis.

This study revealed the following results:

1. A past history of psychoneurotic symptoms was found in approximately 90 percent of both groups with neurosis, but in only 17 percent of the control series.

2. The most striking symptoms in the combat neurosis group were gastro-intestinal disturbances (85%), severe reaction to noise, presence of disturbing nightmares and headaches. The reason for their admission to the hospital on the other hand, in over 90 percent of the cases, was their inability to do their work.

3. The most common diagnosis was anxiety neurosis which accounted for 80 percent of the combat neurosis group.

4. The electroencephalograms of the combat neurosis group were seen to have some of the characteristics which, in another study, have been found to differentiate the EEG's of patients with psychoneuroses from those of normals.

5. An auditory stimulus was found to have more effect on the ventilation, heart rate and, in particular, on the muscle tension, of the group of noncombat neuroses than on those with combat neuroses, the control group being least affected by the stimulus.

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**SULFONAMIDES IN TRAUMATIC DENTISTRY**

Local application of the sulfonamides proved to be an effective prophylactic measure in those areas in the mouth where the spread of infection is accelerated by fossae, lymph channels, glandular tissue and veins about the face that are lacking in valves and the walls of which are somewhat rigid.

Pain, trismus, and edema were less prevalent, or present in a milder form, in a treated than in a control series of patients.

A CONTRAST BETWEEN THE ELECTROENCEPHALOGRAMS OF 100 PSYCHONEUROTIC PATIENTS AND THOSE OF 500 NORMAL ADULTS 1

MARY A. B. BRAZIER, PH. D., JACOB E. FINESINGER, M. D., AND STANLEY COBB, M. D.

Recent work in electroencephalography has demonstrated that a direct relationship exists between cortical potentials and the oxidative processes in the cortical cells (1, 2, 3, 4). These findings bring new emphasis to studies which are concerned with frequency of the oscillations seen in the electroencephalogram. Experience in previous work (5, 6) has shown that significant differences in EEG tracings can be revealed by accurate measurement when they escape assessment by the naked eye. The importance of measurement of the frequencies has been recognized by several workers (7, 8, 9) and more recently an apparatus has been devised for the mechanical registration of frequencies in the EEG (10). Such an approach has been made in the present study, which is concerned with the quantitative evaluation of EEG tracings in a series of 100 psychoneurotic patients. The results obtained from the various measurements of the EEG are compared with those of a series of 500 normal adults, whose EEGs were obtained under similar conditions and evaluated by the same method.

CLINICAL MATERIAL

The series consisted of 100 psychoneurotic patients, 57 females and 43 males, most of whom were studied on the psychiatric wards and the psychiatric clinic of the Massachusetts General Hospital. A small number were males rejected from the armed forces because of the diagnosis of psychoneurosis. The age range was from 17 to 58. The diagnoses were made primarily on the basis of symptoms elicited by examination. All of the patients had complete medical, neurological and routine laboratory examinations. Only cases in whom these examinations were within normal limits were included in the series. Patients with other illnesses in addition to psychoneurosis or with a history of head injury or unconsciousness were rejected.

The patients were classified as follows:

1. Anxiety Neurosis.—In this group were 31 patients (16 males and 15 females) whose ages ranged from 20 to 58. These patients described as their major complaints feelings of anxiety or tension, localized or generalized feelings of shakiness, palpitation, shortness of breath and headache. In some cases the symptoms occurred in acute episodes, in others they lasted from hours, to weeks and years. Most of the patients described difficulties in sleeping, and in their work and sex lives.

2. Hysteria.—This group consisted of 23 patients (5 males and 18 females) whose ages ranged from 17 to 53 years. These patients described as their major symptoms disturbances in their motor activity, such as paralyses or weakness of the extremities. Fainting, vomiting, dizziness, aphony, abdominal pain, blindness, convulsions, trances and hyperventilation tetany were among the other symptoms. Several patients had acute episodes of amnesia, and in many of them disturbances in cutaneous sensation could be demonstrated on examination. Most of this group complained of occasional episodes of anxiety.

3. Reactive Depression.—This group consisted of 27 patients (11 males and 16 females) whose ages ranged from 17 to 58. These patients presented as their major complaint brief or longer episodes of depression. The mood changes in most cases were not profound, and were transitory, lasting from days to months. As a rule the mood changes were accompanied by occasional cry-
ELECTROENCEPHALOGRAMS IN PSYCHONEUROSIS

ing, moderate disturbance in sleep, and occasional lack of appetite. Several expressed suicidal ideas. Many of these patients complained of other psychoneurotic symptoms found in anxiety neuroses and in hysteria; however, the predominant symptomatology was that of depression. None of these patients had ever reported a typical manic episode characteristic of manic-depressive psychosis. Patients in whom the diagnosis of manic-depressive depression could be made were not included in the series.

4. Mixed Psychoneurosis.—This was a series of 19 patients (11 males and 8 females) whose ages ranged from 15 to 45 years. It was impossible to decide in which of the three preceding groups these patients should be classified. The symptoms consisted of anxiety attacks, obsessive ideas, depressed states, and occasionally complaints characteristic of hysteria were elicited. In these patients there was a marked overlapping of symptoms usually associated with various psychoneurotic diagnoses. These patients represent the most heterogeneous group studied.

METHOD OF ANALYZING AND EVALUATING THE ELECTROENCEPHALOGRAM

The method for recording EEGs is well known, and has been previously described (5). The standard method has been used throughout, with, however, one added control condition: this is a control of the blood sugar level. This is done because another study (6) revealed that even during normal breathing accurate measurement brought out changes in the EEG due to fasting blood sugar levels. The subjects for this study were therefore given glucose by mouth half an hour before the test as one of the standard conditions, and they breathed at their normal rate and depth throughout.

In this particular study the report will be based on the analysis of the recording from the bipolar occipital leads, since experience has shown that this lead is the one least interfered with by muscle movement, and it has also been found to be the most consistent from test to test in the same person. One should observe here that analysis of leads from other parts of the head would yield a different set of data, but for the purposes of the present paper only the findings from the bipolar occipital leads will be reported.

The analysis is made on a two-minute tracing which at the standard speed of recording measures 3600 millimeters. The record is first inspected for the presence of artifacts. Any portion showing artifacts due to eye-blinks or muscle movements is omitted from the sample for analysis. The remainder of the record is measured for total length of time, and this figure is used as the total on which all percentages are calculated. First of all, the number of millimeters covered by waves of beta frequencies (i.e., 18.0 cycles per second or faster) is measured; no attempt is made to differentiate between the various beta frequencies since no great degree of accuracy can be achieved in this range. For frequencies below this range, however, accurate measurements are made by means of a transparent grating marked off in intervals corresponding to the various cycles per second and thus the number of millimeters covered by waves of each frequency can be totalled, and the results may be expressed as percentages of the whole period measured. When these figures have been compiled they can be presented either in tabular or in diagrammatic form. On the whole the diagram is to be preferred because it gives an immediate representation of the most characteristic features of the EEG.

The distribution curve of all the frequencies slower than 18 cycles per second is charted for one normal subject in Fig. 1. The advantages of this treatment of the data are many: one can see immediately which frequency is present in the greatest amount; it is the one at the mode of the curve. This we define as the dominant frequency of the record (in this case it occurs at 10.0 cycles). From such a curve one can also assess the degree of regularity of the EEG. For example, Fig. 1 shows a regular rhythm composed for the most part of its dominant frequency with only small percentages of other frequencies. A less regular record would have many more frequencies present, with no single frequency dominating the picture, and the result would be a curve with no marked peak, but with many low peaks scat-
tered throughout this frequency range. Additional information available from such a curve is the ratio of alpha to beta activity in the total record. The sum of the percentages of these frequencies shown in such a chart will more nearly equal 100 in a record which is predominantly alpha, than in a predominantly beta type of record where they will total a low percentage in this range.

**Results**

In a previous study (5) frequency distribution curves were made by the method described above for each of 500 normal adults. One of the characteristics examined in detail was the dominant frequency. It was found that over 25 percent of this normal series had dominant frequencies at 10.0 cycles per second, with a normal distribution curve around this mode.

If, however, one makes the same plot for the group of 100 psychoneurotic patients, as has been done in Fig. 2, it is immediately clear that they do not give a normal distribution, but have a weighting on the slow side at 9.0 cycles, and another in the faster frequencies; in fact it suggests a bimodal curve such as one finds in a heterogeneous population. The data of these curves have been analyzed by the method of the separation from the mean, and have been found to be significantly different by the criterion of \( X^2 \) and by the critical ratio. This finding constitutes the first statistically significant difference between the normal group and the group of psychoneurotic patients. An attempt was made to determine whether any one symptom group was responsible for the slow peak on the one hand or for the faster frequencies on the other. When the series of 100 patients was broken down into sub-groups determined by their clinical diagnoses, the one clinical group which stood out in respect to the dominant frequency was that of the anxiety neuroses (Fig. 3). From Fig. 3 it is clear that in the cases of anxiety neurosis the dominant frequencies are in the faster range. They, in fact, have a mean value of 11.2 as against 10.6 for the normal controls, and the curve has a normal distribution around its mode.

Another characteristic of the EEG which has yielded interesting results in this series is the percent time beta activity. This char-
characteristic also showed a statistically significant difference between the two groups.

**TABLE I**

<table>
<thead>
<tr>
<th>PERCENT TIME BETA ACTIVITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>500 normal controls .........</td>
</tr>
<tr>
<td>Standard deviation = 13.7</td>
</tr>
<tr>
<td>100 psychoneurotic patients</td>
</tr>
<tr>
<td>Standard deviation = 19.2</td>
</tr>
</tbody>
</table>

Critical ratio = 6.54

The critical ratio of the difference is 6.54, which represents beyond doubt a significant difference. Broken down into sub-groups we find that the reactive depressions constitute the group of patients most responsible for this finding. The critical ratio for the difference between the group of reactive depressions and the normals is 4.56, which is again significant.

**TABLE II**

<table>
<thead>
<tr>
<th>PERCENT TIME BETA ACTIVITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>500 Normal controls .........</td>
</tr>
<tr>
<td>Standard deviation = 13.7</td>
</tr>
<tr>
<td>27 Reactive depressions ......</td>
</tr>
<tr>
<td>Standard deviation = 19.2</td>
</tr>
</tbody>
</table>

Critical ratio = 4.56

One might attempt to explain this finding on the basis that the patients are more jittery and less relaxed during the test than are the normals. We do not believe that this can explain the difference; in most cases in the psychoneurotic series multiple tests were made, the personnel of the laboratory became known to the patient, and confidence was established.

Another point of interest lies in an additional finding concerned with the beta activity. We have, in the past 2 1/2 years, had the opportunity of examining the EEGs of 450 pilots. Of these 450, 140 were trainees in the first stages of flight training. At the present date, 2 1/2 years later, we have information about the eventual history of these trainees and know which made the grade as pilots and which failed during the training course. Figure 4 shows a trend in the percent time beta activity in a comparison of successful pilots, unsuccessful pilots and psychoneurotic patients.

**PER CENT TIME BETA ACTIVITY**

<table>
<thead>
<tr>
<th>PER CENT</th>
<th>MEAN VALUES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta</td>
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<td>2</td>
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</table>

**DIFERENCE BETWEEN GROUPS 1 AND 3 GIVES A SIGNIFICANT CRITICAL RATIO**

Fig. 4.—Trend of incidence of beta activity in a comparison of successful pilots, unsuccessful pilots and psychoneurotic patients.

A third characteristic of interest is the percent time alpha activity. The examination of the percent time alpha activity also showed a difference between the 500 normal controls and the psychoneurotic patients, although the critical ratio (3.38) is not so significant.
TABLE III

<table>
<thead>
<tr>
<th>PERCENT TIME ALPHA ACTIVITY</th>
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</thead>
<tbody>
<tr>
<td>500 Normal controls ..........</td>
</tr>
<tr>
<td>Standard deviation = 18.8</td>
</tr>
<tr>
<td>100 Psychoneurotic patients ...</td>
</tr>
<tr>
<td>Standard deviation = 20.8</td>
</tr>
<tr>
<td>Critical ratio = 3.38</td>
</tr>
</tbody>
</table>

No significant differences in voltages were found between the two groups. No correlation could be shown between any of the electroencephalographic findings reported here and the basal metabolic rate of the patients; nor was sedation allowed to play a part, since this was omitted as a standard condition for the tests.

**Discussion**

When one collects data on large groups of patients such as we have done here for the psychoneuroses, the fact emerges that although the values for each patient fall within the normal range, yet the distribution of the data is not that of the normal population. In the present study the differences between the patients and the controls have been shown to be statistically significant, yet the rhythms are all within the normal range, with no abnormal wave formation such as delta activity, or wave and spike patterns. When dealing with data the distributions of which overlap in the two groups, differences can be established only by using the data for each group as a whole, rather than the individual findings.

The most striking finding in this study is the bimodal distribution of dominant frequencies in the psychoneurotic group, thus differentiating it from a normal population. We have presented evidence indicating that the weighting factor in the faster frequencies is due to the faster dominant frequencies found in the anxiety neuroses. The reason for the peak in the slow frequencies is not so clear, since the patients whose dominant frequencies fall within the slower range were distributed through all four diagnostic subgroups.

Another approach to the interpretation of these data is through the understanding of the underlying physiological mechanisms responsible for the character of the oscillations in the cortical potentials. Since the initial work of Hoagland(1, 2) on the pacemakers of the cerebral cortex, several other workers have confirmed the rôle of local respiratory processes in the cells in determining the frequencies of electrical discharges from the cortex. Of the various agents used by these workers to influence the condition of oxygen supply to the cell, pyrexia(11, 12), thyroid administration(12, 13, 14, 15), and excess oxygen in the inspired air(8) increase the rate of oscillations, whereas anoxia(16, 17, 18, 19, 20), hypoglycemia(21), and hypothyroidism(22) decrease the rate.

In the psychoneuroses one wonders about the rôle of anoxia of the brain in producing the symptoms and signs found in these patients. Recent work indicates in certain types of patients that there is a disturbance in the oxygen uptake mechanism, as manifested by increased ventilation after effort (23), and after ideational stimuli(24) without the expected increase in oxygen consumption. It may well be that some degree of anoxia affecting the local respiration and subsequent carbon dioxide production of the cells of the cortex may be the factor responsible for the high incidence of slow frequencies found in some psychoneurotic patients.

Another mechanism which is receiving increasing attention in the psychoneuroses is the rôle of acetyl choline and other cholinergic and adrenergic substances. These substances may also affect the rate of the oscillation of the brain potentials. We have therefore initiated an investigation on the effects of adrenalin and mecholyl on the EEG. Few data are as yet available, but there is some evidence that adrenalin may cause an increase in the faster frequencies. The explanation of the increase in beta activity found in the psychoneurotic patients may be due to these factors.

**Summary**

1. The EEG of the psychoneurotic patient shows no gross abnormalities of wave pattern and in general falls within the normal range.

2. Nevertheless, a study of the findings on a group of 100 psychoneurotic patients...
reveals that their electroencephalographic data lie only just within the range for normals and that the distribution of their data is statistically different from that of a group of 500 normal adults.

3. The statistically significant differences between the total psychoneurotic group and the normal group were in the following characteristics of the EEG.

(a) The distribution curve of dominant frequencies in the psychoneurotic group was not that of a normal population.

(b) The incidence of beta activity (18.0 cycles and over) was higher in the psychoneurotic group than in the normals.

4. The clinical subgroup diagnosed as anxiety neurosis had a normal distribution curve for dominant frequencies but in a range faster than normal (mean 11.2 for anxiety neurosis as against 10.6 for normals).

5. A discussion is presented of the possible physiological mechanism which may be responsible for these findings.

BIBLIOGRAPHY


ACTION OF BARBITURATES ON THE CEREBRAL CORTEX
ELECTROENCEPHALOGRAPHIC STUDIES

MARY A. B. BRAZIER, PH.D., AND JACOB E. FINESINGER, M.D.

The work of Quastel and associates has shown that narcotics even in low concentrations inhibit specifically the oxidation in vitro by brain cells of d-glucose, lactic acid and pyruvic acid.

This inhibitory action takes place, not by preventing the access of oxygen to brain cells nor by interfering with the activation of oxygen by brain catalysts, but by impairing the hydrogen-liberating mechanisms (dehydrogenase activity) which normally result in activation of lactic or pyruvic acid.

Narcotics inhibit this dehydrogenase activity, presumably by forming surface films or adsorption compounds which prevent the access of hydrogen donators to their activating enzymes. Thus, the effect of the narcotic is to diminish the ability of the brain cells to oxidize lactic or pyruvic acid or d-glucose. The access of oxygen to the cell is quite unimpaired, but the diminished oxidizing ability of the cells results in a lowering of the amount of energy available for these cells to accomplish their functional activities. This depression of the normal functional activity of the cells in question results in, or is, "narcosis."

The chain of oxidative processes in brain cells may be represented in outline by the following simplification: At the beginning of the chain the principal substrate is d-glucose, which, through a long chain of intermediary changes, is finally oxidized to carbon dioxide and water, with liberation of large amounts of energy. One of the chief intermediary stages in the first part of the breakdown of d-glucose is the oxidation of lactic acid to pyruvic acid. Meyerhof showed the dependence of this stage on the presence of a coenzyme which acts as a specific carrier linking lactic dehydrogenase with lactic acid in such a way that the dehydrogenase can remove hydrogen from the lactic acid, with the production of pyruvic acid. The dehydrogenase which activates lactic acid as a hydrogen donator is highly specific and is present in greater quantities in brain than in muscle.

It is this stage of dehydrogenase activity which is inhibited by narcotics of the barbiturate type. To repeat, these narcotics do not interfere with the catalytic activation of oxygen, or with the access of oxygen to the brain cells, but inhibit the activity of the dehydrogenase stages of pyruvic and lactic acid catabolism.

The mechanism of this dehydrogenase activity may well be, as Quastel and Wooldridge suggested, a polarization of the molecule of the substrate by an electric field at the cell surface to which the molecule is attached. If the polarization is sufficient, the molecule will receive its critical energy of activation and will then be able to function as a hydrogen donator.

This chain of events in the cell respiration of brain tissue has been worked out from data gained from in vitro experiments with minced fresh brain and with brain slices, variations of the Barcroft and Warburg technics being used for the most part. To extend these studies to the respiration of brain cells in vivo necessitates some other technic. Electroencephalography may well furnish pertinent data in this field.

The work of Hoagland demonstrated clearly the influence of changes in brain cell respiration on the frequency rates of cortical potentials. It is probable that cortical cells build up potential gradients in the process of their respiratory metabolism, and, as Hadidian and Hoagland stated:

These may be of the nature of diffusion potentials across cell membranes which possess definite electrical impedance and which discharge when the potentials reach a critical value. In such a system the discharge frequency depends on the speed with which the metabolic factor can load the capacities of the cell walls to their critical discharge potentials. The absolute frequency would thus depend on the rate of cellular respiration and on the electrical impedance of the cell walls.

The purpose of the present study was to determine whether the electroencephalogram of the intact human being would give any evidence with regard to impairment by barbiturates of cortical cell respiration or of the impedance characteristics of the cell membranes.

**METHOD**

Electroencephalograms were recorded by the standard method, which is too well known to need repetition here. Standard placement of six scalp electrodes was used, one electrode being placed on each frontal, parietal and occipital region. Dextrose (d-glucose) (50 Gm.) was given by mouth to every subject to insure adequate amounts of initial substrate.

A base line electroencephalogram was made with a Grass six channel ink-writing oscillograph (the heart rate being recorded on one channel), and the recording was continued through intravenous injection of the barbiturate and for approximately one hour after its administration.

Three drugs were used: sodium amytal, sodium pentothal and sodium pentobarbitol, the doses of sodium amytal varying from 0.25 to 0.65 Gm. and the doses of sodium pentothal from 0.125 to 0.5 Gm. The dose of sodium pentobarbitol used was 0.3 Gm.

**RESULTS**

The initial effect of slow intravenous injection of any of the three drugs was completely consistent and dramatic. It was characterized by the appearance of high voltage fast activity, which is defined here as a frequency of 21 to 32 cycles per second, and of voltages certainly above 25 microvolts, and frequently reaching 100 microvolts. Fast frequencies resulting from injection of sodium amytal were described by Cohn and Katzenelbogen and by Rubin, Malamud and Hope. Electrical activity of the kind just described was observed in every subject to whom these figures are the extremes of the range of frequencies observed. The most commonly occurring rate was 25 to 26 cycles per second.


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Fig. 1.—Effect of sodium amytal on the electroencephalogram.
these drugs were given. Sodium amytal was given to 16 patients (twenty experiments); sodium pentothal to 22 patients (50 experiments), and sodium pentobarbital to 2 patients (two experiments). The subjects were patients from the psychiatric wards of the Massachusetts General Hospital with psychoneuroses of various kinds. There were 18 males and 16 females, with an age range of from 14 to 59 years.

In figure 1 is shown the type of electrical activity characteristic of the effect of slow administration of small doses of these drugs. In the upper record are bipolar tracings from the frontal, parietal and occipital regions respectively taken before administration of sodium amytal. In the lower record, taken four minutes after the beginning of the injection, the same leads are represented; here high voltage fast activity is present in every lead. The procedure employed in slow administration of the drug was to take two minutes in giving the first grain (0.065 Gm.) of the drug and from that point to administer 1 grain (0.065 Gm.) per minute. Thus, this tracing of the action of the drug four minutes after the beginning of the injection represents the effect of the injection of 3 grains (0.195 Gm.) of sodium amytal.

When a larger dose of sodium amytal was given, a second effect was seen in the electroencephalogram. This consisted of slowing of the frequencies until delta waves of 3 to 4 per second developed (see fig. 2). These were not waves characteristic of sleep and were present while the patient was still responsive.

Sodium pentothal when injected intravenously produced a similar effect. When the dose was small high voltage fast activity dominated the record, but when the dose was increased delta waves appeared.

![Fig. 2.—Effect of intravenous injection of sodium amytal on the electroencephalogram.](image)

It thus appears that barbiturates may have two distinct effects on the electroencephalogram: one, the production of high voltage fast activity by low concentrations of the drug, and the other, slowing of the frequencies when the concentration is increased. This concept of a dual effect receives support from the observation that swift administration of sodium pentothal, as in the induction of surgical anesthesia (0.2 Gm. in ten seconds), produces delta activity within one minute of the start of injection. Barbiturates are known to be rapidly destroyed in the body, so that the period of high concentration is necessarily brief.
The development of high voltage fast activity as the initial result of slow intravenous injection of these two barbiturates occurred in every subject to whom they were given, without exception. The same effect was also observed in 2 subjects who received sodium pentobarbital (0.3 Gm.) intravenously.

The development of 25 per second waves in the brain potentials of cats under anesthesia induced with pentobarbital was reported by Derbyshire and his co-workers. With anesthetic doses of this drug Hoagland and associates demonstrated slowing of the alpha rhythm and development of delta waves in dogs.

The most striking observation relating to the high voltage fast waves was their appearance in the electroencephalogram in various parts of the cortex at different times. In every case the effect of the drug began to manifest itself in the form of high voltage fast activity in the frontal leads before it did in any other lead (tables 1 and 2).

**Table 1.—Latent Period of Response* in Various Cortical Regions to Intravenous Administration of Sodium Pentothal**

<table>
<thead>
<tr>
<th>Case</th>
<th>Dose, Gm.</th>
<th>Frontal Region</th>
<th>Parietal Region</th>
<th>Occipital Region</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
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<td>0 45</td>
<td>3 15</td>
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</table>

* The arbitrary criterion of response used in this table, and in table 2, is the first appearance after the beginning of the injection of three consecutive waves each of which is above 25 microvols.

1 Not measurable because of muscle movement.

In fig. 4, the normal base line record is shown first, and the second tracing is that taken one minute after the beginning of the injection, i.e., after 0.25 Gm. of sodium pentothal had been injected. The frontal leads already show pronounced change, and three minutes after the beginning of the injection the change has appeared in the parietal leads; but not until seven minutes after the beginning of the injection, that is, when 0.3 Gm. had been administered, did the change appear in the occipital leads. This striking progression of the effect from the frontal lobes through the parietal to the occipital region was observed in every subject to whom these barbiturates were given.

**Table 2.—Latent Period of Response in Various Cortical Regions to Intravenous Injection of Sodium Amytal**

<table>
<thead>
<tr>
<th>Case</th>
<th>Dose, Gm.</th>
<th>Frontal Region</th>
<th>Parietal Region</th>
<th>Occipital Region</th>
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* Not measurable because of muscle movement.


Moreover, when the patient was allowed to recover from the effect of the drug, the regression of the effect was in the opposite direction, i.e., the occipital region recovered first, followed by the parietal areas, whereas in the frontal lobes the effect lingered for a long time.

Fig. 5.—Stages in recovery from the effect of intravenous injection of 0.5 Gm. of sodium pentothal.

In the subject whose record is shown in figure 5, the occipital regions were free of high voltage fast activity within twelve minutes of the injection, but it took eighty minutes to clear the frontal lobes.

Fig. 6.—Progression and regression of high voltage fast activity in different regions of the cortex after intravenous injection of 0.5 Gm. of sodium pentothal.

In this graph the time relations are plotted for the development of each of three steps in the rise in voltage. The moment, timed from the beginning of the injection, at which the voltage first reaches 25 microvolts is plotted, and then the times for 50 and 75 microvolts respectively. In charting the progress of recovery, the last moment at which voltages as high as 75 microvolts were recorded is plotted; then the drop from 50 microvolts and, finally, the drop from 25 microvolts. For the subject whose record is shown in this figure, the only region of the cortex to reach voltages as high as 75 microvolts was the frontal, and forty minutes later the tracing from the frontal lead had not returned completely to the base line wave pattern.

The same effect was observed with the intravenous administration of sodium amytal, as can be seen in figure 7. Although with this drug the change in the electroencephalogram lasted rather longer, the preponderance of the effect on the frontal lobes is again evident.

It thus appears that these barbiturates—sodium amytal and sodium pentothal—have an effect on the electroencephalogram which is most pronounced in the regions of the cortex which are of most recent ontogenetic and phylogenetic development. Salmon showed that pentobarbital has less narcotic effect on young animals in which the cortical layers are not yet fully developed than on adult animals. The progression from one region of the cortex to another is too slow to be explained by differences in cerebral circulation.

Three patients were given sodium amytal by mouth in doses of 9 grains (0.585 Gm.); the electroencephalogram of 1 patient showed no effect; the second patient went to sleep and his

The electroencephalogram showed normal sleep waves but no other effects; the third patient's record showed all the effects observed with intravenous injection, but with a longer latent period from the time the drug was taken. High voltage fast activity appeared first in the frontal leads twenty-two minutes after the capsules were taken and reached the occipital areas in thirty-one minutes. This effect was maximal in one hour and forty-six minutes, after which delta waves appeared. There are obviously wide individual differences in reaction to the drug. At the height of the action of the drug, in the doses indicated, its effect is preponderant, and even though the patient is unconscious, the electroencephalographic record may show only high voltage fast activity. At a later stage, when the patient goes to sleep under the influence of one of these drugs, the electroencephalogram may change from the abnormal pattern characteristic of administration of barbiturates to a normal sleep pattern (fig. 8). At this depth of sleep there is no difference between the electroencephalogram taken with the patient under the influence of the drug and that which is taken during normal sleep. But when the patient is roused from this drugged sleep, the electroencephalogram does not return to its normal pattern but shows the high voltage fast activity typical of the drug.

**COMMENT**

In the introduction to this paper the reasons for the design of these experiments were outlined, the essential purpose being, as stated in the final paragraph, to use the electroencephalogram in elucidation of the action of barbiturates on the respiration and on the membrane permeability of the cortical cells.

The results obtained show that the barbiturates—sodium amytal, sodium pentothal and sodium pentobarbital—influence profoundly the frequency and voltage of brain potentials in the intact human subject. Barbiturates are known to inhibit the activity of the dehydrogenase systems of cellular respiration, and changes in cellular respiration are believed to modify the frequencies of brain waves. Other agents which impede the processes of cellular respiration are known to slow the frequency of brain potentials (e.g., low blood sugar, low oxygen tension, cretinism), whereas agents which stimulate metabolism accelerate the rhythm (thyroxin, diathermy, dinitrophenol). These barbiturates—depressors of activity of the central nervous system—slow the electric potentials of the brain to delta activity (3 to 4 per second) when given in such a way as to produce a high concentration in the

**Fig. 8.**—Sleep and arousal under medication with sodium pentothal.


brain, but the initial, and more striking, effect is the breaking of high voltage fast activity into the record, not as an acceleration of the original frequency, but as a new rhythm already established at a frequency higher than 20 cycles per second. In other words, there is no gradation through the intermediate frequencies between the normal alpha rate and the ultimate fast activity.

This suggests that two effects may be taking place; if one is interference with the dehydrogenase systems, the other may be a change in permeability of the cell membrane.

The cortical cells are separated from each other and from the substrate-bearing blood supply by semipermeable membranes; it is at these surface interfaces that the enzyme mechanisms previously outlined operate—it is here that the dehydrogenase becomes “activated,” i.e., changes its electronic structure in such a way that electrons become available for the oxidation of the substrate. In fact, this transfer of electrons is the fundamental mechanism, which in popular speech is called the “liberation of energy.” It is actually the transfer of electrons by steps, from the system of more negative potential to the system of more positive potential until finally molecular oxygen is reached.20

When the metabolic oxidations in the brain are regarded from this basic electronic viewpoint, the importance of the characteristics of the surface interfaces becomes obvious.

It has long been known that narcotics decrease the permeability of cell membranes; Lilie,21 in 1912, concluded that they caused an alteration in the surface membrane, and hence in the intracellular respiration, since reactions inside the cell are governed by the surface conditions. This conclusion has since been amply confirmed by Gelhorn and Weidling,22 by Winterstein23 and others.

Not only does the change in total permeability of the cell affect the internal chemical processes, but the changes in differential permeability are also influential. For example, a relatively greater increase in permeability for lactic acid with a relatively smaller increase in permeability for oxygen would result in an increase in the ratio of glycolysis to total oxidation in a cell.24

No change in cell permeability of this magnitude is likely without a resultant effect on the electroencephalogram, since however dependent the frequency of brain waves may be on chemical velocity within the cells, the ultimate rate of oscillation will also be governed by the impedance characteristics of the cell membrane.

It is likely that there may be two effects at work—one, the depressant effect of barbiturates on the dehydrogenase mechanisms, and the other, their effect on the dielectric of the cell membrane.

Elucidation of the relative importance of these two factors might be obtained from experiments designed to by-pass in some way one of these effects. Such a series of experiments, based on the substitution for dextrose of a substrate the dehydrogenase system of which is not vulnerable to barbiturate poisoning, is now in operation. A suitable substrate is available in the form of succinic acid; this acid, too, has its specific dehydrogenase, but its activity is not inhibited by narcotics.

It is reasonable to speculate that if the frequencies of brain potentials were dependent solely on intracellular respiration, it should be possible to maintain the rate of oscillation of these waves at the normal level in spite of the presence of barbiturates provided the cells were supplied with sufficient substrate in the form of succinate. If the resistance and capacity of the dielectric composing the cell wall were the preponderant factor in narcosis, it would be improbable that the frequencies of brain waves could be maintained at normal rates even by substrates invulnerable to barbiturates.25 This

25. In discussing our results, Hoagland (in a personal communication) suggested an alternative possibility to account for the appearance of high voltage fast rhythms despite probable over-all slowing of cortical respiration. He suggested that the fast rhythms may be due to the accumulation in the cells of lactate, since the barbiturates block its oxidation. Such an accumulation would raise the internal acidity of the cells. He expressed the opinion that the relation between cell respiration and frequency of brain wave rhythms is normally mediated by production of carbon dioxide, and he pointed out that the internal \( p_C \) of the cortical cells may determine their frequency of discharge, as it may in the respiratory center. Accumulation of lactic acid resulting from blockage of oxidation of lactate might lower the intracellular \( p_C \) and raise the frequency of the discharge.
problem is the subject of an investigation at present being carried out.

SUMMARY

In this study the electroencephalogram has been used in an attempt to elucidate the mechanics of cortical cell respiration in vivo.

One of the barbiturates—sodium amytal (in twenty experiments), sodium pentothal (in fifty experiments) and sodium pentobarbital (in two experiments)—was given intravenously to 32 patients.

For every subject to whom the barbiturate was given the electroencephalogram showed the development of high voltage fast activity.

In the patients who received larger doses per kilogram of body weight a second effect developed; this consisted of slow delta waves (3 to 4 per second).

In every subject the high voltage fast activity appeared first in the frontal leads, then in the parietal leads and finally in the occipital leads, and it disappeared in the reverse order. In other words, the regions of the cortex which are the most recent in phylogenetic development are most vulnerable to the action of barbiturates, as evidenced by the electroencephalogram.

In the first few minutes of injection, at the stage of maximal action of the drug, the patient may be unconscious without the appearance of any of the brain waves typical of sleep. At a later stage the patient may sleep deeply under the influence of the drug, at which time the electroencephalogram may show typical waves for normal sleep, but on the patient's arousal it will revert to the high voltage fast activity specific for the barbiturate.
STUDIES ON MUSCLE INNERVATION IN POLIOMYEUTIS AND NERVE INJURIES *

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An important aspect of physical medicine is the evaluation of muscular function. In poliomyelitis this has been accomplished in the past chiefly by tests of manual strength, grading performance under standardized conditions. The results of these tests have been found useful to physical therapy physicians in planning muscle reeducation and to surgeons in determining orthopedic procedure. In recent years more sensitive methods of study have been developed and also methods allowing quantitation of various components of muscle function. These technics are of particular interest in relation to physical medicine, as they make possible the evaluation of therapeutic agents.

To aid in the problems of diagnosis and prognosis of peripheral nerve injuries, measurements of muscle innervation more sensitive than the galvanic and faradic tests are especially useful, since they give early information as to regeneration.

This report deals with the application of such methods to the evaluation of muscle innervation in poliomyelitis and peripheral nerve injuries.

Poliomyelitis

Tests of Muscle Strength. — The most commonly used methods to assay the strength of muscles in poliomyelitis are similar to that described by Lovett. In this type of examination the strength of individual muscles is graded according to performance against gravitational or manual resistance in prescribed positions. When such tests are repeated by an observer who is well trained in this method of examination, the results can be of considerable practical value. There is inevitably, however, a large subjective element in such evaluations, and for this reason we have attempted to develop more exact measurements of muscle strength.

For this purpose an ergograph has been used, a description of which has been previously published. With this mechanical device the affected muscles perform the work of lifting a known weight repeatedly at a regulated speed. Each excursion of the weight is recorded on a revolving drum by a pen actuated through a string and pulley. An additional device attached to this apparatus enables the operator to quantitate the total amount of work done. This consists of a ticker tape on a revolving wheel, the tape being pulled through a ratchet each time the weight is lifted, in a length equal to the distance traveled by the weight. In this way the total elevation of the weight can be measured by the length of the tape passing through

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the ratchet, this figure multiplied by the weight used equaling the amount of work done. In addition to the measurement of the total work accomplished, the tracing on the drum records the onset and rate of fatigue. The results of a series of such ergographic determinations are shown in figure 1.

![POLIOMYELITIS](image)

The subjective element of voluntary effort is not, of course, eliminated by this method, but with care in the arrangement of the apparatus and with cooperative patients it has been found to be a useful measurement taken as an adjunct to other methods of study. There is also the advantage that simultaneous electromyographic recordings of action potentials may be made and used as an additional measurement of muscular function. The method of recording the latter will be described later.

**Electrical Excitability.** — The threshold response of muscles to electrical current is commonly used to determine their state of innervation. It is well known that four or more days after a nerve injury the contractile response of the muscle to make or break of a direct current shock is altered in its character. Instead of a brisk twitch, a slow wavelike contraction results. A denervated muscle also fails to respond to a tetanizing current, such as faradic or 60 cycle alternating current. This change in electrical excitability is known as the reaction of degeneration. This is of clinical value in the hands of an experienced observer, since it gives qualitative information to the degree of muscle innervation. Such tests have not been used to any great extent in poliomyelitis because in this disease there may be a combination of innervated and denervated muscle fibers in the same muscle group, making interpretation of results difficult. The objection has also been raised that this method of testing is painful and tends to increase muscle sensitivity.

A method of electrical testing giving some quantitative information is that of determining the chronaxie of the affected muscle. Condenser discharges of varying voltages and capacity are used for this purpose. The duration threshold of response to a current of arbitrarily set intensity (twice the rheobase) is the important measurement (chronaxie). Objections to this method are that it is based on a conception of a universal time factor and that results are greatly influenced by variation in type, position and size of electrodes, and also that changes in the voltage parameter of the
voltage-capacity relationship in degenerating nerves may appear without alterations in the time parameter or chronaxie.²

We have accordingly studied the electrical excitability of affected muscles with currents of varying strength and duration so that the threshold excitability could be graphically shown in the form of a curve plotted on logarithmic paper. In this technic the stimulus is a condenser discharge varying from 0.001 to 10 microfarads and from 1 to 400 volts. Muscles were usually stimulated at the motor point by a hypodermic needle electrode inserted in the muscle or by a small hand electrode held at constant pressure as indicated by a spring balance incorporated in the handle. The reliability of this method is to a great extent dependent on the choice of end point taken by the observer. For consistency of results the smallest detectable contraction is used as the end point. In the case of the surface electrode this is a minimal movement of the skin overlying the contracting muscle and with the needle electrode a just perceptible movement of the projecting shank. Less variation is encountered with the needle electrode because it eliminates effects due to changes in skin resistance and the thickness of subcutaneous tissue. Since multiple readings add to the reliability of this method, eight to sixteen observations are made on each muscle.

These studies on electrical excitability yielded interesting information as to recovery and prognosis in poliomyelitis. When the tests were repeated at weekly or biweekly intervals the voltage capacity curves could be compared, and these gave a graphic index of the degree of motor innervation. When the electrical excitability became progressively worse a poor prognosis was apparent. In most cases, however, successive tests showed gradually improving excitability (fig. 2). This would indicate accordingly that the usual improvement in muscle strength of patients convalescing from poliomyelitis is not due entirely to increased function of nonaffected motor units but indicates an actual recovery process in damaged units. As anterior horn cells are thought to be incapable of regeneration, one is led to speculate that the pathologic recovery is due to reversible lesions in some of these cells, perhaps in the nature of chromatolysis.

Electromyograms. — As previously mentioned, action potentials can be recorded from working muscles during ergographic tests. These are recorded by a standard ink-writing oscillograph, bipolar surface electrodes being used according to methods previously described.² The voltage of these action potentials has been found to give a good index of the contractile power and to correlate well with the manual and ergographic tests (fig. 3). A

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POLIOMYELITIS

ANTERIOR TIBIAL

\[ I = 100 \mu V \]

Fig. 3. — Action potentials of dorsiflexion of the foot recorded simultaneously with the ergograms in figure 1, two months and four months after onset. Under each electromyogram are two signal records. The lower one is the time marker, which records every second; the upper one, the integrator, which trips the signal at every condenser discharge. (Calibration: 1 signal per 700 microvolts.)

Further quantitation is possible by means of an integrator which registers the total voltage discharged during the test period.

Electromyograms have also yielded valuable information as to the degree, distribution and nature of muscle irritability in poliomyelitis. The results of these studies have formed the basis of separate reports. The finding of spontaneous electrical discharges from resting muscles during the convalescent period has given us further evidence that there is a recovery process. These discharges have the same pattern as those recorded from a muscle whose nerve is known to be regenerating after a peripheral injury. Their appearance coincides with other evidence of reinnervation of the muscle, such as improved electrical excitability and increased motor power.

Another aspect of muscle innervation of particular interest to the physical therapist, physician is the coordination of muscles during voluntary movement. Simultaneous electromyographic recordings from the antagonistic muscles of an extremity provide a method for studying reciprocal innervation. In poliomyelitis, patients with considerable weakness or painful motion showed marked disruption of normal innervation during movement. The muscles with antagonistic function were found to be simultaneously activated in these instances. This abnormality decreased as the muscle strength improved and with muscle reeducation or therapy for the relief of pain (fig. 4). Another more severe disorder of innervation was demonstrated by electromyograms which revealed not only simultaneous contraction but actual synchrony of individual action potentials in opposing muscles (fig. 5). This disorder was found only in the most severely paretic patients and could not be overcome by muscle reeducation.

We have concluded that these various methods for studying muscle innervation in poliomyelitis are of value in quantitating the degree of muscle involvement and the effects of therapy. Some information has also been added as to the types of muscle dysfunction in this disease, such as muscle irritability, paralysis and incoordination. Evidence has also been presented which suggests that a recovery process may take place in motor units.

Peripheral Nerve Injuries

The same methods of clinical laboratory investigation have been applied.

to patients with peripheral nerve injuries. The evaluation of individual muscle function according to the usual manual tests is useful in charting the anatomic distribution of the lesion. The more sensitive tests of electrical excitability are employed to assess the degree of nerve injury and to determine the onset of regeneration. The galvanic and faradic tests may be used to considerable advantage provided their limitations are recognized. Five to ten days after the trauma, compression and stretch injuries of relatively minor degree can be differentiated by this method from more severe lesions, including severance. In the case of a mild compression injury, although paralysis is complete owing to loss of nerve conduction, the electrical excitability is little altered, for the muscle gives an excellent response to the faradic current. Persistence of faradic response, therefore, aids in making this diagnosis and gives information on which to base a good prognosis for a spontaneous recovery within a few weeks.

In those cases in which a reaction of degeneration is present, however, it is impossible, by this test, to differentiate a loss of continuity from a severe stretch or compression injury. Experience has also shown that this electrical test is not of great value in giving evidence of neural regeneration at an early date. Return of voluntary motion often precedes return of response to faradic stimulation. Experienced observers, nevertheless, are sometimes able to detect changes in the character of response to galvanic stimulation which indicate the beginning of muscle reinnervation. These changes are in the nature of a more brisk muscle twitch.
Generators which provide a galvanic current with a slowly rising increase in potential are useful in detecting other alterations in muscle response to stimulation. Muscles with normal nerve supply have a higher threshold of response, since they are able to accommodate to these slow changes in potential. Denervated muscles, on the other hand, lose this power of accommodation and respond with a wavelike contraction. At the beginning of reinnervation of muscle there may be some diminution in the response to these slow galvanic currents. Interpretation of the results from these tests is dependent solely on the skill and experience of the examiner, since no objective measurements are recordable for comparison. For this reason more exact methods of determining electrical excitability are recommended, such as the voltage capacity studies already described. These tests have been found to be of considerable clinical usefulness, for objective measurements of excitability may reveal evidence of regeneration several weeks before definite clinical signs of returning function appear and before changes in response to galvanic and faradic currents occur. This method has been used in a large number of cases of peripheral nerve injury and has proved to be of considerable aid in establishing evidence of successful nerve suture or in indicating the necessity for operation.

Electromyograms. — The study of denervated muscles by means of electromyographic recordings has also been of real practical value in peripheral nerve injuries. By this method it is possible at an early stage to differentiate easily reversible minor lesions from more severe traumatic paralyses. In the case of minor lesions, action potentials are recordable on attempts to contract the paralyzed muscles; these are not found in completely denervated muscles, although the paralyses may be clinically indistinguishable.

Electromyograms are of unique value in signalizing the onset of reinnervation of paralyzed muscles, since motor unit activity can be detected only by this means. The initial return of motor unit function is characterized by the spontaneous appearance of electrical discharges from resting muscle. These have a distinctive pattern consisting of singly occurring diphasic spikes which are impossible to reproduce voluntarily. Examples of such activity are shown in figure 6. These tracings show the progress of regeneration in the nerve down the arm, it being apparent in the forearm before it reaches the hand. This activity is recordable four to eight weeks before function can be detected clinically. Although sufficient material has not yet been studied to warrant a definite conclusion, it is our present opinion that these electromyographic phenomena precede the changes in electrical excitability as measured by voltage capacity curves. Electromyograms, therefore, appear to be the most sensitive method of detecting minimal innervation of muscle.

As in the case of poliomyelitis, the voltage of action potentials during ergographic tests may be used as an objective measurement of the recovery of muscle function after peripheral nerve injury.

Electromyograms were also valuable in localizing impairment of muscle innervation due to lesions of nerve roots resulting from ruptured intervertebral disks. In such cases, spontaneous discharges may be recorded from resting muscles whose nerve supply is so minimally affected that no clinical sign of impairment is apparent. The distribution of these abnormal discharges is useful in determining the specific root involved (fig. 7).

Data on muscle innervation made available by these methods are of distinct aid to clinical diagnosis and prognosis of nerve injuries and may furnish information unobtainable by other means.
MEDIAN NERVE INJURY

FLEXOR CARPI

ABDUCTOR POLLICIS

FLEXOR CARPI

ABDUCTOR POLLICIS

Fig. 6. — Spontaneous discharges in paralyzed muscles during nerve regeneration after median nerve injury. In the upper tracing, (made six months after injury), only the flexor carpi radialis shows reinnervation. In the lower record, (made one year after injury), regeneration has reached the abductor pollicis brevis.

RUPTURED DISC

BICEPS

TRICEPS

Fig. 7. — Spontaneous discharges in the triceps but not in the biceps, indicating compression of the seventh cervical root.

Summary

Quantitative studies of muscle innervation in poliomyelitis and nerve injuries are of value in physical medicine.

1. Measurements of motor power and fatigue are objectively recorded by an ergograph.

2. Voltage-capacity curves of electrical excitability give quantitative information as to neuronal damage in poliomyelitis. In peripheral nerve injuries this method aids in the detection of regeneration.

3. Electromyograms of action potentials are an additional index of muscle function.

4. Spontaneous electrical discharges from muscles at rest are sensitive indicators of reinnervation.

In poliomyelitis the application of these methods reveals a recovery process in the motor unit. Accurate evaluation of nerve injuries is facilitated by these technics.

Discussions will appear in a later issue.
The acute neuroses of war are in many ways unlike any syndromes seen in peacetime civilian life. In World War II the first severe neuroses were seen in the men evacuated from the beaches at Dunkerque. These men showed several outstanding symptoms, many of which have since been described in the literature. They had all been exposed to severe strain; all were exhausted and dehydrated and in most cases had no sleep for four days. In addition to the trial of physical endurance, they had been in continuous danger of death and had been exposed to the repeated trauma of seeing men die violent deaths.

One frequent symptom was a gross tremor, usually of the hands, and in many cases this tremor was so marked that the diagnosis of paralysis agitans was in question. This diagnosis was supported by the facies, which was often masklike in its listlessness and apathy. In the course of another line of investigation, which included observations on the arm, one characteristic of these tremors was very striking, and this is the subject of the present paper. In these patients the tremor often appeared to be a rhythmic jerking of the whole limb without the alternation of flexion and extension seen in tremors of paralysis agitans. Unfortunately, no electromyograph was available at that time in the hospital in which these patients were being studied (Sutton Emergency Hospital, England).

In the electromyographic laboratory at the Massachusetts General Hospital it has now been possible to make electromyographic studies of similar tremors in cases of combat neuroses. All the subjects studied were patients from the United States Naval Hospital at Chelsea, Mass., and the investigation was undertaken under a project from the Bureau of Medicine and Surgery of the United States Navy (Project No. X369 Gen. 54).

Although a longer period had elapsed between the combat experience and the examination of these men than occurred in the case of the Dunkerque survivors, tremor was still an outstanding symptom.

The purpose of this study was an attempt to use the electromyograph in making a differential diagnosis of tremors due to lesions of the extrapyramidal system, tremors of psychogenic origin and tremors due to metabolic disorders or drug intoxications. The tremors of basal ganglia origin are usually classified in three groups: tremors due to degeneration in the basal ganglia consequent to arteriosclerosis in senile persons; tremors due to lesions which are the sequelae of encephalitis, and post-traumatic tremors presumably associated with some lesion in the basal ganglia, such as damage to small blood vessels. Because of the age range of these service men, the last two types only need be considered.

**METHOD**

For the recording of electromyograms, a three channel ink-writing oscillograph, such as is standard for electroencephalographic technic, was generally used, although in some cases in which simultaneous multiple recordings from many muscles were required, a six channel machine was employed. Since in this study the interest lay in the behavior of the muscle as a whole rather than in the single motor unit, the electrode technic used consisted of the employment of small, flat solder disks, approximately 1 cm. in diameter, pasted on the skin over the belly of the muscle under observation. The currents from the muscles were amplified in the usual manner, the electromyographic technic being in general similar to that described in other studies of muscle potentials.

1. I am indebted to Lieut. Comdr. Herbert I. Harris (MC), U.S.N.R. for the clinical histories of the Navy personnel used in this study.
Previous work in this laboratory, in collaboration with Comdr. Robert S. Schwab (MC), U.S.N.R., and in other laboratories has established certain characteristics of the tremor of paralysis agitans. This tremor is usually in the frequency range of 4 to 7 cycles per second and is of great regularity in any one patient; Schwab and Cobb have shown the maximum variation in any one muscle group to be 10 per cent, but it is commonly much less than this. The form of the electrical potentials is also characteristic, being a smooth build-up to a maximum spike followed by a smooth decrease to relaxation, with a period of comparative quiet between the individual tremor bursts. An example of the tremor of paralysis agitans is shown in figure 1.

Another characteristic of the tremor of paralysis agitans demonstrable by the electromyogram is that when simultaneous recordings are made from opposing muscles at rest, as, for example, from the extensors and flexors of the forearm, the tremor potentials are out of phase in the antagonistic muscles (fig. 2). The alternation of flexion and extension is well known and produces the typical pill-rolling movement of paralysis agitans. It is not to be confused with the opposite phenomenon of disordered reciprocal innervation present in rigid muscles on voluntary movement. This has been described by Hoefer and Putnam.

These three characteristics of the electromyogram of the tremor of paralysis agitans formed the nucleus for observation on the tremor of combat neurosis—that is, the frequency, the electromyographic pattern and the alternation in opposing muscles at rest.

**RESULTS**

In this series, 23 cases of tremor among service personnel were investigated. In 3 of these 23 cases the neurologic examinations gave evidence of tremor of postencephalitic paralysis agitans, and they are omitted from the classification of combat neurosis. These 3 cases will be presented in detail later, but in brief summary it may be said that in each of these cases the tremor had a frequency of 6 to 7 cycles per second and showed extreme regularity. The bursts in the extensors and the flexors were out of phase, and at no time did they occur synchronously.

In the other cases in which the diagnosis was combat neurosis, no tremor slower than 8 cycles per second was found. Synchrony between opposing muscles was common, and in some cases spontaneous diphasic spikes were found in the resting muscles. The cases have been briefly summarized in table 1, and a typical electromyogram of a tremor of psychogenic origin (case 13) is shown in figure 3.

Study of table 1 gives several items of information about the tremors in these cases. It will be noticed that whereas all the cases in the table are classified under the diagnosis in current Naval usage, i.e., combat neurosis, there is made in the fourth column some slight breakdown of this overall diagnosis from the patient's symptoms and history.

A brief description of the type of tremor is given in the fifth column, and in the sixth column is a note as to alternations of the tremor from agonist to antagonist groups.

When one looks for the characteristics which have been listed as typical of the electromyograms of the tremor of paralysis agitans, they are conspicuously absent in this series, with the single exception of case 14. In the first place,
the frequency of the tremor is often so fast as to give a completely diffuse electromyogram, with no discernible rhythm; the clearcut pattern of the rhythmic muscle discharge seen in the tremor of paralysis agitans is entirely absent (compare, for example, figures 2 and 3 with figure 1). There are also no clear interspaces between the tremor bursts (again, with the exception of case 14). Finally, there is no alternation of the tremor from flexor to extensor groups, with, once more, the exception of case 14.

This was not the forward-leaning, propulsive type of gait common in patients with paralysis agitans but, rather, a hunching gait with buckling of the left knee. No rigidity or excessive salivation was noted.

This one exception to the pattern of the electromyogram in this series of cases of combat neurosis is found also to be the only case of tremor of post-traumatic origin. The obvious question arises as to whether this case may not question arises as to whether this case may not...
paralysis agitans can be summarized briefly as follows:

L. C., a 31 year old seaman, presented the following symptoms: cogwheel rigidity of the arms and legs; tremor of the hands, arms and legs; spastic gait; dizzy spells with blurring of vision, and tremor, most marked in the legs, where it alternated from the anterior tibial to the gastrocnemius muscle. He had a history of diphtheria with delirium at the age of 8 years. The electromyogram showed a very regular tremor, of 6 per second frequency, of smooth pattern and with clear interspaces. The diagnosis was postencephalitic paralysis agitans.

P. G., a 34 year old seaman, had tremors of the hand, tongue, head and right leg, dating from an attack of influenza in 1918. The right side of his face was smoothed out. There was a pill-rolling movement of the thumb and finger of the right hand. There was no loss of associated movements or excessive salivation. The electromyogram showed a regular, 7 per second tremor of smooth pattern, alternating from flexor to extensor, with almost clear interspaces between the tremor bursts. The diagnosis was postencephalitic paralysis agitans.

K. M., a 36 year old seaman, had tremor of the right arm, diminution of associated movements in the right arm on walking and a slight stoop suggestive of rigidity of the neck characteristic of paralysis agitans. He had a history of pneumonia with delirium at 9 years of age, blood poisoning with delirium at 22, head injury with loss of consciousness at 33 and a second head injury with loss of consciousness at 35. The electromyogram showed a 6 per second tremor, alternating from flexor to extensor. The diagnosis was early paralysis agitans following multiple cerebral trauma (fig. 5).

In this small series of cases occurring among service personnel, all of whom had seen combat, some differentiating characteristics have appeared in the electromyograms in 20 cases of combat neurosis as compared with the electromyograms in 3 cases of paralysis agitans. These differentiating features were in the main as follows:

1. The frequency of tremors seen in the combat neuroses is in general much faster and more diffuse than that of the tremor of paralysis agitans, and in cases in which the rhythm is well defined it is usually irregular in timing.

2. There is rarely a clear space between the tremor bursts, the potentials usually being diffuse, with some waxing and waning of the voltage, which coincides with the tremor movement.

3. The burst of potential accompanying the tremor movement does not have a smooth build-up to the maximum voltage followed by a smooth decline, such as is usually found in the tremor of paralysis agitans, but has a much more irregular pattern, of great variability.

4. In the cases of combat neurosis the tremor does not alternate from agonist to antagonist and is often even exactly synchronous in opposing muscles.

Since this series is small, it may be of interest to compare these records with the electromyograms in some civilian cases of paralysis agitans and of tremor of other origins.

In table 2 are summarized the observations in 10 cases of paralysis agitans from the wards and the outpatient department of the Massachusetts General Hospital.

It will be seen that an outstanding characteristic in all these cases is the regularity of the tremor. In every case the rhythm was well marked and of a frequency slower than is found in the cases of combat neurosis. In all these 10 cases the frequency was in the range of 4 to 7 cycles per second. In each of the 6 cases in which electromyographic data were obtained for antagonist muscles the tremor was found to alternate in opposing muscles. One of these (case 4) is illustrated in figure 1.

There are also data on 10 cases of civilian psychoneuroses, and these have been summarized in table 3. These cases were all from the psychiatric wards and the outpatient department of the Massachusetts General Hospital. In these cases the tremors were in general much less gross than in the cases of combat neurosis, with the single exception of case 6, which is illustrated in figure 6.

Here, as in the cases of combat neurosis, the tremors were fast in frequency, diffuse in pattern and irregular in timing. Irregularity of rhythm in hysterical tremors was described and demonstrated electromyographically by Cobb, in 1920.  

In no case in the present series did the tremor alternate from agonist to antagonist. In some cases the exact synchrony of discharges in opposing muscles was striking, as, for example, in case 6 of table 3. This is the case illustrated in figure 6.

Another type of tremor on which some electromyographic data are available is the alcoholic tremor. An example of such a tremor in the case but is markedly synchronous in extensor and flexor groups.

There is another differentiating characteristic of these tremors which has not been dealt with here, since it is easily detectable with the naked eye and one does not need the help of an electromyogram to determine it. This is the observation that the tremor of paralysis agitans is usually more intense in the resting state and tends to

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<thead>
<tr>
<th>Case No.</th>
<th>Patient No.</th>
<th>Age</th>
<th>Diagnosis</th>
<th>Type of Tremor</th>
<th>Alternation in Antagonists</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H. B.</td>
<td>48</td>
<td>Postencephalic paralysis agitans</td>
<td>Regular, 5 per sec. tremor of right arm; clear interspaces</td>
<td>Alternation from extensor to flexor</td>
</tr>
<tr>
<td>2</td>
<td>H. B.</td>
<td>25</td>
<td>Post-traumatic paralysis agitans</td>
<td>Regular, 5 per sec. tremor of left arm; clear interspaces</td>
<td>Alternation from extensor to flexor</td>
</tr>
<tr>
<td>3</td>
<td>M. F.</td>
<td>35</td>
<td>Postanoxic paralysis agitans</td>
<td>Regular, 6 per sec.</td>
<td>No data</td>
</tr>
<tr>
<td>4</td>
<td>A. P.</td>
<td>61</td>
<td>Arteriosclerotic paralysis agitans</td>
<td>Regular, 6 per sec.</td>
<td>Alternation from gastrocnemius to anterior tibial muscle</td>
</tr>
<tr>
<td>5</td>
<td>E. B.</td>
<td>25</td>
<td>Postencephalic paralysis agitans</td>
<td>Very regular, 6 per sec.</td>
<td>No data</td>
</tr>
<tr>
<td>6</td>
<td>J. C.</td>
<td>35</td>
<td>Post-traumatic paralysis agitans</td>
<td>Regular, 6 per sec.; clear interspaces</td>
<td>Alternation from flexor to extensor</td>
</tr>
<tr>
<td>7</td>
<td>F. E.</td>
<td>65</td>
<td>Arteriosclerotic paralysis agitans</td>
<td>Regular, 5 per sec.</td>
<td>No data</td>
</tr>
<tr>
<td>8</td>
<td>A. T.</td>
<td>54</td>
<td>Right-sided paralysis agitans</td>
<td>Regular, 4 per sec.; clear interspaces</td>
<td>Alternation in antagonists</td>
</tr>
<tr>
<td>9</td>
<td>P. S.</td>
<td>18</td>
<td>Congenital dysfunction of extrapyramidal system</td>
<td>7 per sec., irregular in pattern</td>
<td>Alternation in antagonists</td>
</tr>
<tr>
<td>10</td>
<td>J. J.</td>
<td>71</td>
<td>Paralysis agitans</td>
<td>Regular, 4 per sec. tremor</td>
<td>Alternation in antagonists</td>
</tr>
</tbody>
</table>

Table 2.—Electromyographic Data on Tremors of Paralysis Agitans

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Patient No.</th>
<th>Age</th>
<th>Diagnosis</th>
<th>Type of Tremor</th>
<th>Alternation in Antagonists</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>O. S.</td>
<td>31</td>
<td>Mixed psychoneurosis with hypochondrias</td>
<td>Diffuse, irregular tremor in arm; some rhythm at 11.5 per sec.</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>M. G.</td>
<td>33</td>
<td>Anxiety neurasthenia with depression</td>
<td>Diffuse; some rhythm at 11 per sec.</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>K. G.</td>
<td>58</td>
<td>Hystera with anxiety</td>
<td>Irregular, with variable frequency; never less than 12 per sec.</td>
<td>Often synchronous in extensor and flexor</td>
</tr>
<tr>
<td>4</td>
<td>M. B.</td>
<td>27</td>
<td>Conversion hysteria</td>
<td>Very diffuse; some rhythm at 7 per sec.</td>
<td>Some synchrony between extensor and flexor</td>
</tr>
<tr>
<td>5</td>
<td>V. M.</td>
<td>18</td>
<td>Hystera</td>
<td>5.6 per sec.; irregular pattern</td>
<td>Synchronous in extensor and flexor</td>
</tr>
<tr>
<td>6</td>
<td>O. B.</td>
<td>31</td>
<td>Hystera with psychopathic behavior</td>
<td>Extremely irregular, rhythm varying from 2.5 to 10 per sec.</td>
<td>Always exactly synchronous in opposing muscles</td>
</tr>
<tr>
<td>7</td>
<td>O. R.</td>
<td>30</td>
<td>Mixed psychoneurosis with hysteria and hypochondrias</td>
<td>Very diffuse, with no defined pattern</td>
<td>Continuous in opposing muscles</td>
</tr>
<tr>
<td>8</td>
<td>O. G.</td>
<td>56</td>
<td>Anxiety neurasthenia</td>
<td>Bursts of potentials of approximately 3 per sec.</td>
<td>Synchronous in flexor and extensor</td>
</tr>
<tr>
<td>9</td>
<td>E. D.</td>
<td>31</td>
<td>Hystera</td>
<td>Diffuse, with no definite rhythm</td>
<td>Continuous in opposing muscles with some synchronous spikes</td>
</tr>
<tr>
<td>10</td>
<td>D. H.</td>
<td>27</td>
<td>Hystera</td>
<td>Diffuse, with some irregular rhythm, from 10 to 12 per sec.</td>
<td>Often synchronous in opposing muscles</td>
</tr>
</tbody>
</table>

Table 3.—Electromyographic Data on Tremors in Civilian Cases of Psychoneuroses

of a patient admitted in delirium tremens is shown in figure 7. In this case the tremor is rather slower than most tremors of paralysis agitans (4 per second) and is fairly regular in pat-

decrease with the patient’s attempt at a fine movement, whereas the reverse is true with the tremor of psychoneurosis; the latter usually becomes far more severe with intention.

![Extensor](image1)

![Flexor](image2)

Fig. 6.—Tremor in a case of hysteria (case 6, table 3). Note the irregularity of the bursts and the exact synchrony between the individual discharges in extensor and flexor muscles.

![Extensor](image3)

![Flexor](image4)

Fig. 7.—Tremor in a case of delirium tremens. Note the slow rhythm and the synchrony of tremor bursts in opposing muscles.
The tremor of paralysis agitans is thought to be due to loss of controlling impulses from the extrapyramidal system which integrate involuntary movement patterns, locomotion and the stabilization of posture. The primitive type of innervation pattern which impairment of these regulating mechanisms releases results in a fairly consistent electromyographic picture in the muscles involved. But the mechanism by which the tremor is caused is still far from clear. There is, for example, the observation of Wechsler 7 that the tremor of paralysis agitans can be abolished by obliterating the arterial pulse by a tourniquet on the limb; there are the various attempts to abolish the tremor by partial section of the motor tracts of the spinal cord (Putnam 8), by section of the precentral cortex (Bucy and Case 9 and Kléme 10) and by section of the ansa (Meyers 11).

Whatever the mechanism of the tremor of paralysis agitans, it is clear that a very different one is concerned with the tremor of psychoneurosis. The electromyographic pattern is quite different and may give leads for further elucidation of the pathways involved. One feature of the electromyogram is the diffuse nature of the potentials in many cases; in this respect they are similar to action potentials of cortical origin. It would be interesting to check this more closely.

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by the use of needle electrodes in the muscle. Another, and perhaps the most outstanding, feature is the absence of alternation in opposing muscles. The alternate innervation of opposing muscles in paralysis agitans has some similarity to clonus, which is a reflex mechanism in the cord. This clonic type of activity is not seen in the tremors of psychoneurosis.

**SUMMARY**

Electromyographic studies were made on the tremors of 23 men of combat personnel. Of these patients, 3 had symptoms of lesions of the extrapyramidal tract, and 20 had a condition diagnosed as combat neurosis.

In addition, studies were made on 10 civilians with paralysis agitans and 10 civilians with tremors associated with psychoneurosis.

Electromyographic data are given on tremor in a case of delirium tremens.

The following electromyographic differences were found between the tremor of paralysis agitans and tremors of psychoneurotic origin:

1. The rate of tremors associated with psychoneurosis is usually faster than that of tremors of paralysis agitans and is often so fast as to give a completely diffuse electromyogram, with no discernible rhythm.
2. The tremor of psychoneurosis does not have the clearly patterned discharge of smooth increase in the voltage to a maximum followed by a smooth decrease that is typical of tremor of paralysis agitans.
3. Clear interspaces between the individual tremor bursts are rarely found in cases of psychoneurosis.
4. Tremor bursts associated with psychoneurosis do not alternate from agonist to antagonist as in paralysis agitans but usually appear simultaneously in opposing muscles, and sometimes are even exactly synchronous in the timing of the individual discharge.

The author is indebted to Comdr. J. M. Heminger (MC), U. S. N. R., for his interest and for continuing to make available the facilities for this work after Lieut. Comdr. H. J. Harris had gone overseas, and to Miss Margaret Gray for technical assistance in recording the tremors.

Massachusetts General Hospital.
OBSERVATIONS ON MUSCLE SPASM IN POLIOMYELITIS*

Electromyographic Studies on the Effect of Various Forms of Thermal Therapy and of Prostigmine §

ARTHUR L. WATKINS, M.D.

MARY A. B. BRAZIER, Ph.D.

BOSTON

The widespread hypersensitivity or "spasm" of muscles during the acute stage of poliomyelitis has been emphasized recently as one of the most characteristic findings in this disease. For some years a major aspect of treatment has been the attempted relief of this symptom, and for this purpose elaborate physical therapeutic methods requiring constant attention of trained personnel have been used. It thus seems of considerable practical, as well as theoretical, importance to determine the comparative effectiveness of these methods in reducing muscle spasm.

In previous reports from this laboratory quantitative methods have been described for measuring the degree of spasm by the voltage of the electrical potentials discharged by the muscles on passive stretching. This method has been standardized in the present study in order to evaluate the comparative effects of hot packs, radiant heat and diathermy. In view of the recent reports of Kabat and Knapp on prostigmine in the relief of spasm, use of this drug was included among the treatments studied.

This preliminary report is restricted to one aspect of the effect of treatment, namely, the influences of single applications of a therapeutic agent on muscle spasm during the first weeks of the disease. This is a portion of a longer study now in progress which is concerned with the total course of the disease, including the nature of the recovery process. Since all the patients were in the early infectious stage, studies were restricted to adult patients readily accessible in the isolation ward. Six such patients were available for study, and each received intensive tests during the acute stage. In all, 835 measurements were made, the first test usually being done within a few days after diagnosis had been established. These patients are still under treatment and observation in the outpatient clinic, and final evaluation is not yet possible.

Methods

The degree of muscle spasm was measured by the response of the muscle to passive stretching, and the technic of stretching was standardized to make it comparable from test to test. The force used for stretching was constant, consisting of a known weight, and the duration of stretch was uniformly five seconds. In the upper extremity, to stretch the flexors and extensors of the wrist and elbow, the suspended weight was attached distally to the respective joint. In the lower extremities the force of the weight was appropriately directed by use of overhead pulleys. The hamstrings were stretched both by straight leg raising and by extending the knee with the hip flexed at an angle of 90 degrees.

*From the Department of Physical Medicine and the Electromyographic Laboratory of the Massachusetts General Hospital.

§ Prostigmine used was a diagnostic ampoule supplied by Hoffmann-La Roche, Inc., containing prostigmine methylsulfate 1/40 gr. with atropine sulfate 100 gr.


As mentioned, the measure used for quantitation of the degree of spasm induced by stretching was the total voltage of electrical potentials discharged by the muscle during the five-second stretch period. A normal muscle gives little or no discharge when subjected to passive stretching, but a muscle in spasm will release a continuous burst of potentials which can be recorded on the electromyograph, as shown in the accompanying illustration. The use of a calibrated integrator in circuit with the electromyograph makes possible the quantitation of the voltages from the muscle. This device works on the principle of a condenser which discharges on receiving its complement of electricity, and in discharging records on the electromyographic tracing. This type of voltage integrator has been described in more detail elsewhere.16

For this work the electrodes consisted of the standard type of solder disks approximately 1 cm. in diameter applied in pairs with electrode paste and adhesive tape to the skin over the body of the muscle. An additional electrode was placed on some neutral point to act as a ground.

The currents from the muscles were amplified by the standard types of power amplifier used in electroencephalographic work and were recorded by an ink-writing oscillograph.

On each test day a number of control observations were made on every muscle before the therapeutic procedures were begun. The therapeutic methods investigated were: twenty-minute applications of the Kenny type of hot packs, infra-red irradiation, luminous heat, short wave diathermy by induction technic and intramuscular injection of 1.6 mg. of neostigmine (prostigmine methylsulfate).

In the case of hot packs and diathermy the therapeutic technic necessitated the removal of the electrodes, so that these had to be reapplied to the same positions on the muscle for the post-treatment recording. In the other instances the electrodes remained in place throughout the procedure.

In every case the strength of the muscles was graded according to the standard manual examinations as described by Lovett3 and others.

Results

**Hot Packs.** — The effects of twenty-minute applications of the Kenny type of hot packs have been summarized in table 1. Forty-six base line observations were made on the passive stretching of ten different muscles before therapy, showing an average response of 1,687 microvolts per stretch period (five seconds). The tests were repeated forty-three times after therapy, with no significant change in the mean electrical discharge (1,740 microvolts).

Infra-Red Irradiation. — Sixty-one observations on the stretching of thirteen muscles were made prior to infra-red irradiation for twenty minutes, the average value being, 1,771 microvolts. There was only a negligible change after therapy, as revealed by fifty-seven readings averaging 1,889 microvolts.

Luminous Heat. — After twenty minutes of this therapy in over seventy tests the average discharge was 26 per cent less than in a similar number of base line observations, a decrease in the mean of 510 microvolts.

D iathermy. — Twenty minute applications of this therapy in forty tests caused no change in the discharge released.

Prostigmine. — Seventy tests were made before and after the intramuscular injection of 1.6 mg. of this drug. At the period of maximum effectiveness of the drug, namely, twenty minutes after the injection, there was 24 per cent less irritability than during the control period.

Comment

In table 1 the initial irritability before diathermy is seen to be considerably greater than that observed before the other methods of treatment. This may be explained by the fact that diathermy could not be given until at least eighteen days after the onset of the disease, when the patient was no longer confined to the isolation ward. Analysis of the data in table 2 revealed that the muscles became increasingly irritable after the first week. The increase was twice as great in the more severely weakened muscles as in those with less than 50 per cent loss.

In this series no effort was made to study the effect of the different types of heat on the degree of spasm in those muscles which had no impairment of strength. When the effect of prostigmine was being tested, however, muscles with normal strength were used for comparison and, as in all these cases the paresis was unilateral, the corresponding muscle group in the opposite extremity was used as a control. As observed by Schwartz, many muscles which show no loss in strength exhibit hyperirritability in patients with poliomyelitis. This was true in the majority of our patients, and it was found that injection of prostigmine was followed by a decrease in irritability amounting to 21 per cent. The muscles with full strength but no spasm, on the other hand, showed an increased irritability to stretching after injection of prostigmine (table 3).

It is obvious that no definite conclusion concerning the value of physical therapy or of prostigmine in the treatment of poliomyelitis should be drawn

| TABLE 2. — Degree of Irritability to Passive Stretching for Five Seconds* |
|-----------------------------|-----------------|-----------------|-----------------|
| Strength of Muscle Tested   | Days After Onset|                  |
|                             | 1 to 8          | 9 to 16         | 17 to 30        |
| Under 50%                   | 996             | 1,345           | 2,103           |
| (120 tests on 7 muscles)    |                 |                 |                 |
| Over 50%                    | 2,166           | 2,293           | 3,075           |
| (135 tests on 11 muscles)   |                 |                 |                 |

| TABLE 3. — Effect of Intramuscular Injection of Prostigmine on Muscles of Normal Strength in Poliomyelitis* |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| No. of Muscles Tested                          | No. of Tests    | Mean Before Therapy | Mean After Therapy | Percentage Change |
| 100% strength with some spasm, 16             | 112             | 1,822            | 1,432            | -21               |
| 100% strength with no spasm, 3                | 33              | 342              | 1,292            | -1.28             |

* Measurements are in microvolts.

from studies of this limited scope. Observations were not made on the effects of repeated use of these agents, but only on the effect of a single application to determine whether any one agent showed a marked superiority over the others in the temporary relief of spasm. With single tests of this kind, only changes of 50 per cent or more would be convincing in so small a series, but in these 6 cases no change greater than 26 per cent was found. There was no evidence to suggest that any one method of applying heat had any specific effect on the spasm, and the same is true of prostigmine.

During the course of the present studies all patients but one were receiving the Kenny type of hot packs four to five times daily except on the day of the test. However, since no specific effect of hot packs was demonstrated, it seems justifiable to omit their routine use in the future and to study a repeated application of a single method of treatment throughout the course of the disease. This should be a more effective comparison of their relative value.

From the subjective point of view, the patients felt that the different types of heat were all moderately comforting, there being no consistent preference for one type of therapy. Patients uniformly disliked prostigmine, however, because of its effect on the gastrointestinal tract.

Several of the patients had rather severe pain in the affected extremity for the first few days. None of our methods of treatment can be said to have been outstandingly effective in relieving this, and from clinical observation alone one would conclude that the pain tended to decrease spontaneously rather than as a definite result of treatment.

The degree of muscle paralysis in these patients varied from nearly complete loss of power to barely perceptible weakness, and in every instance there was some slow but steady improvement in muscle strength during the follow up period of four to five months. It is expected that further improvement will be seen as time goes on. As an isolated observation it is interesting to note that, to date, the one patient who had no hot packs or other treatment, except that of the test and the usual muscle reeducation, has shown the same degree of improvement in muscle power as the others in the series.

As already noted, muscle irritability was observed to be of widespread distribution, occurring in muscles which were paralyzed as well as those without paralysis, and there seems to be no direct correlation between the degree of hyperirritability to stretching and the degree of paralysis. On the other hand, these quantitative studies indicated that there was less irritability in the more severely paralyzed muscles, as seen in table 2. The increase in irritability of weak muscles late in the disease may be explained by a background of spontaneous discharge in the resting muscle. This type of activity has been reported as a feature of motor neuron regeneration.16

Summary

1. Muscle spasm in patients with acute poliomyelitis was measured by quantitation of the electrical discharges released on five seconds of passive stretching by known weights.
2. The effect of twenty-minute applications of hot packs, infra-red radiation, luminous heat, short wave diathermy and the intramuscular injection of prostigmine (1.6 mg.) on this electrical component of spasm was tested.
3. Single applications of hot packs, infra-red radiation and diathermy had no effect.
4. Luminous heat and prostigmine caused a decrease in spasm of approximately 25 per cent. This degree of change was not great enough to indicate a specific effect on spasm.
5. Further studies on repeated use of a single method of treatment will be necessary for final evaluation.
THE EFFECT OF ANOXIA AS MEASURED BY THE ELECTROENCEPHALOGRAM AND THE INTERACTION CHRONOGRAM ON PSYCHONEUROTIC PATIENTS

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During the past ten years we have been interested in investigating the autonomic nervous system in the psychoneuroses. Previous studies have shown that psychoneurotic patients differ from control subjects in respect to heart rate (1), ventilation (2), sighing respiration (3), and other aspects of the respiratory pattern (4) during basal conditions and during sensory and ideational stimuli. More recent studies (5, 6) from this and other laboratories indicated that psychoneurotic patients, especially those with anxiety neurosis and neurocirculatory asthenia, show a disturbance in the oxygen uptake or oxygen utilizing mechanisms. Further in a series of studies on the selection of aircraft pilots, in collaboration with the Bureau of Medicine and Surgery of the U.S. Navy, a correlation was found between failure in flight training and behavior and between failure in flight training and autonomic overactivity (7), and certain characteristics of behavior which are found in states of anoxia.

In pursuing this problem we felt it wise to study the direct effect of inhaling mixtures low in oxygen upon the CNS activity as determined by the electroencephalogram and behavior as measured by the interaction chronogram. It is the results of these latter studies that are presented in this paper.

The effects of anoxia on the EEG in man were studied by Berger (8), and later by many others, most notably Gibbs and Davis (9), Lennox, Gibbs, and Gibbs (10), Gibbs, Williams, and Gibbs (11), David, David, and Thompson (12), and Gerard (13) and his collaborators. All investigators report that in breathing mixtures low in oxygen a shift to the slower frequencies occurs in the EEG.

Many observations are available on the effects of anoxia on behavior and on certain psychological functions. MacFarland (14), Barach and Kagan (15) describe changes in behavior during anoxia. These changes, not so readily measurable, refer to loss of emotional control, excitement, garrulosity and destructiveness on the one hand or apathy and unresponsiveness on the other. Simultaneous observations on the EEG and the performance of subjects as exemplified by the critical flicker fusion frequency, as studied by Gellhorn and Hailman (16), indicate a parallelism between the degree of change in critical potentials and in the critical fusion frequency. The effects of anoxia on more elaborate psychomotor responses and in phantasy formation (17) have also been reported. In the present study a series of psychoneurotic patients and normal control subjects was interviewed by the use of a standardized procedure while sitting in an anoxia chamber and while breathing mixtures of room air (approximately 21% O2) and while breathing mixtures low in oxygen. Electroencephalographic records were made at various intervals throughout the procedure and the activity as indicated by the length of the periods of talk and gestures was measured throughout both interviews (18). Data are presented comparing the results obtained at low oxygen levels with those obtained while breathing air.

This study was aided by a grant from the Milton Fund.
The subjects, both patients and normal controls, were subjected to the same procedure. The subjects were all under non-basal conditions, and the experiments were all done in the morning. Each subject was given 50 c.c. of 50% glucose p.o. while sitting in an adjacent laboratory and the scalp electrodes were attached. The subject then sat in the anoxia chamber while the leads from the scalp electrodes were attached to cables leading to the EEG apparatus. A capillary blood sample was drawn for the determination of the blood sugar level. This was done because we have previously shown (19) that blood sugar levels of 110 mgm./100 c.c. and below might influence the frequency of cortical potentials. After this the subject was asked to close his eyes and an EEG record was obtained for a period of 2 minutes. This served as a base line for the EEG determinations. The hood of the anoxia chamber was then closed and the patient was then interviewed. The anoxia chamber was connected directly with a spirometer, whose capacity was 350 liters. A circulatory pump in the circuit insured complete mixing of gas in the spirometer and in the chamber. The CO was absorbed by means of soda lime, through which the gas was pumped. At the beginning of the experiment the spirometer contained about 50 liters of room air.

After the first interview which lasted about 30 minutes an amount of N₂ was introduced into the spirometer to attain the desired oxygen mixture. It was found that a 10 minute mixing period was sufficient to obtain adequate mixing. After the mixing period the subject was interviewed again for a similar period. When the second interview had been completed, the hood was then lifted and the subject was in most instances asked to describe his reactions during the experiment. Samples of gas were taken from the chamber every 15 minutes from the beginning to the end of the entire experiment for analysis of oxygen and CO₂. Electroencephalographic records were obtained every 15 minutes throughout the interview and continuously for a five-minute period at the very end of the experiment and throughout the whole period while the hood was lifted and for 3-5 minutes after that. Each of the EEG runs was at least two minutes in duration and all were recorded with the subject sitting quietly with his eyes closed.

THE INTERVIEW

In the course of our work it was found expedient to adopt a standard, or controlled, interview. Experiment showed that variations in the interaction rate of the interviewer brought about specific changes in the interaction rate of the subject, and the interviewer—unless very skilled—tended to persist in his natural rate. It was possible to set constants for the differences between interviewers, but it was more effective to get them to control their behavior by learning to follow a specific timing pattern. This pattern, made up of standardized variations, formed the standard experimental interview for determining the effect of controlled changes in the interviewer's behavior upon the subject's own pattern. A detailed description of the interview follows:

The interview is divided into 5 periods, each of which is introduced by a general topical question relating to the subject's own experience. Three of the periods, the 1st, 3rd, and 5th, are alike in the prescriptions for the interviewer's behavior, although the 1st takes 15 minutes, while the other 2 last 5 minutes only. In these 3 periods, the interviewer, after introducing the general topic (such as: "How do you get along at home?") is instructed to wait one or two seconds before replying when the subject stops and to use only such encouraging phrases as "Isn't that interesting?" "Why?" "Can you give me an example of that?" or to rephrase the last phrases of what the subject has just said.

After the first 15 minute period, a new topic is introduced by the interviewer and during the period devoted to that topic, the interviewer is instructed to change his behavior systematically from that previously used. When the subject stops talking, the interviewer waits 10 seconds before replying. If the subject starts to talk without waiting for the interviewer, the interviewer waits again when he pauses, and repeats the procedure ten times.
Only if the subject waits for the full 10 seconds after one of his actions will the interviewer reply, rephrasing the original question or the subject's previous answer. This period during which the interviewer fails to reply is followed by a five-minute adjustment period introduced by a question on a new topic. At the end of the 5 minutes, a new topic is introduced and the interviewer now starts to talk during the subject's first reply and tries to talk him down, using a normal voice, and rephrasing the question just asked. These interruptions are repeated ten times. If the subject does not reply after the interviewer stops interrupting—that is, the interviewer has succeeded in out-talking him—then the interviewer waits 3 seconds and then asks another question. The next and final period is a period of readjustment of 5 minutes, in which the interviewer tries to adjust to the subject.

In order to judge the time accurately, a large clock with a sweep second hand is placed behind the subject, where the interviewer can see it without having to turn his head. The five periods should take approximately 25 to 30 minutes, and on the graph each period is marked by the signal marker, which is pushed by the observer when the key question is asked.

DATA

In the present study experiments were performed on 67 patients and on 36 control subjects. The patients were individuals treated on the wards and in the Out-patient Department of the Psychiatric Department of the Massachusetts General Hospital and individuals undergoing treatment at the U.S. Navy Hospital at Chelsea, Mass. Most of the patients were diagnosed as having psychoneuroses of various kinds—the largest group consisting of patients with anxiety neurosis. They ranged in age from 15 to 43—there were 20 females and 16 males. There were 36 control subjects who were chosen from the medical students, doctors, hospital technicians and W.A.V.E.S. working at the Chelsea Navy Hospital. Their ages ranged from 19 to 38. The control subjects were not under treatment. Complete data as to the presence or absence of symptoms for the control group is not available. However, in a small series of 10 control subjects who were interviewed, one subject merited a diagnosis of psychoneurosis. Two subjects showed evidence of occasional psychoneurotic symptoms. As far as could be determined the other 7 had no psychoneurotic symptoms. If this sample is reliable, one would have to conclude that a small percentage of the control subjects merited the diagnosis of psychoneurosis.

GENERAL REACTIONS TO ANOXIA

On the whole the changes in behavior noticeable were of two distinct types. At one extreme subjects became restless, appeared distressed and demanded to have permission to leave the anoxia chamber—this was likely to happen during the mixing period. At the other extreme subjects became more and more uncommunicative and then ceased to respond altogether so that the experiment had to be interrupted. These two extremes: acute apprehension with restlessness on the one side and apathy with failure to respond on the other side, seemed to be two poles of a continuous series presenting various combinations of the factors mentioned. It is of interest that the restless state was often attended by phenomena suggesting autonomic stimulation; sighing respiration, flushed face, profuse sweating, while the apathetic state seemed to develop insidiously without any dramatic manifestations.

In addition to the detailed observations to be presented below, there were certain general differences in the reactions of the subjects at low oxygen. Approximately 20% of the subjects were unable to finish the experiment. About 10% discontinued because they fainted, felt faint, dizzy or were nauseated. There was little difference between patients and controls in these items. Two of the patients were excited and felt jittery, and 2 of the patients were uncooperative.

Many of the subjects complained of subjective feelings in response to anoxia. About
half of the patients and control subjects complained of fatigue, about one-fifth of the patients and controls complained of dizziness. Approximately 40% of the patients complained of headache, restlessness and tenseness. These complaints were mentioned by only two of the control subjects. Difficulties in thinking, and "heaviness," were mentioned by one-third of the control subjects, but by only 2 of the patients. A few patients and a few control subjects complained of numbness, sensation in their ears and faintness. Three of the patients complained of fear during the experiment and three of the control subjects mentioned breathing difficulties.

In addition to the subjective sensations reported, the effects of anoxia could also be observed in the manner in which the patients communicated with the interviewer. A change in the flow of speech was noted. During low oxygen the pauses before answering the interviewer's questions became longer. Sometimes there was a complete failure to respond to the questions of the interviewer. At times the answers to the interviewer's questions became short and often monosyllabic. Occasionally there was an increase in the number of repetitions. Often these were simple repetitions of an idea, and some subjects repeated phrases without stimulation by the interviewer's questions. In many cases there was an apparent reduction in the choice of words and the vocabulary seemed to be constricted and it was as though the patient were operating on a simple level of language structure. In many instances there was a marked change in the rate of speech and it seemed as though the subject were less able to follow and to respond to the interviewer's questions. The subjects tended to lose contact with the interviewer and would continue to speak in an irrelevant fashion. It was the impression of the observers that the subjects seemed more preoccupied with internal phenomena.

There was some evidence that the subjects tended to shortcut their ideas, leaving out connectives. In a few instances certain symptoms which the patients had were apparently aggravated by low oxygen. Two of the group began to stutter toward the end of the interviewing.

The Effect of Anoxia on the Electroencephalogram

As mentioned above Berger was the first to show that lowering of the O2 concentration of the inspired air slowed the rate of the cortical potentials and this observation has since been abundantly confirmed by other workers. It was our purpose in this study to apply this fact as an objective method for assessing the degree of response of an individual to low O2 concentrations. This entailed the development of a method of measurement of these rhythms in order to be able to quantitate any changes which took place. As the purpose of any such index of measurement was to demonstrate slowing of rate, a distribution curve was made of the frequencies up to 17 cycles per second present in a two-minute sample of each electroencephalographic recording. One such is shown in Fig. 1. The method for preparing such a distribution curve has been described in a previous paper (20). In Fig. 1 a normal EEG is seen at the top and the curve of its frequency analysis is shown below. In this particular example the greater portion of the record was occupied by waves of 10 and 10.5 cycles per second frequency with lesser amounts of other frequencies. If any slowing of this EEG were to take place due to the subject's breathing low O2, one would expect the whole distribution curve to move to the left into the range of slower frequencies. This is, in fact, what was found in 85% of the subjects tested (59 persons). In some cases the slowing was so gross that it would easily be seen by inspection of the original tracing and one such example is shown in Fig. 2.

In some records, however, one would have more difficulty in deciding whether a slowing of a rate had taken place if only inspection of the original tracing were used. For example, in Fig. 3 the EEG is shown of a subject in air and when breathing 8.1% O2.
One Example of the Distribution of Frequencies in the Record of an Individual Breathing Air and of the same Individual Breathing 8.1% Oxygen.

EFFECT OF ANOXIA ON THE ELECTROENCEPHALOGRAM

Breathing Room Air

\[ I = 100 \mu V \]

8.8% Oxygen

Figure 2

EFFECT OF ANOXIA ON THE ELECTROENCEPHALOGRAM

Breathing Room Air

\[ I = 100 \mu V \]

8.8% Oxygen

Figure 3

EFFECT OF ANOXIA ON THE DISTRIBUTION CURVE OF THE ALPHA FREQUENCIES

- = Breathing Air
- - = Breathing 11.2% O_2

Per Cent

Frequency in Cycles per Second

Figure 4

Figure 5
The distribution curve of the frequencies, however, which is shown in Fig. 4, demonstrates quite clearly a significant slowing.

Since some index was wanted for use as a quantitative measurement to correlate with other factors, some expression of this shift of the curve to the slower frequency was searched for which could be expressed as an integer. There are many features of this shift which might be used as measurement. For example, the amount of activity slower than a certain frequency could be used and this would obviously be greater in the left hand curve than in the right and would give some measurement of the slowing of the EEG, or one could use the shift of the peak of the curve which we call the dominant frequency since that is the frequency which dominates the whole of the electroencephalographic tracing. It is obvious that the dominant frequency is not an infallible index, since the body of the curve could shift to the left without a change in the peak, but it has proved to be a reasonably adequate measurement of slowing. Since all aspects of the data cannot be presented here, this will be the one measurement discussed and used in the computations which follow. As noted above, its use does mask the effect of anoxia in some cases and thus gives an understatement of the effect of low O₂ on the EEG.

Fig. 5 is another example of a shift of the curve to the left when breathing low O₂, in this case only as low as 11.4%. In any large group of individuals breathing air, the dominant frequency varies from person to person, but when charted out shows a distribution curve around the most common value for normal people which is 10.0 to 10.5 cycles per second (20).

The distribution curve of the dominant frequencies of 37 individuals breathing air charted as a solid line is shown in Fig. 6. On the same figure the broken line shows the shift for these same 37 individuals with O₂ levels below 11%. This figure shows a difference between the EEG of a group of people in air and at low O₂ levels, but it does not give information as to whether this slowing takes place suddenly or whether it is a response which is graded with the level of anoxia involved.

**DISTRIBUTION OF DOMINANT FREQUENCIES AMONG 37 SUBJECTS**

**Solid Line - Air**

**Broken " - Oxygen Levels Below 11%**

**NUMBER OF SUBJECTS**

<table>
<thead>
<tr>
<th>Dominant Frequency in Cycles Per Second</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
</tr>
<tr>
<td>8</td>
</tr>
<tr>
<td>9</td>
</tr>
<tr>
<td>10</td>
</tr>
<tr>
<td>11</td>
</tr>
<tr>
<td>12</td>
</tr>
<tr>
<td>13</td>
</tr>
<tr>
<td>14</td>
</tr>
</tbody>
</table>

**MEAN CHANGE IN DOMINANT FREQUENCY AT VARIOUS LEVELS OF ANOXIA**

<table>
<thead>
<tr>
<th>Oxygen Level</th>
<th>No. of Subjects</th>
<th>Mean Slowing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Below 10%</td>
<td>29</td>
<td>-0.4 Cycles</td>
</tr>
<tr>
<td>10% Up to 11%</td>
<td>28</td>
<td>-0.2 Cycles</td>
</tr>
</tbody>
</table>

**INFLUENCE OF CO₂ LEVEL ON DEGREE OF SLOWING OF EEG AT TWO LEVELS OF ANOXIA**

<table>
<thead>
<tr>
<th>O₂ Below</th>
<th>CO₂ Below 3%</th>
<th>CO₂ 3% To 5%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Below 10%</td>
<td>-1.1</td>
<td>-0.3</td>
</tr>
<tr>
<td>N=5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>O₂ 10% Up To 11%</th>
<th>CO₂ 3% To 5%</th>
</tr>
</thead>
<tbody>
<tr>
<td>-0.4</td>
<td>-0.1</td>
</tr>
<tr>
<td>N=10</td>
<td>N=18</td>
</tr>
</tbody>
</table>

**SLOWING OF DOMINANT FREQUENCY (IN CYCLES PER SEC.)**
In Fig. 7 this same group of 57 subjects has been divided into two portions: those who were breathing O₂ levels below 10%; and those between 10 and 11%. It is immediately clear that the average slowing is greater the lower the O₂ levels. Here then is one variable which affects the degree of slowing. In other words the degree of slowing is dependent upon the degree of anoxia. There is, however, another variable at work and this is the CO₂ level. Great technical difficulty was experienced in eliminating all the expired CO₂ from the circuit since it accumulates so quickly that some inevitably remains to be rebreathed. In none of the 57 cases reported here was the CO₂ over one-half of 1%, but a marked difference was found between the degree of response to low O₂ between those subjects who were breathing less than 0.3% CO₂ and those who were breathing between .3 and .5% CO₂. There was a greater slowing of the EEG at the lower CO₂ levels.

In Fig. 8 both variables are reported—the degree of anoxia and the amount of CO₂ rebreathed. Where both the O₂ and the CO₂ were low there was the greatest slowing of the EEG. Where the O₂ is only reduced to the 10 or 11% level and the CO₂ is over 0.3%, the dominant frequency shows a mean slowing of —.3 cycles per second.

The influence of CO₂ on the reaction of the EEG was expected from all the work that has been done in this field, but it was an unexpected result to find that CO₂ exerted its influence at such low concentrations as 0.3%.

There seemed to be little difference between the patients and the control subjects in their reactions to anoxia when the records were analyzed as described above.

Effect of Anoxia on the Interaction Chronogram

The interaction chronograph is operated by an observer seated behind a screen through which a one-way mirror gives a view of the interview. In front of him is a small box with two keys, one for the subject and one for the interviewer, and a push-button switch, which operates as a signal marker. All he has to do is press down the appropriate key when either person starts to act—by talking, smiling, nodding or gesturing—and hold it down until the action is over. He watches closely the visible activity of the facial muscles, recording contractions as activity and relaxation as inactivity. Any fixed grimace or nervous twitching which is not part of a sequence of interactions is not recorded.

By this simple operation the five pens of the chronograph trace out five curves which record the relative duration of the subject's periods of activity and of silence. Two of them, the activity and the speed curves, record the subject's behavior; the other three record aspects of two individuals' interaction with each other. They are the subject's adjustment curve, the interviewer's adjustment curve, and the initiative-dominance curve. For the purpose of this report the activity curve alone will be considered.

Activity Curve.—When the subject's key is pressed down first, a pen starts to move along a vertical bar in a positive, or upward, direction, and continues on until the action ends. When the subject's key is released at the end of his action, the pen reverses its course and moves downward in a negative direction while the subject is silent. Each time the subject begins to act, a mechanism moves the paper one step to the left. Thus the resulting graph represents the cumulative sum of the differences of the actions and inactions. If, for instance, a man talks on for 60 seconds and is silent for only 1 before beginning again, the curve will ascend at the rate of 59 seconds for the complete unit of action and inaction; if he is silent for 60 seconds and talks for only 1, the curve will descend with the obverse slope.
The activity values were obtained by direct measurement from the charts as produced by the interaction chronograph. For the purpose of this report the data on two variables will be presented: the A-S values and the A values.

The A-S value represents in seconds the algebraic difference between the period of activity (talk and gesture) and the period of inactivity (silence). The values were obtained by measuring (for a period of the interview or for the total interview) the cumulative height of the curve. Similar measurements were made for the interview while the patient was breathing air in the chamber and for the interview while the patient was breathing various low oxygen mixtures. The composition of the air in the chamber was from 21 to 19% \( \text{O}_2 \), and the \( \text{CO}_2 \) varied from .5 to .16%. "Low oxygen levels" refers to oxygen levels of 15% and below.

In a series of 28 patients and 14 control subjects a decrease in activity as described by the A-S curve occurred in about 77% of the subjects, when the values for the total interview are considered. Similar changes were observed in 60% of the subjects when the values were calculated for the first 15 minutes of the interview. A slightly higher percentage of individuals (80%) showed a decrease in activity when the values for the last 5 minutes of the interview were taken (Fig. 9).

On comparing patients and control subjects (Fig. 10) the same percentage (75%) of each showed a decrease in activity for the total interview period as described by the A-S curve. The mean decrease for the patients was 1.1 seconds and for the control subjects .65 seconds.

Relation of Activity in Air to Changes at Low Oxygen Levels.—The results of this comparison are presented in Figs. 11 and 12. It can be seen that subjects with high

**Percent of Subjects Showing Decrease of Activity at Low Oxygen Levels as Compared to Air**

<table>
<thead>
<tr>
<th>Percent</th>
<th>N=42</th>
</tr>
</thead>
<tbody>
<tr>
<td>First 15 Minutes</td>
<td>60%</td>
</tr>
<tr>
<td>Last 5 Minutes</td>
<td>80%</td>
</tr>
<tr>
<td>Total Interview</td>
<td>75%</td>
</tr>
</tbody>
</table>

**Relation of Initial Activity in Air to Decrease of Activity at Low Oxygen Levels**

<table>
<thead>
<tr>
<th>Percent</th>
<th>N=7</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.00 and over</td>
<td>80%</td>
</tr>
<tr>
<td>2.99 to 1.00</td>
<td>97%</td>
</tr>
<tr>
<td>1.99 to 1.99</td>
<td>15%</td>
</tr>
<tr>
<td>1.00 and below</td>
<td>15%</td>
</tr>
</tbody>
</table>

**Effect of Low Oxygen Levels on Activity**

<table>
<thead>
<tr>
<th>Subjects Showing Decrease in Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Interview</td>
</tr>
<tr>
<td>28 Patients</td>
</tr>
<tr>
<td>13 Normal Controls</td>
</tr>
</tbody>
</table>

**Relation of Initial Activity in Air to Mean Changes at Low Oxygen Levels**

<table>
<thead>
<tr>
<th>Means of Changes from Air to Low Oxygen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Interview</td>
</tr>
<tr>
<td>2.99 to 1.00</td>
</tr>
<tr>
<td>-2.00 and below</td>
</tr>
<tr>
<td>N=6</td>
</tr>
</tbody>
</table>
initial activity rates as determined by the A-S value showed greater changes at low oxygen, whereas subjects with initial low activity rate tended to show an increase in activity at low oxygen. All of the 7 subjects with activity rates of 3 seconds and over per interaction unit showed a decrease at low oxygen. The mean value for this decrease was 2.5 seconds per interaction unit for the total interview and 5 seconds for the last 5 minutes of the interview. Twelve out of 15 subjects (80%) whose initial values were from 2.99 to 1.00 showed a decrease. The mean change for these 15 subjects was a decrease to 1 second for the total interview and a decrease of 3 seconds for the last 5 minutes of the interview. Ten out of 11 subjects (75%) whose initial values were from 0.99 to -1.99 showed a decrease. The mean change of these subjects was a decrease of 5 seconds for the total interview and 1.5 seconds for the last five minutes of the interview. Only 2 of 6 subjects, whose initial value was 2.00 and below, showed a decrease at low oxygen. The remaining 12 showed an increase during low oxygen. The mean values for these subjects at low oxygen indicated an increase in activity of 0.5 seconds for the total interview and a slight decrease of 0.25 seconds for the last 5 minutes of the interview. The same relationship holds for the larger series of 35 patients and 30 control subjects.

For comparison the value of activity alone was calculated from the charts produced by the interaction chronograph and is presented as mean activity in seconds per minute for the total interview. The mean activity rate for the patients for the entire interview was 32.6 seconds per minute, which was slower than that for the control subjects. Both the patients and the control subjects showed a decrease in activity at low O2 (15% and below). This change, however, was greater for the patients than it was for the control subjects (Fig. 13). It was found also that subjects with high initial activity rates in air tended to show greater changes in amnesia than did those subjects whose initial rates were low.

<table>
<thead>
<tr>
<th>Differences Between Mean Activity</th>
<th>Relation Between Changes in Activity Per Minute and Changes in EEG</th>
</tr>
</thead>
<tbody>
<tr>
<td>32 Patients</td>
<td>30 Controls</td>
</tr>
<tr>
<td><strong>Critical Ratio of Differences Between Air and Low Oxygen</strong></td>
<td><strong>Correlation Between Values For Same Subjects in Air and in Low Oxygen</strong></td>
</tr>
<tr>
<td>Patients: -3.28</td>
<td>Controls: -1.60</td>
</tr>
<tr>
<td>Patients: 0.71</td>
<td>Controls: 0.80</td>
</tr>
</tbody>
</table>

Figure 13

**Relation Between Changes in Activity Per Interaction Unit and Changes in EEG**

**Figure 14**

**Figure 15**
If the change in activity during anoxia is merely a function of the initial activity rate, one would not expect the patients whose initial activity rate in air was lower to show greater changes in low oxygen. This would indicate that a second factor in determining the effect of low oxygen is the disease.

Relation Between the Electroencephalogram and Activity.—In an attempt to understand other factors which could play a role in producing the changes in activity at low oxygen, the relationship between the EEG and the activity was investigated. In a series of 15 subjects it was found that at low oxygen levels the subjects who showed the greatest decrease in activity in low oxygen showed little or no change in the EEG, whereas the subjects who showed little change in activity during low oxygen or whose activity rate was increased during low oxygen showed the greatest changes in EEG. This relationship held whether activity was measured in terms of activity per minute (Fig. 11) or activity per interaction unit (Fig. 15). This relationship, however, did not hold when the oxygen levels between 10.5 and 15% were considered. This would indicate that there is a third factor, namely the activity of the central nervous system as measured by changes in cortical potentials which relates inversely to the change in activity.

In an attempt to determine what other factors could play a rôle in the change of activity during low oxygen, a few experiments were conducted in which changes in the heart rate were measured at various levels of anoxia. These experiments indicated that the individuals whose heart rate was markedly increased during anoxia showed considerable decrease in their activity, whereas the individuals whose heart rate showed little or no increase during anoxia showed little or no change in their activity. This again would indicate a direct relationship between increase in heart rate, which is an indication of autonomic activity, and a decrease of verbal and gestural activity. Only a few of these experiments have been done to date, and conclusions are necessarily tentative. However, in a previous study (21) it was shown that intramuscular injection of adrenalin caused a decrease in word production which was associated with marked subjective feelings. The present study adds additional weight to the hypothesis that the decrease in verbal and gestural activity is associated with an increase in autonomic activity, resulting in an increased awareness of internal phenomena. This problem is at present being further investigated.

SUMMARY

1. Observations on the effect of breathing low oxygen are reported in a series of 67 patients and 42 controls, in whom changes in central nervous system activity were measured by the EEG and changes in behavior by the interaction chronogram.

2. Most subjects showed a shift in EEG to the slow frequencies during low oxygen. This was more marked and consistent when the CO₂ was less than .3%. There was no difference between patients and controls.

3. A decrease in verbal and gestural activity was found in about three-fourths of the subjects. The decrease was greater for the patients than the controls.

4. Subjects with high initial activity while breathing air showed the greatest decrease as a result of low O₂. Subjects with low activity rates in air showed slight decreases and, in many instances, an increase.

5. Subjects with marked changes in EEG tended to show an increase in activity.

6. Four factors are discussed as playing a rôle in determining the changes in activity due to low O₂.
   (a) Initial rate of activity.
   (b) Diagnosis.
   (c) Electroencephalographic changes.
   (d) Autonomic activity as measured by heart rate.
BIBLIOGRAPHY


PSYCHIATRIC AND PHYSIOLOGIC STUDIES ON
FATIGUE *

Preliminary Report

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JACOB E. FINESINGER, M.D.
MARY A. B. BRAZIER, Ph.D.
HARLEY C. SHANDS, M.D.
and
GREGORY PINCUS, D.Sc.

This is a preliminary report of investigations which have been done on fatigue and related symptoms as found in psychoneurotic patients. The general plan of the research has been, first, to analyze the symptoms of fatigue from the point of view of the subjective reactions of the patient by means of data collected in psychiatric interviews; second, to investigate the nature of fatigue in regard to its physiologic and chemical concomitants. In addition to generalized fatigue, the phenomena associated with fatigue in localized muscle groups have been studied. The first results to be presented deal with the psychiatric aspects of the problem.

Psychiatric Studies

The term fatigue has so many different meanings that some definitions are in order. By derivation and as generally used here, fatigue means a feeling of tiredness, weariness or lassitude. This is in contrast with the physiologist's use of the word to mean a reduction in output of work, or the biochemist's meaning of changes in chemical constituents in the body associated with work. The particular group of patients in which we have been most interested have been those who complain of feeling tired over long periods of time when there is found to be no obvious exertion or medical illness to account for the feelings.

Symptoms. — At the present time we have collected data from 45 patients who complained of fatigue as one of their principal symptoms. Of these 45, there are 16 about whom we have considerable detailed information, having spent from twenty to sixty hours of interview time with each one. Our knowledge about the remaining 29 is primarily of a descriptive nature and usually has been obtained during one to three interviews.

In the entire group, it has been possible to make a satisfactory diagnosis in almost every case. As one sees these diagnoses tabulated, it is striking that about 80 per cent of patients complaining of fatigue had anxiety neurosis. The remaining patients were infrequently distributed among the other diagnostic groups (table 1).

In making out a questionnaire to obtain information from a great number of persons, we tabulated every separate statement made by patients concerning the way they felt when tired. When this was finished, we found

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* From the Department of Medicine and the Department of Neurology and Psychiatry of the Harvard Medical School and the Department of Physical Medicine and the Department of Psychiatry of the Massachusetts General Hospital. This study was aided by a grant from the Baruch Committee on Physical Medicine.

* Read at the Twenty-Fourth Annual Session of the American Congress of Physical Medicine, New York, Sept. 5, 1946.
over 125 different ways of expressing their feelings when fatigued. The most striking thing about these complaints is the fact that such feelings may be referred to any organ, system or function of the body.

Thus, it appears, for instance, that these patients have difficulty in sleeping. This usually is found to mean that, although most patients think longingly of going to bed when they feel tired, upon getting to bed they find it difficult to go to sleep. In the morning it is characteristic for them to say they feel as tired as, or more tired than, they did upon going to bed. They frequently feel nauseated in the morning and may even vomit. Typically these patients feel worst in the morning and then become progressively better as the day wears on. Many feel best just before going to bed at night and may stay up till 2 or 3 a.m. for this reason.

A frequent complaint is that of difficulty in thinking clearly, inability to concentrate or a feeling of confusion. This may appear as a "cloudy feeling" in the head.

Somatic complaints are extremely numerous. Taking random ones from our list, we find blurring of vision, dizzy feelings, tightness in shoulders, back and chest, heaviness in various parts of the body, soreness here and there, nausea and so on (table 2).

<table>
<thead>
<tr>
<th>Table 1. — Psychiatric Diagnosis in 45 Fatigue Patients.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage ___________________________</td>
</tr>
<tr>
<td>Anxiety neurosis ...................................78</td>
</tr>
<tr>
<td>Hysteria .................................................... 2</td>
</tr>
<tr>
<td>Reactive depression ..................................... 9</td>
</tr>
<tr>
<td>Psychosomatic disorders .............................. 7</td>
</tr>
<tr>
<td>Psychopathic personality .............................. 4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2. — Symptoms in 45 Fatigue Patients.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per Cent _______________________________</td>
</tr>
<tr>
<td>No ambition .................................... 55</td>
</tr>
<tr>
<td>Depression ........................................ 55</td>
</tr>
<tr>
<td>Palpitation ........................................ 51</td>
</tr>
<tr>
<td>Nervousness .......................................... 51</td>
</tr>
<tr>
<td>Anorexia ............................................. 49</td>
</tr>
<tr>
<td>Irritability .......................................... 47</td>
</tr>
<tr>
<td>Headaches ............................................. 47</td>
</tr>
<tr>
<td>Weakness ............................................... 40</td>
</tr>
<tr>
<td>Confusion ............................................. 40</td>
</tr>
<tr>
<td>Insomnia ............................................... 33</td>
</tr>
</tbody>
</table>

Many are depressed in varying degrees. As a rule, those patients with relatively mild depressions complain most of fatigue and less of depressive symptoms. Several patients have described how they feel "helpless and hopeless"; other frequent adjectives are "blue," "defeated" and "inferior."

There is a considerable proportion of patients who say that when they feel tired they are irritable. The expressions used to describe this part of the symptom complex include "irritated" and "antagonistic." Among those with a military background, the complaint is apt to appear as "I get burned up" and as a result these patients sometimes "blow their top." The irritation may be suppressed; it may be expressed as "speaking with a sharp tongue" or it may even come out as violence. A few of the 10 veterans included in these 45 patients got into difficulty because of a propensity for getting into fights, especially when they had been drinking.

There are a number of statements used by patients to describe the difficulty in initiating activity. They have "no pep," "no ambition"; they want to put things off; everything "seems to be an effort" or "requires more energy" than before. Another group of complaints is closely related to those
which are familiar to every one following muscular activity. Some of these feelings are described as being “all in,” “all gone,” “worn out,” “dragged out” or “faint.” They feel “slowed up” and “drowsy.” A similar but apparently distinct set of sensations center around weakness: these patients may feel “weak as a cat”; their knees “give way” or “turn to water”; their hands may feel “nerveless.”

Questions as to the presence of anxiety symptoms elicit affirmative answers from most of our patients. They feel jumpy, jittery or nervous; they complain of sweating in the axillas and palms; they sigh and have feelings of not being able to take a full breath.

It was found that these feelings of fatigue were dependent on various situations. Rest relieves few of them, but a majority of the patients say that they feel better when doing interesting work. The movies help many; alcohol offers relief to some, particularly young men. Tobacco seems to be of help, but almost as many say it makes them feel worse. Sexual activities tend to increase the symptoms, especially in women who are frigid.

One of the most striking facts which has come to light in patients with chronic fatigue who have been intensively studied is that there are certain situations in which they suddenly feel extremely tired or weak. In some of these patients it has been possible to reproduce the feeling tone several times by discussing the same or similar incidents on different occasions. This type of investigation has led us to the conclusion that certain feeling tones are most often associated with the onset of fatigue symptoms. The two most frequent of these are feelings of being guilty of wrong-doing and feelings of being rejected or discounted by someone important to the patient.

The prominent situations leading to abrupt sensations of feeling tired have been tabulated from information obtained from 16 patients studied intensively. Since 2 patients showed two types of situation in which fatigue occurred, there are in all eighteen situations. These may be classified into “rejection” and “guilt” situations. In an attempt to class these roughly, we find that in the “guilt” group (table 3) there are three instances of guilt over sexual practices considered to be reprehensible by the patient; three instances in which the patient felt responsible for some injury to a member of her own family, and three related to marital difficulties.

In the “rejection” group, the situation is simpler (table 4); 4 of these patients had distress in connection with real or possible future rejection by a spouse; 5 had fatigue following real or fancied rejection by some one in a position of authority relative to them.

<table>
<thead>
<tr>
<th>Table 3. — Guilt Situations Precipitating Fatigue Episodes.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Masturbation; sex play with older woman</td>
</tr>
<tr>
<td>2. Memory of sex play with old man as child</td>
</tr>
<tr>
<td>3. Masturbation</td>
</tr>
<tr>
<td>4. Unkindness to murdered sister</td>
</tr>
<tr>
<td>5. Aggression toward mother</td>
</tr>
<tr>
<td>6. Feeling of contributing to mother’s illness</td>
</tr>
<tr>
<td>7. Husband’s mistress commits suicide</td>
</tr>
<tr>
<td>8. Hostility toward husband and child</td>
</tr>
<tr>
<td>9. Hostility toward husband and child</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 4. — Rejection Situations Precipitating Fatigue Episodes.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Husband philandering</td>
</tr>
<tr>
<td>2. Husband philandering</td>
</tr>
<tr>
<td>3. Possibility of fiancee’s leaving him</td>
</tr>
<tr>
<td>4. Deserted by wife</td>
</tr>
<tr>
<td>5. “Kicked upstairs” from responsible job</td>
</tr>
<tr>
<td>6. Hard work discarded by boss</td>
</tr>
<tr>
<td>7. Misunderstanding with doctor</td>
</tr>
<tr>
<td>8. Reprimand by boss</td>
</tr>
<tr>
<td>9. Turned down for job “politics”</td>
</tr>
</tbody>
</table>

The most striking findings have been: (1) the extreme variability in the patient’s feelings from day to day and hour to hour; (2) the onset of symptoms in connection with specific situations. This is illustrated in the
following summary of the case of a patient diagnosed with anxiety neurosis. This patient found relief from an unpleasant home situation in the psychiatric ward. His symptoms vanished, and he boasted of his energy. Then, following misunderstanding a statement made by his doctor which he took to mean that the doctor, too, had deserted him, he felt “burned up,” couldn’t sleep, arose the next morning feeling very tired and too nauseated to eat breakfast. Later in the day, when the situation was cleared up to his satisfaction, he at once felt much better, “in the pink,” and jumped out of bed the next morning feeling greatly refreshed by a good night’s sleep.

Physiologic and Chemical Studies

General Fatigue. — In these same patients we have done physiologic and biochemical studies during exercise tests. The first group of experiments were concerned with muscular work involving a great many muscles of the body, using a bicycle ergometer. The exercise situation was one which was designed not to carry the patient to exhaustion. A standard braking resistance was used in all tests, and the duration was constant at three minutes. The number of revolutions per minute was registered and for males was 37 r. p. m. and for females 30 r. p. m., as this was found in both instances to lead to subexhaustive work.

Blood samples were taken for determination of (1) lactic acid, (2) pyruvic acid, (3) cholinesterase and (4) glucose, before the test, immediately at completion and at three and fifteen minute intervals later. Heart rate and ventilation were recorded throughout the experiments, as well as the electroencephalogram.

Results: In both male and female patients blood lactate immediately at the end of exercise increased to a level consistently higher than that of the control group, as seen in chart 1. Another point of difference which was even more striking between the patients and controls was the maintenance of a high lactate level fifteen minutes after exercise.

Chart 1. — Effect on blood lactic acid of subexhaustive bicycle ergometer test.
Blood pyruvate levels also showed greater increase after exercise in the patient group, particularly fifteen minutes after exercise. The mean blood pyruvate increase and the per cent increase have been tabulated in table 5.

**Table 5. Three Minute Bicycle Test — Blood Pyruvate.**

<table>
<thead>
<tr>
<th></th>
<th>Number</th>
<th>Before Test, Mg. 100 cc.</th>
<th>Increase After 15 Min., Mg. 100 cc.</th>
<th>Per Cent Mg. 100 CC.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>24 M.</td>
<td>0.45</td>
<td>0.51</td>
<td>113</td>
</tr>
<tr>
<td></td>
<td>9 F.</td>
<td>0.45</td>
<td>0.27</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>33</td>
<td>0.45</td>
<td>0.39</td>
<td>87</td>
</tr>
<tr>
<td>Controls</td>
<td>15 M.</td>
<td>0.47</td>
<td>0.31</td>
<td>66</td>
</tr>
<tr>
<td></td>
<td>10 F.</td>
<td>0.66</td>
<td>0.02</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>0.55</td>
<td>0.17</td>
<td>30</td>
</tr>
</tbody>
</table>

Blood cholinesterase levels were determined before exercise, immediately after and three and fifteen minutes later. As expected, no significant variation was found in the first 4 patients and 1 control; hence these measurements were abandoned in the later cases.

The mean increase in heart rate at the end of exercise was 41 per minute in the 14 male and 4 female patients. In 11 female controls the increase was only 28.

A correlation of 0.6 was found when the increase in heart rate immediately after exercise was plotted against the increase in lactate acid fifteen minutes after exercise. This correlation suggests that the factors associated with physical fitness play a role in our results.

Ventilation was measured in 25 controls and 28 patients. Preliminary values were higher in both male and female patients than in the controls, the mean value in liters per minute 4.95 for the controls and 6.8 for the patients. Increase with exercise was essentially the same in the two groups.

The electroencephalogram was recorded for two minutes before the bicycle test and for two minutes immediately after the end of pedaling, in an attempt to discover whether any change took place as a result of this degree of exertion. The records were analyzed for the distribution of the component frequencies in order to determine whether a change in any frequency band had taken place. No change as a result of exercise was found either in the control series or in the patients. It is concluded that this degree of exertion for this period of time has no effect on the electroencephalogram.

These results of these measurements suggest that there is some physiologic variant in this group of patients as compared with the controls. This is shown most clearly by the blood lactate and heart rate increase after exercise. We are not as yet in a position to conclude whether this can be ascribed to the psychiatric state or to the condition of physical fitness.

**Local Fatigue.** — In order to study the effects of exercise upon a smaller number of muscles limited to a single extremity, a grip test was designed. This consisted in having the subject squeeze a metal-handled spring dynamometer at a constant degree of tension for a period of one minute. All subjects were able to complete the tests, as effort of this duration did not produce exhaustion. We found it necessary, however, to regulate the tension at 15 Kg. for the female and 20 Kg. for the male subjects. During this experiment action potentials were recorded by surface electrodes from the flexor muscles of the forearm on an ink-writing oscillograph equipped with an integrating instrument such that the total voltage discharge was registered.

Results: In both patients and controls a considerable increase in blood lactate was observed from samples taken immediately at the end of the test and three minutes later, the degree of increase being greater in the patient group. Males and females were separated in tabulating, as the dynamometer tension was different. We also observed that the mean voltage of the action...
potentials was consistently greater in the patient group in both sexes. The relationship between blood lactate level at the end of the test and voltage of action potentials has been diagrammatically shown in chart 2. It can be seen that the patient group apparently were less efficient in this test, as they discharged more electrical activity and produced more lactate while doing the same amount of work as the control group.

The blood pyruvate levels were determined in the same blood samples and were found to follow the same pattern as the lactate results, there being a somewhat higher level in the patients at the end of the test than in the controls.

The cholinesterase levels were measured in terms of millimols of carbon dioxide liberated per hour per liter of serum. There was no difference related to either sex, control, or patient groups.

Ulnar Nerve Stimulation. — In order to further investigate fatigue produced locally and particularly to explore the possibility of fatigue of the neuromyal junction or transmission fatigue, other experiments were set up. The ulnar nerve was stimulated electrically at the elbow by a surface electrode held in place at as nearly constant tension as possible with a spring balance electrode or by an elastic bandage. Mechanical recordings of the contraction of the wrist and fourth and fifth fingers were obtained on a kymograph. The stimulating current was that of unidirectional, square wave impulses of 0.05 millisecond duration with a frequency of 500 per second and a voltage of 49. The skin resistance was measured and always reduced to less than 5000 ohms by the use of electrode paste. This strength of current found to be that which was nearly maximal as far as sensation was concerned, but it was not always supramaximal in relation to the muscular contraction. The current was applied for a period of four minutes. Blood samples were taken from the antecubital vein immediately before the test and at the end of stimulation.

Results: The blood lactate level was observed to rise over 100 per cent immediately following stimulation (table 6).
Table 6. — Ulnar Nerve Stimulation, Four Minutes.

<table>
<thead>
<tr>
<th>Number</th>
<th>Blood Lactate — Mg./100 cc.</th>
<th>Increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 patients</td>
<td>11.1</td>
<td>13.05 = 116%</td>
</tr>
<tr>
<td>11 controls</td>
<td>9.5</td>
<td>9.8 = 103%</td>
</tr>
<tr>
<td>49 volts — 0.05 msec. square waves — 500/second.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

This increase in lactate was observed in both patient and control subjects and is of interest in view of the statements commonly found in physical therapy texts to the effect that electrical stimulation of muscles is not followed by increase in lactic acid.

Corresponding increase was noted in the blood pyruvate levels after stimulation in all subjects.

Blood cholinesterase was measured before and after stimulation but no significant changes were observed. The mean resting values ranged between 86 and 121 millimols of carbon dioxide liberated per hour per liter of serum. At the end of stimulation the values varied between 89 and 122 millimols.

These results have given no indication of a defect of neuromuscular transmission as far as chemical studies are concerned. In some subjects muscles gradually relaxed, although the stimulation was continued, but because of certain technical difficulties in stimulation we could not be convinced that this was true transmission fatigue.

Endocrinologic Studies

An attempt was made to study the role of adrenal cortex secretion in patients with fatigue. It has been shown that an adrenal cortical hormone, presumably 11-oxygenated corticosteroid, regulates the production of circulating lymphocytes. In a series of 21 patients diurnal rhythms were established for a period of three days by counting the absolute number of circulating lymphocytes at specific periods during the day. On subsequent days the patients and controls were subjected to stress situations lasting for a period of one hour between 2 and 3 p.m., when normally a slight rise is expected. The stress situations consisted in exposure to cold for a period of one hour, inhalation of low oxygen mixtures, performance on a pursuit meter and a stress interview during which topics disturbing to the patient were discussed.

The diurnal rhythms showed the morning decrease and afternoon rise, which have been previously described, but several of the patients had unusually low absolute counts. About half the patients showed a marked drop in lymphocyte count immediately after the various stress situations. Others showed a delayed response in that the decrease in lymphocytes did not occur until about one hour later. In about one-third of the patients there was no change or a slight rise in lymphocytes.

These results suggest that most of the patients in this group react to the stress situation by an increased production of 11-oxygenated corticosteroid, which in turn decreases the circulating lymphocytes.

The breakdown of circulating lymphocytes resulted in an increase in excretion of uric acid in the urine without change in the blood level.

Summary

A series of psychiatric, chemical and physiologic studies were done on 45 psychoneurotic patients complaining of fatigue and on a comparable control group.

The clinical material indicated a great variability in the symptoms, but 80 per cent of the patients were given diagnosis of anxiety neurosis.

In 16 of these patients studied intensively, specific situations associated with feeling tones of guilt and rejection preceded the onset of fatigue episodes.

The blood lactate and pyruvic acid showed a significant increase following an exercise test on a bicycle ergometer, which rise was considerably greater in the patients and was maintained for a longer period of time.

There was a correlation of 0.6 between the blood lactate and the heart rate increase after exercise.

A grip test for local fatigue showed a greater increase in action potentials and lactic acid production in the patients.

Blood lactate acid level increased 100 per cent following four minute stimulation of the ulnar nerve with a tetanizing current.

Most of the patients showed a decrease in circulating lymphocytes resulting from a variety of stress situations of one hour's duration, which is ascribed to increased adrenal cortex activity.
PHYSIOLOGICAL MECHANISMS UNDERLYING THE ELECTRICAL ACTIVITY OF THE BRAIN *

BY

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From the Department of Neurology and Psychiatry, Harvard Medical School, and the Department of Psychiatry and the Electro-encephalographic Laboratory of the Massachusetts General Hospital, Boston †

(RECEIVED JANUARY 8, 1948)

Eighteen years after the first detailed work appeared on the electrical activity of the brain (Berger, 1929) we have still no adequate understanding of its mechanism. There have been many hypotheses, and to review all the supportive data for each would be too space-consuming, but since they are described in the journals a reference list may suffice. For example, there is the evidence, based on the observed behaviour of the EEG with rising body temperature and with metabolic stimulants and depressants (Hoagland, 1936), for the dependence of the electrical rhythmicity on continuous steady-state chemical events within the cortical cells. This hypothesis attempts only an explanation of the resting rhythm, and Hoagland (1944) states that the findings should not be interpreted as meaning that the only modifiers of brain wave frequencies are necessarily changes in cell respiration. There is the hypothesis of Gerard (1941) that the EEG is a rhythmic variation of a somatic potential, demonstrated as a steady DC potential difference between the pia, where the axones end, and the area near the ventricle where cells lie (in the frog’s brain). Gibbs and others (1940) suggested that the electrical activity of the cortex is a manifestation of the activity of a great number of chemical oscillators having different natural periods.

The hypothesis that interplay between the deeper centres and the cortex is responsible for the alpha rhythm grows out of the work of Bishop (1933, 1936), of Lorente de Nó (1934, 1935), and of Dusser de Barenne and McCulloch (1938). It was suggested that the cortical cells are in continuous interactivity with the thalamic cells; that each thalamic neurone projects to many cortical cells, and thus, by recurrent paths through their axones, interacts with great numbers of cells in the thalamus; and that the alpha rhythm may be determined by the delay in these reverberating circuits, or in other words, by the number of synapses involved. However, evidence has been produced by Morison and Dempsey (Morison and Dempsey, 1942; Dempsey and Morison, 1942) that the alpha rhythm of the resting cortex is not dependent on impulses travelling along the primary projection fibres from the recognized thalamic nuclei, and this opens the possibility for transmission by separate neuronal pathways of non-specific afferents from undifferentiated thalamic nuclei (Dempsey and Morison, 1942; McCulloch, 1947). There are data from Fortuyn and Jasper’s experiments on cats which show that rhythmic potentials in the entire cortex can be co-ordinated from a very restricted thalamic area of less than 2 mm. in diameter (Jasper and others, 1946; Fortuyn and Jasper, 1947). It has been suggested (Dempsey and Morison, 1942) that this rhythm of 8 to 12 per second activity may result from constant bombardment by subliminal impulses which sum periodically in the cortex rather than a reverberation in a closed circuit.

There is reason to doubt that this mechanism operates for the frequencies faster than the alpha range, since these persist after section of the thalamic radiations (Bishop, 1933; Chatfield and Dempsey, 1942), and therefore presumably represent intrinsic cortical activity.

Later work by Morison threw more doubt on the dependence on reverberation involving cortico-thalamic connexions, since an 8-12 per second...
ELECTRICAL ACTIVITY OF THE BRAIN

rhythm could be recorded from the thalamus for as long as three days after bilateral decortication (Morison and Bassett, 1945; Morison and others, 1943).

Most of these hypotheses have assumed as a premiss that the electrical activity in the brain travels only along an axonal or dendritic pathway, but, as Adrian (1947) has emphasized, the possibility that neurones may influence one another not only by impulses in neuronal pathways but by electrical field effects. Such a mechanism in the development of continued rhythmic activity has been demonstrated in isolated neurones, in the spinal cord, and in the brain.

From observations on isolated nerve preparations it has been shown that the action potential of an active portion of nerve can influence a resting portion across an imposed block (Hodgkin, 1937; Lorenzo de Nó, 1939; Blair and Erlanger, 1939), and that in certain circumstances activity in one nerve fibre can affect adjacent ones (Hoagland, 1933; Katz and Schmitt, 1940). Bremer's (1947) work on spinal cord discharges, in which he found that synchronized beats could be maintained in two adjacent segments although all neuronal connexion between them was severed by complete transection of the cord, supports the concept of a synchronization maintained by electrical spread in the absence of fibre connexions. And in the brain, Libet and Gerard's (1938) finding that after complete transection one half of a frog's brain could influence the beat of the other half, demonstrates a spread of excitation in the absence of any fibre connexion. These same workers (Gerard, 1941; Libet and Gerard, 1938 and 1939; Gerard and Libet, 1940) have demonstrated that the cortical rhythms of the frog's brain can persist when all synaptic transmission has been blocked by nicotine. In this context O'Leary's (1944) reminder that we are only the uncovering of more facts, and it is probable that each will be found to play some part in contributing to the final explanation. It is not suggested that experiments in human physiology

are likely to give the final proof for any hypothesis of a mechanism so complex, but, since any such hypothesis needs to cover the observed data of the EEG in man, perhaps human experiment may yield evidence of a supportive nature.

The Present Study

In the present paper the results of three types of experiment on the human subject will be examined with such an object in view. The experimental data consist of studies of the effect of anoxia, of hypoglycaemia, and of pentothal anaesthesia on the wave frequencies in the electro-encephalogram of the human subject.

ANOXIA

In the course of several years' work on the effect of anoxia (or, to be more exact, of hypoxia) on man we have had plentiful opportunity to confirm the original observations of Berger (1934), and of many other workers since that time (Bremer and Thomas, 1936; Davis and others, 1938; Lennox and others, 1938), that oxygen lack causes the appearance of slow waves in the EEG. Sometimes the change in the EEG trace is visible in the record on inspection by the unaided eye, but the finer developments of this change can better be studied by automatic analysis of the wave complex, since the presence of slower frequencies may sometimes be masked by more prominent waves of higher amplitude. In the present work an electronic analyser of the type designed by Walter has been used.* For a full description of this technique the original publication should be consulted (Baldock and Walter, 1946).

The type of record obtained is seen in Fig. 1. For the sake of simplicity only the EEG trace which is being automatically analysed is reproduced here, although recordings were also made from many parts of the head by a Grass inkwriting oscillograph. The tracing illustrated was recorded from two electrodes, one on the occipital region and one on the parietal region of a normal man who had in this area a strong alpha focus which blocked to a visual stimulus. Throughout this report the alpha band will be defined as frequencies of 8 to 13 cycles per second. Below the EEG is seen the heart rate recording, and below this the frequency analysis of

* This instrument consists of two banks of 24 oscillators, each designed to resonate to a specific frequency. A resonating circuit is available for each of the usual EEG frequencies, 1-5 cycles per second to 30 cycles per second, and each resonator is connected to an integrating circuit and storage condenser. Every 10 seconds a mechanical scanner discharges these storage condensers in turn through the circuit of a recording pen which gives a deflection at each discharge, the height of the deflection being a function of the activity at that frequency. By the device of having a suitably longer pen for the analyser's trace, this can be written immediately over that part of the original EEG of which it is the analysis. As one bank of storage condensers is discharging, the second is charging, so that a continuous analysis in epochs of 10 seconds each is made possible throughout the whole period of the EEG recording.
the 10-second strip of EEG shown here. The height of the peaks in the analyser's trace is a function of the amount of activity at each frequency, a very small pip (approximately equal to the height of the calibration mark for the EEG on the right of the illustration) representing the baseline for each frequency when no signal is being received. The EEG shows a slowing at the level of reduced oxygen as compared with that in air, and the analysis shows a shift of the alpha activity from a predominantly 11 and 10 cycle rhythm, through a stage at 10 and 9 after 13 minutes of low oxygen, to 8 and 9 cycles at 19 minutes and finally to 8 and 7. It will be noticed that the heart rate also has changed, having accelerated from 66 to 90. His capillary blood sugar level at the time of the test was 120 mg. per 100 c.cm.

Such an effect as is shown in Fig. 1 is typical when breathing for a short time a gas mixture moderately low in oxygen content. In a series of some 150 experiments on subjects examined in an anoxia chamber from which the exhaled carbon dioxide was removed, and a further series of 50 in which a mask with a one-way valve was worn for the administration of low oxygen, we have found essentially the same type of response. The latter part of this series has been examined by automatic analysis and we have been interested to study the results in the light of the various hypotheses briefly outlined at the beginning of this paper.

This gradual shift of the alpha activity, with the dominant frequency of the alpha band moving step by step to the slower side, confirms our previous results found by manual analysis, and also those of Engel and others (1944). It differs in detail from the case analysed by the method of Grass and Gibbs (1938) illustrated by Gibbs and others (1940), where the dominant peak in the alpha band remained at the same frequency (although dropping in height) as long as consciousness was maintained, while the energy in the frequencies slower than alpha increased markedly.

Of course, taking isolated moments in time such as are shown in Fig. 1 does not tell us very much about the way the slow waves have developed, and it is of interest to know whether they develop as a gradual deceleration of the normal synchronized beat, such as would be expected were the rate to have a direct relationship with the metabolic activity of cortical cells, or whether they appear as discrete slow frequencies extraneous to the alpha band originating in other, perhaps sub-cortical, cell groups and rising in voltage until they mask persistent alpha.

In Fig. 2 has been plotted the amplitude of the peak (expressed as a percentage of the maximum possible deflection) at each frequency of the analyser's trace as it was found by measurement at approximately one minute intervals throughout the whole experiment in this same subject. When plotted in this way the highest peaks, that is, the frequencies at which there is most activity, are seen to be at 11, 10, and 8 cycles per second in the baseline record, with no significant activity slower than 9 per second. The breathing of 8.5 per cent. oxygen begins at the first vertical line and continues for nearly thirty minutes to the next vertical line. As this period of anoxia progresses there is a slow fall in the 12, 11, and 10 peaks, with an initial increase in 9 cycles per second which later falls as 8 cycles per second activity increases and the peaks in the slower frequency band become more prominent. The heavy dots indicate the highest peak at each minute step, that is, the dominant frequency at that time, and if we follow this through the whole period we see it decelerate gradually from 11 cycles per second through 10 and 9 to 8, and finally to 7 and 6 cycles per second. All activity slower than 9 cycles per second disappears with the first few breaths of air.

In Fig. 3 an experiment on another normal subject in the anoxia chamber has been plotted in a similar manner. The highest peaks during the baseline period in air in this case are 11, 12, and 10 with lesser peaks at 9 and 8, and minimal activity below 8 cycles per second. The breathing of 8.5 per cent. oxygen begins at the first vertical line, and in this case continues for only fifteen minutes. As this period of anoxia progresses there is a slow fall in the 12, 11, 10, and 9 cycle peaks, little change at 8 cycles, and a marked rise in the frequencies slower than 8. The dominant frequency at each minute step (again indicated by the heavy dots) falls from 12 through the intermediate frequencies to 6 and 5 cycles per second. There was no significant activity slower than 3 cycles at any time in this record. In the last minute of anoxia there is little evidence of persistent alpha, but it returns with spectacular rapidity with the first few breaths of air, and there is a simultaneous disappearance of the slow activity.

Looked at in this way the data are suggestive of a slow deceleration of the synchronized beat of the cell group under observation rather than an eruption of slow waves among persistent alpha activity, but there are some assumptions here the validity of which need to be established by experiment. One is that the change in the relative heights of the peaks represents a change in activity. This arises from our ignorance as to whether a decrease in the prominence of the alpha band in an original EEG tracing represents a decrease in electrical
activity or whether it indicates a lesser degree of synchronization of the same amount of activity. Only experiment can decide the issue. Another question is whether the observations charted here are indices of the activity of a given synchronised cell group rather than a changing interplay of many independent sources each contributing its own frequencies to the composite picture. The view that Fig. 1 represents a deceleration of the rate of beat of a cell-group entity is supported by the fact that opening the eyes, which blocks the activity in the alpha band, produced blocking of the slower frequencies at 6, 7, and 8 cycles per second later in the experiment when the effect of anoxia was operating. This problem can be further met by making use of interchannel analysis (as described by Baldock and Walter, 1946). By this method only those potential changes which are out-of-phase in the two channels reach the analyser. By searching with electrodes on the head, a position can be found for the electrode which is common to the two channels, where the analysis shows a strong alpha rhythm, out-of-phase in the two channels and blocked by visual stimuli. Presumably such a positioning of the electrode then approximates very closely to an alpha focus. This method has been used in all the later work.

It is known that the cortex is more vulnerable to anoxia than the subcortical and phylogenetically older areas of the brain (Heymans and others, 1934; Sugar and Gerard, 1938) and the EEG data just discussed might well point to a slackening in metabolic rate of cortical cell respiration, but it might also indicate a decreasingly influential role of the cortex in a cortico-thalamic interplay. We have not carried any of our experiments on human subjects to an oxygen level low enough for consciousness to be lost as a result of anoxic anoxia. We have had one subject who, in a sitting position, fainted after some minutes of breathing a mixture low in oxygen although the oxygen content did not go below 10.5 per cent. and his capillary blood sugar...
level was 113 mg. per 100 c.cm. Here presumably
anoxemia produces a more sudden oxygen lack (as
well as a glucose lack and accumulation of carbon
dioxide) due to the insufficient blood flow, in
contrast to the slowly decreasing supply of oxy-
hemoglobin in the circulation in anoxic anoxia.
And if loss of consciousness indicates a depression
of the cortex so that thalamo-cortico-thalamic
circuits are now disrupted, the EEG might be
expected to record waves originating in deeper
centres.

The EEG findings in this case are shown in Fig. 4.
Here the more exact localization of an alpha focus was
made by interchannel analysis as described above. In
this experiment the recording paper was being run at
half speed to save paper. Again for the sake of clarity
only the original tracings of which the interchannel
analysis is being made are reproduced here, although
simultaneous recordings were also made from other parts
of the head. As would be expected at this blood sugar
level and with such a mild degree of oxygen lack, there
was little change in the EEG except for some occasional
5 and 6 per second activity. At the twelfth minute there
was a transient increase in the height of some of the
alpha peaks and the appearance of some 4 to 7 cycle
activity; at this time the subject began to show marked
pallor and profuse sweating, and his pulse became weak
and slow. He complained of nausea, and shortly afterwards (thirteen and a half minutes after he began
to breathe the mixture low in oxygen) delta waves
appeared in the record and he fainted. He recovered
within one minute and the EEG promptly returned to
normal.

Thus, in this record, steady activity of alpha
frequency is suddenly broken by the eruption of
slow waves as the subject faints. This effect is
seen more clearly in Fig. 5, where the height of the peaks is charted by the method used in Fig. 2.
In this case the delta waves appear to replace the
alpha during the short period of unconsciousness.
This change in the EEG on fainting closely resembles
that described by Romano and Engel (1945) in
vasodepressor syncope.

HYPOGLYCEMIA

Similar methods have been applied to the study
of data on subjects whose blood sugar level has
been artificially lowered by insulin, since hypo-
glycemia is known to affect the EEG (Berger, 1937;
Hoagland and others, 1937; Lennox and others,
1938; Gibbs and others, 1940; Brazier and
Finesinger, 1944; Heppenstall, 1944; Engel and
others, 1944). From a large series of subjects so
treated, Fig. 6 is representative of the effect found.
In this case the electrode placements and connexions
were those indicated in the illustration, with
localization of an alpha focus made by interchannel
analysis; the insulin dosage was 25 units.

In the case shown in Fig. 6 the occipital electrode
common to the second and third channels was placed in
such a position that the recorded alpha activity was out
of phase between them. In this illustration the EEG is
seen at three levels of blood sugar—98, 60, and 52 mg.
per 100 c.cm. The shift of activity from frequencies
centering round 11 cycles per second to 7 cycles is clearly
seen. At the time of the second EEG sample shown here,
43 minutes after the intravenous injection of insulin,
there was no sweating, no subjective sensation, and the
heart rate was 88. Sixty-three minutes after the injection
the heart rate had dropped to 64 and the subject was

![Fig. 2.—Progression of EEG changes in anoxia. Chart depicting the height of the peak at each frequency of the analyser's trace from 5 to 12 c/s during a period of anoxia. With the exception of four and a half minutes near the beginning of the experiment the plots have been made at approximately one-minute intervals. The period of anoxia began at the first vertical line and ended at the second. The heavy dots indicate the dominant frequencies at each given moment in time. This is the same experiment and the same electro-encephalogram as that shown in Fig. 1.](image-url)
sweating profusely. After this he began to recover spontaneously and the EEG also showed some improvement. On the intravenous injection of 50 g. of glucose the clinical signs disappeared almost immediately but the EEG did not return so rapidly to normal.

We have found this delay in recovery of the alpha band in all our cases with mild hypoglycemia induced by insulin; it is in sharp contrast to the behaviour of delta waves accompanying insulin coma, which disappear promptly on injection of glucose. The frequency shift in the alpha band does not bear a direct relationship to the sugar level of the circulating blood, and persists long after the autonomic disturbances have ceased. This delay in return of normal cortical activity after intravenous administration of sugar is similar to that found in dogs with insulin hypoglycemia (Hoagland and others, 1939). It is interesting to note that the individual whose EEG is shown in Fig. 6 had fast activity in the 20 to 30 cycles per second band and that, in contrast to the alpha band, this did not slow as the blood sugar level fell.

In contrast to the effect of mild anoxia where the slowing of the EEG is accompanied by an increase in heart rate, in the insulin effect there is a slowing of the heart rate as well as of the EEG. When the data from the whole experiment are plotted by the method already used in the anoxia experiments the result, given in Fig. 7, shows the same gradual deceleration of rate. This chart also illustrates the incipient spontaneous recovery and the delayed response to glucose injection: 15 minutes after the glucose was given, there is very little activity at 11, 12, and 13 cycles per second although the blood sugar at this time was 232 mg. per 100 c.cm. Although this subject had a less regular EEG pattern than those whose records are charted in Figs. 2, 3, and 5, with more minute-to-minute variation, the general trend shows through quite clearly.

At the beginning most of the activity was at 11, 12, and 13 cycles per second. As the insulin began to take effect 9 and 10 cycles per second activity increased, until finally almost all these frequencies were replaced by 6, 7, and 8 cycle waves. At about seventy minutes after the injection the effect of the insulin spontaneously began to wear off, and at eighty minutes the recovery was accelerated by the intravenous injection of glucose.

This gradual shifting of the activity down the frequency range towards the slow side confirms our
previously findings by manual analysis (Brazier and others, 1944), and also those of Engel and others (1944), who used a different form of manual analysis. It is also in agreement with the case illustrated by Gibbs and others (1940) depicting the change found in the Grass frequency spectrum with a similarly small lowering of the blood sugar level (in their case from 105 to 74 mg. per 100 c.cm.). Their illustration shows a shift of the dominant alpha peak from 10 to 9 cycles, with a rise in the amplitude of the 8 and 7 cycle peaks. The result is, however, at variance with these authors' statement that “there is no definite shift in peaks until the sugar level falls below 29 mg. per 100 c.cm.”

The mode of development of the slow activity resulting from mild anoxia and from mild hypoglycaemia is so similar that it suggests a similar underlying mechanism, one in which a cell-group entity is responsible for the effects seen. Opening the eyes has the same effect on the slow activity in hypoglycaemia as in anoxia, for the activity centering around 7 cycles per second at the low blood sugar level is blocked by opening the eyes, just as is the original alpha band before the insulin takes effect. The mode of appearance of slow waves in the record of the subject who fainted is, however, strikingly different. Here, with loss of consciousness, there is a momentary loss of all alpha frequencies and replacement by delta waves. In the case illustrated in Figs. 4 and 5 the recording was being made from an alpha focus localized by phase-reversal and interchannel analysis, and such a result suggests that the cell group responsible for the alpha activity at this focus has, on loss of...
consciousness, become disorganized or depressed in such a way as to release slower rhythms from deeper structures.

**PENTOTHAL ANAESTHESIA**

We have been interested to study by similar methods of analysis the EEG changes accompanying loss of consciousness induced by anesthetic drugs. We have in the first place used sodium pentothal, since the mode of action of barbiturates on the brain has been worked out in more chemical detail than that of many other anaesthetics. The procedure followed has been to give the pentothal by intravenous injection of a 2 per cent. solution given at a rate calculated to induce third-stage anaesthesia within about three minutes. In the course of an investigation on the mode of action of pentothal we have recorded electro-encephalograms in 112 experiments on 75 subjects. We have found the EEG changes to be strikingly consistent: in every case the first change is the appearance of fast activity, usually of rather high voltage, followed later by slow waves (Brazier and others, 1945). The fast activity first appears during the first stage of anaesthesia and is not seen while the subject is truly alert but only when there is some degree of clouding or euphoria. In most cases the fast waves increase in amount as the first stage of anaesthesia progresses.

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**Fig. 5.—Progression of EEG changes during a faint in 10.5 per cent. oxygen.** Chart showing the height of the peak at each frequency of the analyser’s trace from 2 to 12 c/s in an EEG recorded during a short period of mild oxygen lack, at the end of which the subject fainted. With the exception of a two-minute period beginning at the ninth minute, during which the subject was being interrogated, the plots have been made at half-minute intervals. This is the same individual and the same electroencephalogram as that shown in Fig. 4.
Analysis shows them to have a frequency usually of 24 to 27 cycles per second.

The second change regularly occurs when the subject becomes unconscious, that is, when he loses contact with his environment and enters the second stage of anaesthesia. Concurrently with this loss of consciousness the fast waves in the EEG disappear and are supplanted by slow waves.

One example of these changes is seen in Fig. 8. In this illustration EEG recordings are shown from three parts of the head, as indicated in the legend accompanying the figure, and the simultaneous analysis of the strong alpha focus in the third channel is superimposed. During the first stage of anaesthesia, while this subject was euphoric, activity was mostly in the fast frequencies from 20 to 27 cycles per second. When he became unconscious, bands of slow waves centering around 2.5 and 6 cycles per second dominated the record.

In this individual the alpha frequencies have been almost extinguished, but it is common to find these persisting even in the second plane of the third stage of anaesthesia. An example is shown in Fig. 9. In this illustration, for clarity only the EEG tracing which is being analysed is reproduced. It is from an alpha focus in the parieto-occipital region. The disappearance of the fast waves when the delta and slow frequencies come in is again seen and the persistence of alpha frequencies is marked.

To illustrate more clearly the sequence of changes in EEG frequencies which accompany shifting levels of consciousness in pentothal anaesthesia a different method of charting has been used. This is seen in the analysis of an alpha focus in another EEG given in Fig. 10. The chart reads from top to bottom, and the width of the white band indicates the spread of frequencies found in the EEG by automatic analysis, plotted every half-minute throughout the whole experiment. The black spots
represent the actual frequencies present as indicated on the abscissa, and the larger black dot the dominant frequency of each recorded sample. The column on the right indicates the levels of anaesthesia from its induction to the second plane of the third stage, and then the gradual return to a normal state of consciousness.

There are certain quite striking data to be seen in this chart. The development of the fast frequencies in the EEG begins during the first stage, when the cortex is still functioning and when the subject is still conscious. These abnormal fast frequencies are not found when the subject is truly alert, but, as noted above, are evident only when there is some degree of clouding or euphoria. Up to this point all activity in the EEG is in the alpha range. The coincidence of loss of consciousness and the first appearance of slow waves is dramatic, and the fast activity is gone at the same moment. It will be noted that at no time are alpha frequencies absent from the record, although in these cases, when the subject is unconscious, lifting the lids and shining a light directly into the eyes does not block out the activity in the alpha band.

In all cases on emergence from pentothal anaesthesia fast activity returns some time before the slow waves disappear. Neither the EEG changes nor the clinical signs associated with the various planes and stages of anaesthesia are as clear during emergence as they are during induction.

The distribution of frequencies on loss of consciousness from pentothal is different from that found in our record of the subject who fainted, and whose record has been described above. When the EEG frequencies of his record are plotted by the method used in Fig. 10, the distribution is found to be almost entirely within the alpha band until shortly before he faints. Some 4 to 7 cycles per second then appear in the record, and as he faints the alpha disappears for the first time and delta

Fig. 7.—Progression of EEG changes in hypoglycaemia. Chart depicting the amplitude of the peak at each frequency of the analyser's trace from 6 to 13 c/s from minute to minute in an EEG recorded during and after the intravenous injection of insulin. This is the same experiment and the same electro-encephalogram as that shown in Fig. 6.
waves replace it (Fig. 11). The faint lasts less than a minute; on recovery alpha frequencies return and the delta disappears, but a slow band of activity between 4 and 7 cycles per second persists. EEG recording could not be continued for more than a minute following recovery, because of the desirability of moving the subject. At no time was there any EEG activity at frequencies faster than 13 cycles per second.

Discussion
The striking similarity between the effect on EEG frequencies of inadequate supplies of oxygen and of sugar is understandable on a basis relating these potentials to brain respiration rates, since these two substances play the major roles in cerebral metabolism. That lack of either produces the same effect is in keeping with several known facts, such as that cerebral oxygen uptake is decreased at low levels of blood sugar and increased on administration of sugar (Himwich and others, 1939), and that the action of hypoglycaemia on the EEG can be offset by the inhalation of pure oxygen (Gellhorn and Kessler, 1942).

The data reported here on oxygen lack and on hypoglycaemia at levels where consciousness is retained show a progressive slowing of the alpha rhythm suggestive of a deceleration of the synchronized beat of a uniform neurone population. This view is further supported by the observation that opening the eyes blocks the observed activity in the EEG even when this has slowed to frequencies outside the alpha band. Such observations would be covered by the hypothesis that there is a correlation between the rate of metabolism in the intrinsic cells of the cortex and the relative alpha frequency.
That the cortical cells are likely to be implicated before the thalamic nuclei is suggested by the work of, among others, Sugar and Gerard (1938), who, in a comparative study of various regions of the brain (in cats), established that the cortex was more vulnerable to anoxia than the thalamus, and that this paralleled the oxygen requirements determined directly by Dixon and Meyer (1936).

Interpreted in terms of reverberation in thalamocortical circuits one would need to consider not only the thalamic and cortical cell bodies, but the axones and synapses in the neurone chains. Synaptic conduction has proved to be very resistant to anoxia, at least as much so as fibre conduction (Bronk and others, 1938). From studies of fibre conduction in peripheral nerve it is known that the spike potential which is associated with the passage of the nerve impulse is extremely stable to changes in metabolic environment; it is the afterpotentials which are affected by anoxia, and, as Erlanger and Gasser (1937) have demonstrated, a nerve can be brought by mild asphyxia to a state in which it produces good single spikes but poor negative afterpotentials so that the preparedness of the fibre to receive repetitive impulses is impaired. Such an impairment would clearly affect any process involving the summation of trains of action potentials to produce waves of alpha frequency. Similar conditions apply to the cell bodies: any mechanism relying on summation of repetitive stimuli would result in a rate of discharge dependent not only on the frequency of these impulses but on the rate of oxidative recovery in the neurones under bombardment. Bartley and Bishop (1933), in their original work on responses of the optic cortex, expressed the opinion that cortical cells play a more dominant role than the fibres in the electrical activity. They based this not only on the vulnerability of the cortical potentials to degrees of anemia and anesthesia to which fibres would be impervious,
but also on the magnitude of the potentials recorded, which they thought too great to be accounted for by the summation of fibre potentials in a tissue environment found by them to act as a shunt.

Turning back to the data reported here, one finding would be at variance with this line of interpretation. In the one case illustrated in Fig. 6 there is some activity of beta frequency; unlike the alpha activity present in the same record this does not slacken in rate as the blood sugar falls, an observation which is difficult to reconcile with the theory that the cortical cell plays the dominant role in frequency determination if these beta frequencies are to be considered as representing intrinsic cortical activity (Chatfield and Dempsey, 1942). However, this is an observation on a single individual and need not be given importance until confirmed.

The data from the pentothal studies are more complex. From biochemical studies of the metabolism of glucose by brain slices the sequence has been found to progress through pyruvate, lactate, glutarate, and other metabolites to oxalacetate. At each step two hydrogen atoms are detached by the enzyme action of dehydrogenases. It has been clearly demonstrated *in vitro* (Quastel, 1939) that the inhibitory action of barbiturates on the oxidation by the brain of glucose, lactate, and pyruvate is by the inactivation of this dehydrogenase activity. On this basis it could be postulated that the initial change to fast frequencies could be due to increased intracellular acidity caused by accumulation of unoxidized acid metabolites (for it is known that lowering the $pH$ of blood raises the frequency of the alpha rhythm). If this were the mechanism it would appear that a point is reached as the depth of anesthesia progresses at which the initial effect due to the accumulation of acid metabolites is overwhelmed by the second effect due to the slowing up of the principal chemical reaction caused by the accumulation of its metabolites.

If, on the other hand, the rhythm of the EEG were dependent on reverberation in thalamo-cortical
circuits, the two stages of EEG change might represent two loci of attack by the drug. The studies of Etsten and Himwich (1946) have demonstrated the pattern of pentothal anaesthesia to be a descending depression of cerebral oxidations starting with the cerebral hemispheres and progressing down to the lower parts of the brain. During the first stage of anaesthesia (when the EEG shows fast frequencies) there is slight depression of the cortex but it is still the controlling centre. The cortical cells would therefore presumably still be active in any thalamo-cortical circuit. When the subject loses consciousness the cortex has become suppressed and predominant control is by the subcortex. It is at this stage, when the thalamic levels presumably take control, that the slow waves appear in the EEG.

The possibility that the loss of consciousness in pentothal anaesthesia is due to the blocking of afferent impulses from the periphery rather than to a depression of the cortex needs also to be considered. It has been noted above that shining a light into the eyes of subjects under pentothal anaesthesia does not block any EEG rhythms although some are usually of the frequencies defined as alpha (8 to 13 cycles per second). Such a concept would introduce the picture of a cortex isolated by the anaesthetic rather than depressed by it. A different mechanism has been advanced by Brooks...
and Eccles (1947) as an extrapolation of their theory of inhibition, namely that narcotics would, by depressing the excitation in the Golgi cells, augment the inhibition, and that lowered cortical activity due to deprivation of incoming sensory impulses would convert excitatory Golgi cells into inhibitors.

Clearly more data are needed. More cannot be said at the present stage of our knowledge. Human electro-encephalography alone cannot answer all the questions, but its role should not be minimized since it is a study of the brain in its natural environment. And it can give some answers: for example, the data from the experiments with mild hypoxia and hypoglycemia demonstrate that at levels where there is no loss of consciousness the slow activity in the EEG is not a masking of persistent alpha by the eruption of slow activity. The data are evidence for a unitary effect, for a progression of frequency changes in the same neurone population, although the anatomical identification of these units cannot be made from experiments of this nature.

In summary, the data reported here are consistent with a postulate that the alpha rhythm results from the repetitive action of cells in neurone chains, that the rate can be modified within certain limits by metabolic changes in the respiration of cortical cells, that it can be disrupted by any agent which inactivates a link in the chain, and that it is thrown out of synchrony by the arrival of action potentials originating as sensory impulses.

Summary

The results are reported of continuous automatic frequency analysis of electro-encephalograms recorded from human subjects throughout periods of: (1) mild hypoxia without loss of consciousness; (2) mild hypoglycemia without loss of consciousness; (3) loss of consciousness induced by pentothal anesthesia; (4) loss of consciousness occurring briefly in one case of fainting.

The data are reviewed in the light of existing hypotheses as to physiological mechanisms, and evidence is presented to show that the observed frequency changes caused by oxygen lack and low blood sugar level are changes in the same neuronal population rather than a replacement by activity from other cell units. The changes in pentothal anesthesia are more complex and are discussed in comparison with those found in loss of consciousness in the absence of the drug.

The data reported here have been accumulated during the course of several studies in progress in Dr. Stanley Cobb's Department at the Massachusetts General Hospital. The results are the outcome of the collaboration of a team of workers to whom the author is indebted. She especially wishes to thank Dr. J. E. Finesinger and Dr. H. H. W. Miles of the Department of Psychiatry, Dr. J. H. Tucci of the Department of Anesthesia, and Dr. R. S. Schwab of the Electro-encephalographic Laboratory. Miss M. N. Gray, Mrs. G. Lothrop, and Mr. J. U. Casby have given invaluable technical help.

References

— (1934). Ibid., 102, 538.
ELECTRICAL ACTIVITY OF THE BRAIN


Since we have no real understanding of what takes place during anesthesia (1–6), anything which promises to throw some light on this process must be examined with care (7, 24). The suggestion has been made that anesthesia occurs as the result of diminished oxidation in brain tissue with a consequent loss of the energy normally available for the brain’s energy requirements (8, 9). This inhibition of both the glucose and pyruvate metabolism in the brain cells seems to be localized in certain areas owing perhaps to the differential distribution of barbiturates in brain tissue (10). This localized decrease of activity would have little effect on the oxygen consumption of the brain as a whole (11).

A major finding has been that the oxidation of succinic acid, an intermediary step in the metabolic cleavage of sugars, is not greatly affected by the barbiturates (8). It is also well known that other than the barbiturates, certain drugs such as chloretone, urethane, scopolamine and diphenyloxazolidinedione (an experimental drug chemically similar to the barbiturates) are also specific depressants of oxidation in that they will decrease the oxidation of glucose and pyruvate at levels of concentration that do not affect succinate (12).

According to Meyerhof, the energy derived from these oxidative steps in the metabolism of glucose is collected by and into certain phosphate groups which act as “paymasters” for these reactions as well as storehouses (9). Szent-Gyorgyi demonstrated the presence of certain four-carbon acids in oxidation, i.e., succinic, fumaric, malic, and oxaloacetic acids (13). To these Krebs added citric, glutaric, and cis-aconitic acids. These are the enzymes through which 70 per cent of
cellular respiration occurs; the entire system is called the "citric acid cycle" (10, 14).

Each step in the oxidation of glucose involves the passage of electron energy as well as the transfer of two hydrogen atoms to an oxygen acceptor (15). This process has been schematized in figure 1. These steps are facilitated and catalyzed by an important enzyme, diphosphopyridine nucleotide, more commonly known as "DPN" (16). As the two hydrogen atoms leave the "flow line" in their travel to the oxygen acceptor, they are intercepted three or four times by certain chemical devices which, according to Lipmann, transform their electron energy into the phosphate bonds. These devices or "transformers" are at the first levels the pyridines, at the next the flavoproteins and the cytochrome system last (17, 18) (figure 2). It is thought that the greatest inhibiting action of the barbiturates occurs rather specifically at or near the flavoprotein level (19).

Recent work on the effects of oxygen at high tensions on the oxidation of carbohydrates has demonstrated conclusively the vulnerability of the thiolflavoprotein to oxygen when administered under pressures of over one atmosphere (20, 21). Perhaps a parallelism between anesthetic action and oxygen toxicity may be evident (21, 23).

Thus Soskin and Taubenhaus, on finding that succinate alone remains oxidizable both in anesthesia and oxygen poisoning, first sug-
gested, in 1942, that this simple aliphatic drug might be a valuable and physiologic antidote in anesthetic states (24). It was claimed by them that the shortening of recovery time from amytal and nembutal anesthesia was in direct proportion to the amount of succinate used. In their opinion, 100 mg. of succinate could protect the body against 8 mg. of a barbiturate per 100 Gm. of body weight.

Koppanyi has shown that while ammonium chloride increases the excretion of urine and barbiturate in acute poisonings it does not significantly hasten the recovery time (25).

Proger claimed that the A–V oxygen difference is increased greatly through the utilization of more oxygen by the tissues with succinate therapy (26). Lardy and his associates disclaimed the effectiveness of succinate on the basis of their own work (27). Corson et al. recorded the following in their detailed work with succinate: (1) animals treated with succinate recovered in half the time required by the controls, and (2) urine volumes in these animals were markedly greater than those in the controls (28). The first mention of the possible toxic effects of succinate was made by Pinschmidt who found pulmonary edema, hemorrhage, and respiratory failure with doses of 1 Gm. per kilogram of body weight (29).

Because of the scarcity of knowledge of the effects of succinate on man and with the realization that its use might be beneficial on purely theoretical grounds we set out to make an objective study of succinate therapy on barbiturate anesthesia in man.

**Experimental Data**

Since the electroencephalogram shows well recognized changes in barbiturate anesthesia, this type of objective test was used in every case studied. Furthermore, since it has been suggested by Hoagland (30)
that the electrical rhythmicity of the cortex is dependent on continuous steady-state chemical events within the cortical cells, such changes in the electroencephalogram might be indicative of interference with the normal procedure of glucose metabolism. If succinate were to prove of value in combating the effects of barbiturate by giving the brain a source of fuel impervious to attack by the drug, the electroencephalogram might by the above hypothesis be expected to indicate this, since some oxidation would be proceeding unchecked.

Electroencephalograms, therefore, were recorded from all subjects studied, the tracings being made by a Grass ink-writing oscillograph and further analyzed by an electronic frequency analyzer of the type designed by Walter. Such an analyzer, a detailed description of which will be found in Walter's original publication (31), enables one to see at a glance the component frequencies present in the original tracing where they may be so intermingled as to confuse the naked eye.

Two groups of subjects were studied during the past three years. One consisted of normal, healthy adult males, the other of patients drawn from the ward population of the Department of Psychiatry at the Massachusetts General Hospital. The latter had been given complete medical, neurologic, and routine laboratory examinations. For all patients in this present series the results of these examinations were within normal limits. Various types of psychoneuroses comprised the clinical diagnoses. All such patients chosen were young, intelligent and cooperative adults, and their subjective impressions seemed to be uniformly accurate and sensitive.

The subjects were prepared in the following manner: breakfast was limited to one cup of coffee and one slice of toast at no later than 8 a.m. Also at this time they were given 50 Gm. of glucose in 3 ounces of water by mouth to avoid the possibility of hypoglycemic reactions affecting the electroencephalogram. No further nourishment or water was allowed until after the experiment, and neither atropine nor other premedication was given. Approximately six hours after breakfast the patient was taken to the electroencephalographic laboratory where the electrodes were applied to the head. The positions were measured in such a way as to place electrodes over each of the frontal, parietal and occipital lobes. The electroencephalogram was then recorded in the usual manner from pairs of electrodes on the scalp.

The general tendency has been to carry over to pentothal anesthesia from work with ether the criteria for the various levels of consciousness. There are, however, important differences. One hundred and twelve experiments on 75 subjects (60 patients and 15 controls) were conducted to obtain an independent measure of the effects of pentothal on the electroencephalogram and on neurologic signs. The characteristics of the successive levels of pentothal anesthesia were quite consistent in the subjects studied. We modified to some extent the criteria described by Himwich and Etsten (32), substantiating most of them.
The criteria may be summarized as follows: **Stage of Clouding:**

**Stage 1.** The first change found as the injection proceeds may be a slight thickening or blurring in speech, and a hesitancy in answering specific questions. The subject sometimes is drowsy, sometimes talkative and euphoric, and occasionally restless (8 per cent). Acute excitement is rare. Eyeball movements are uniformly under voluntary control, as is body musculature. Eyelid tone and corneal reflexes are normal. The pupils are normal in size and react very promptly to light and to pain. The response to peripheral stimulation is slightly hyperactive and, in contrast to the effects of ether, there is no analgesia at this stage. Half of the patients exhibited some evidence of anxiety; but it must be remembered that not only were these psychiatric patients, but also that they had not been given premedication. Pulse rate and respiration remain unchanged. As the injection continues, the speech becomes more blurred as in alcohol intoxication. Attention wanders easily and if the patient has been counting he may repeat the same number over and over, or may stop entirely until commanded to start again. Quite suddenly, contact with the environment is lost and the subject enters the second stage of anesthesia. In 60 per cent of cases a yawn precedes this stage.

**Stage of Exaggerated Response:** **Stage 2.** The subject is now unconscious. Respiration has suddenly become deeper, more rasping in tone and slightly faster in rate. Peripheral stimulation, such as pinching the skin, at once brings about movement. These movements, however, are purposeful, coordinated and quick, unlike the wild and unrestrained actions often seen under ether anesthesia at this stage. The corneal reflex is absent in 75 per cent of cases. Eyelid tone is normal in half of the cases and only slightly depressed in the other half. The eyeballs show slight rolling motion in 50 per cent of the subjects and are rolled up and divergent in the rest. In 70 per cent of cases pupils are larger than normal, and all react well to light and to pain. Heart rates remain unchanged. As the anesthesia deepens and the third stage is approached the eyeballs remain divergent and tend to roll up in all cases.

**Stage of Surgical Anesthesia:** **Stage 3: Light.** The subject now makes no spontaneous movements. The corneal reflex is absent in all cases, but eyelid tone is still present to a slight degree in one-third of the cases. Slow oscillations of the eyeballs in a horizontal plane are still present in a few cases; most eyeballs are already fixed. The pupils have become small but still react to pain and to light after a momentary delay. The response to peripheral stimuli is still present though diminished, and reaction time is gradually prolonged by two to four times the normal value. Respiratory activity has settled down after the unevenness of the second stage to a quiet rhythm with a slight increase in rate. Ten per cent of the subjects are snoring. None tolerate an airway at this point. Stimuli to certain sensitive areas or muscle spindles
cause very definite and coordinated responses even while the subject is snoring peacefully and all eye signs are absent. As the deeper plane of the third stage is approached eyeballs in all cases become fixed.

Stage 3: Deep. The pupils are small and pinpoint in all cases. A few may show reaction to light and to pain. Eyelid tone is entirely absent. An incipient relaxation is apparent in the muscles of the extremities and in the abdominal wall in older and more obese subjects. The reaction time to painful stimulation is increased markedly but response is still present in 20 per cent of cases. This, certainly, is in marked contradistinction to the total lack of response to pain found at

![Waveform diagrams](image)

**Fig. 3.** The effect of intravenous sodium pentothal on the electroencephalogram.

In each of the tracings illustrated, the top recording labelled "F" is from 2 electrodes over the frontal region, the second ("P") from 2 over the parietal region, and the third ("O") from 2 over the occipital region. The amplification and time scale is the same in all records as indicated in the top sample.
the corresponding level of ether anesthesia. The pulse rate begins to climb slightly and for the first time a change occurs in the blood pressure which drops almost in proportion to the rise in pulse rate. On no occasion was an alarming reaction observed. At this plane half of the subjects will tolerate an airway and the jaw must be supported in nearly all of them. Strangely enough, in almost 200 experiments of this type insertion of an airway at this time did not serve in itself to produce the slightest sign of a laryngospasm.

This was the deepest level studied on these subjects; they were then allowed to recover from the effects of the drug while observations were made of the steps in the return to consciousness. There seemed no point to be gained in taking the subjects into Stage 4 of pentothal anesthesia with its rather severe attending states of hypoventilation and hypotension.

In a previous study here Brazier and Finesinger (33) had noted that...
small doses of the barbiturates produced faster frequencies than normal in the electroencephalogram and that these were followed by slow waves if the anesthesia were deepened. In figure 3 samples are shown of each of these electroencephalographic changes. Figure 4 shows these effects even more clearly and includes the automatic frequency analysis of the waves present at each stage. While the subject is in the first stage, the appearance of this high voltage, fast activity is striking. This is never found when the subject is truly alert but only when some degree of mental clouding or euphoria is present. Further, this tends

![Diagram of EEG Frequencies and Stages of Anesthesia]

**Fig. 5.** The E.E.G. in pentothal anesthesia.

Chart showing which frequencies were present in the E.E.G. of an individual throughout a period of anesthesia induced by pentothal. The experiment begins at the top of the chart and proceeds vertically downwards. Each dot indicates a significant peak in the analyzer's trace at the frequency indicated on the abscissa. The heavy dots indicate the dominant frequency of the E.E.G. in each plotted sample. The E.E.G. data are charted at 30-second intervals throughout most of the experiment. The concurrent stages of anesthesia are charted on the right of the diagram and follow the same time scale as the E.E.G. from the top of the chart to the bottom.
to increase in amount as the first stage progresses. To illustrate more clearly the sequence of changes in electroencephalographic frequencies which accompany shifting levels of consciousness in pentothal anesthesia, a different method of charting has been used. This is seen in the analysis given in figure 5. The chart reads from top to bottom, and the width of the white band indicates the spread of frequencies found in the electroencephalogram by automatic analysis, plotted every half minute. The black spots represent the actual frequencies present as indicated on the abscissa and the larger black dot, the dominant frequency of each recorded sample. The column on the right indicates the levels of anesthesia.

The onset of the second stage at the moment of loss of consciousness is coincident with the abrupt appearance of high voltage slow waves. These electroencephalographic changes on induction of anesthesia are strikingly constant (34). During emergence from anesthesia however, the electroencephalographic changes, as well as the clinical signs, are not as clearly cut.

Since, as we have seen, the available evidence would seem to indicate that the blocking of glucose metabolism caused by the barbiturates occurs somewhere in the center of the flow line and, moreover, that the metabolism of succinic acid is invulnerable to the barbiturates, we might expect that the use of succinate intravenously and in large amounts might circumvent this block and thus supply an auxiliary fuel for purposes of brain oxidation. If the brain can utilize succinate in this way, then the electroencephalographic pattern, were it indeed dependent on these oxidative processes, might be expected to revert from one of slow waves characteristic of anesthesia to one more nearly normal. We have conducted over 50 experiments on man to test this hypothesis.

The procedure was as follows: After an adequate preliminary electroencephalographic tracing had been obtained in the resting state the intravenous administration of a 2 per cent solution of sodium pentothal was begun, using either a continuous drip or the fractional method of injection. The rate of injection was adjusted to produce and maintain the particular level of anesthesia desired for study at that time, or in the subjects who were given succinate, to produce the identical pattern of administration which was obtained in the previous experiment with pentothal. When the subject was in the desired plane of anesthesia as shown by clinical observation and by the electroencephalographic pattern the intravenous injection of disodium succinate was begun. We have used the standard 30 per cent solution put up by Brewer, and lately the product called soduxin, from the same company. According to the advice of other workers, we have always used fresh solutions and have stored them in cool, dark places. The amounts of succinate used have ranged from 15 to 36 Gm., and have been given in time periods of from nine to forty-five minutes. The maximum dose at any one time was 35 Gm. in fifteen minutes.
Over half of our subjects have complained of a transient feeling of "mild choking" and thickened voice occurring within the first three to four minutes of the administration of succinate. We have also observed in all cases a confluent flush of the anterior aspect of the neck, chin and face, similar to that produced by moderately large doses of atropine. One-third of the patients showed slight edema or brawniness of the involved skin. Usually, the flush as well as the edema subsides within fifteen minutes. We have, therefore, not recommended the use of succinate in children, tracheotomized patients, or in elderly or debilitated persons with pulmonary disease.

BLOOD SODIUM VALUES IN PENTOTHAL STUDIES

<table>
<thead>
<tr>
<th>Before Injection</th>
<th>After Sodium Lactate (6 Gm)</th>
<th>After Sodium Succinate (9 Gm)</th>
</tr>
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<tr>
<td>141.4 mEq/L</td>
<td>143.4 mEq/L</td>
<td>141.3 mEq/L</td>
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<td>139.2 mEq/L</td>
<td>141.3 mEq/L</td>
<td>138.8 mEq/L</td>
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<tr>
<td>138.8 mEq/L</td>
<td>140.9 mEq/L</td>
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In control experiments, some subjects were given other sodium salts instead of succinate. Both sodium bicarbonate and sodium lactate were used. Sodium determinations to estimate the effect on the system of the rather large amounts of the sodium radical given were found to be well within normal limits whether the subject were given sodium lactate, sodium bicarbonate or sodium succinate. For example, figure 6 shows the results on one subject (O. P.) who was tested on three separate occasions, once with succinate, and twice with sodium lactate, having in each case received 0.5 Gm. of pentothal intravenously. In all other cases similarly tested the range has been within 2 to 3 millequivalents per liter.

In some experiments disodium succinate was injected at times varying in relation to the administration of the pentothal in order to determine its relative effect when given prior to anesthesia, during anes-
Anesthesia and Succinate

Anesthesia, or at the end of anesthesia. It was not possible to demonstrate any definite advantage in the administration of the succinate prior to anesthesia. The results ranged from the most spectacular awakening of the subject in earlier cases to a complete absence of reaction as evidenced both by clinical signs and the electroencephalographic rhythm.

One subject (S. S.) received 50 cc. of a 2 per cent solution of pentothal (1 Gm.) in fifteen minutes and remained in the third stage of anesthesia for nineteen minutes, recovering in approximately forty minutes. When she was given 50 cc. of a 30 per cent solution of succinate (15 Gm.) at the end of fifteen minutes, the third stage lasted twenty-two minutes, and she recovered in about forty-five minutes. No beneficial effect can be claimed here since the time relations of the anesthesia levels were not significantly changed. In a subsequent experiment with the same amount of pentothal, during which she received 95 cc. of succinate (28.5 Gm.), the third stage was reduced to fourteen minutes, but she still required forty-five minutes to recover.

Another person (C. P.) who maintained third plane anesthesia for eight minutes on 800 mg. of pentothal given in ten minutes, did not recover for over an hour. When she was given 50 cc. of succinate (15 Gm.) which was started four minutes before anesthesia, the third stage lasted only seven minutes, but again recovery was not complete for well over an hour. There is no difference of any significance here.

A third subject, however, showed a most spectacular result. This man (O. P.) who received ½ Gm. of pentothal in forty-five seconds developed delta waves in the electroencephalogram in forty seconds. These increased rapidly in number to occupy 50 per cent of his tracing and disappeared entirely after 120 seconds. On 9 Gm. of succinate, a relatively small dose, delta waves did not appear until sixty seconds after the administration of pentothal, rose to occupy only a bare 10 per cent of his record and disappeared completely after 100 seconds. This man never reached the third stage with the succinate although he had done so on pentothal alone. Repeated tests on this man, using lactate and bicarbonate as controls, failed completely to effect the same diminution in delta activity.

In an effort to approximate actual operating room conditions, one subject (D. D.) was given pentothal by the conventional fractional method. Eleven cubic centimeters (220 mg.) was given in three and a half minutes, mostly during the second minute. The subject was then allowed to recover for another two minutes, and was finally “snowed under” with 14 cc. (280 mg.) in the next two minutes. On six separate occasions within the space of twenty-eight days, this man received this exact amount of pentothal (560 mg.) in the same time sequence. The average times for each stage are shown in figure 7. Note especially the percentage variations. On two separate occasions this subject was given 16.5 Gm., and 33 Gm. of succinate respectively, the injection beginning four minutes before the onset of anesthesia and proceeding throughout. With the smaller dose third stage anesthesia was reached.
SUBJECT D.D.: SIX ADMINISTRATIONS
PENTOTHAL DOSAGE 0.5 GRAMS IN A TOTAL OF 75 MINUTES

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<tr>
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<th>AVERAGE TIME</th>
<th>PERCENT VARIATION</th>
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<tr>
<td>to Onset of Light Plane</td>
<td>7.8</td>
<td>± 6 %</td>
</tr>
<tr>
<td>to Onset of Deep Plane</td>
<td>9.4</td>
<td>± 9 %</td>
</tr>
<tr>
<td>Duration of Deep Plane</td>
<td>1.8</td>
<td>± 44 %</td>
</tr>
<tr>
<td>to Moment of Complete Recovery</td>
<td>24.0</td>
<td>± 21 %</td>
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Fig. 7. Time relations of third stage anesthesia.

in nine and three-fourths minutes, and lasted one and one-fourth minutes. In twenty-five minutes he had recovered completely. With the larger amount of succinate there was no significant difference in his reactions.

In a few of the earlier subjects, large amounts of pentothal were given rapidly; i.e., up to 0.5 Gm. in less than fifty seconds, approximating more closely the overwhelming blood concentration of barbiturates which may occur in suicidal cases. The following are a few of the results. M. C., having received 0.45 Gm. of pentothal in forty-five seconds, went into third stage uncomplicated by anoxia in thirty seconds and maintained this plane for four minutes. With 15 Gm. of succinate started simultaneously with the pentothal, delta waves appeared in twenty seconds and persisted two and a half minutes. Thus, her recovery seemed to be accelerated slightly by the succinate.

Another individual (D. B.) showed a much more profound narcosis, measured both clinically and by the brain-wave pattern, when 10.5 Gm. of succinate was administered with the pentothal than when she had received 0.3 Gm. of pentothal alone. This was also true in the case of G. M., who not only failed to respond to succinate therapy, but actually seemed the worse for it.

Finally, a brief summary is given in table 1 of another case (J. W.) which was very extensively studied. The times are recorded from the beginning of the pentothal injection. In this case succinate was of value in reducing the amount of abnormal electroencephalographic ac-

<table>
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<th>TABLE 1</th>
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<tr>
<td>Pentothal 16 cc in 115 seconds</td>
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<tr>
<td>Pentothal + Bicarbonate</td>
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<tr>
<td>Pentothal + Succinate (15 Gm.)</td>
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</table>
Anesthesia and Succinate

Activity, but neither the onset of anesthesia nor the recovery-time was materially affected.

The remainder of the cases shows the same doubtful or equivocal results. A really critical review of all data obtained reveals questionable advantages in a few of the experiments conducted (35). It may well be that these results are owing to our inability to equilibrate precisely the concentrations of the two drugs in the cerebral cells. Our work on blood concentrations should soon aid in that perplexing question.

![Diagram of anesthesia effects](image)

**Fig. 8.** Pentothal anesthesia effects of repeated doses.

Of interest at this point is the change in response of a subject to repeated injections of the same amount of pentothal sodium given on five or six occasions at intervals of three to four days. Although this observation was made on only a few subjects, it is noteworthy to record that the following occurred. Figure 8, which depicts the duration of each stage in 7 experiments on 7 different days, suggests the possibility that a tolerance to the drug has been developed. With this dosage and rate of injection the period of induction is short and proves to be almost constant, however frequently repeated. On the other hand, the dura-
tion of the subject's unconsciousness is clearly influenced by recent experience of the drug. In spite of identical dosage and rate of injection, there is a tendency for this individual to remain in the third stage for a shorter period on each occasion and seemingly to recover faster with each successive administration of pentothal.

Such an effect as is shown in figures 7 and 8 brings out two points of some importance. One is that acclimatization to sodium pentothal can occur. This may have clinical meaning in surgical procedures by stages requiring repeated anesthesias. The second point grows out of the first; it emphasizes the caution one must exercise in judging the efficacy of antidotes when comparison of anesthetic effect is made between two experiments in which the antidote is given in the second of the pair.

Since this was the case in some of our earliest work, we believe this to account for some of our former observations in which we obtained an apparently beneficial effect with succinate. Our next procedure is to reverse the order of experiments and eliminate the influence of acclimatization. The results will be covered by a later report.

Our purpose in presenting these data now is to emphasize the number of variables involved in the problem of assessing the antidotal value of succinate in pentothal anesthesia. Until the influence of each variable has been determined by carefully controlled experiments, conclusions made on clinical observation alone are premature.

Summary

Some basic biochemical considerations pertinent to the "Oxidation Theory" are mentioned.

Objective neurologic levels of pentothal sodium anesthesia, employing the electroencephalogram, are described.

The rationale, the use and effects of disodium succinate (Sudoxin) are discussed and some typical cases reported.

In spite of extensive experimentation along the lines described in this paper, we believe that a definitive decision as to the value of succinate would be unjustifiable at this time.

Several variables, such as tolerance to pentothal sodium, are suggested as reasons for the need of caution in assessing the antidotal effects of disodium succinate.

References

NEURAL NETS AND INTEGRATION OF BEHAVIOUR

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This essay first appeared in the volume entitled "Perspectives in Neuropsychiatry."
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NEURAL NETS AND THE INTEGRATION OF BEHAVIOUR

“As long as a life phenomenon has not yet found a physico-chemical explanation it usually appears inexplicable. If the veil is once lifted we are always surprised that we did not guess from the first what was behind it.”

Jacques Loeb.

Recent developments in neurophysiology are having a profound influence on psychology, philosophy and sociology. It is probably that they will be shown to have as great a significance for neuropsychiatry.

Essentially the expansion in neurophysiology has come with the recognition that the nervous system is not a passive system but a continuously active one, one which is never at rest, never passive even in the sense of being solely concerned with the maintenance of its own metabolism. The older theories which pictured the nervous system as a series of conducting lines whereby impulses travel unidirectional from the receptors through a varying number of interneurones in the cord or brain to the effectors, were oversimplifications which have not proved adequate for the observed facts.

The new concepts which have entered the field include that of feed-back mechanisms in the central nervous system, by which is meant activity in closed circuits such that some of the output returns as input and influences the subsequent activity in that circuit. It is the error, (the degree of failure,) which determines the return input until the error becomes zero. The other closely related concept is that of chains of neurones in the central nervous system which are dedicated neither to the carrying of specific afferent messages nor to any specific effector system, but which are the structure for a circulating process which functions as a scanning mechanism. This idea of scansion, introduced into physiology independently by Craik and by McCulloch, is analogous to the time-sweep in television; it has a definite period: the time taken for an impulse to circulate through the entire loop. Its periodicity will thus be determined partially by the conduction rate in the neurones, but mostly by the number of synaptic delays in the circuit.

The subject of closed-cycle control systems or servo-mechanisms is new only in physiology; in other sciences such as engineering and electronics it has been elaborately studied and applied — in fact Clerk Maxwell gives us the first classical example in the governor of the steam engine, and in magazines of popular science one reads descriptions of the target-finding gun. Craik broke the ground for physiologists in his studies of the human operator in control systems but recently the mathematicians, Wiener and Pitts, and the physiologists, Rosenblueth and McCulloch have combined to give us a well-developed application of its principles to physiology; indications of its interest to psychologists have been given at a symposium at the 1948 meeting of the American Psychological Association entitled “Human beings as servo-mechanisms”.

What is the evidence for these statements? For example what evidence have we that the nervous system is not simply a passive network which comes to rest when unstimulated?

There are many data from animal experiments indicative of continuous inter-
activity of various cell groups keeping a fine balance between excitation and suppression of activity, between release and restraint. Such data are found, for example, in studies of animal locomotion; there is Young's work with cuttlefish,\(^9\) where removal of the higher centres releases a wild continuous swimming motion, unceasing until death. Gray and Sand\(^{10}\) also produced this restless fatal swimming in spinal dogfish. Flynn\(^{11}\) has found a remarkable increase throughout the day in the activity of cats after hemidecortication and an even greater one after bilateral decortication. And Bailey\(^{12}\) has shown that cauterizing the interpeduncular nucleus develops in these animals an obstinate progressive movement in which they walk continuously forward until they die. If they meet an obstacle such as the wall of the cage they press ceaselessly forward until all the hair is rubbed off and the scalp macerated. In monkeys\(^{13}\) constant hyper-activity follows removal of area 13, and in man the remarkable restlessness sometimes observed after prefrontal lobotomy may well be due, as Russell\(^{14}\) suggests, to damage of a suppressor band lying in the frontal lobe. All these lesions would appear to have removed the usual restraint, to have upset the balance between excitation and inhibition. The opposite picture, a removal of excitation and release of inhibition is shown in the sleep-inducing effects of many experimentally produced (and morbid) lesions of the mid-brain. Mauthner\(^{15}\), von Economo\(^{16}\), Ranson\(^{17}\) and others have described these conditions.

These few examples, taken from many, are evidence of a balance of nervous activity going on in the central nervous system often independently of the external events signalled by the receptors. But what is the evidence for reverberating circuits situated entirely in the nervous system, as well as those which go out and back through the outside world as, for example, do the homeostatic reflexes?

The theory of reverberating circuits is not new to physiology. It is really an elaboration of Forbes' theory of delay-paths\(^{18}\) originally advanced to explain after-discharge; in 1929 Forbes\(^{19}\) stated that "the most prolonged after-discharge of the crossed extension reflex would require a sort of central reverberation". Following this, Lorente de Nö\(^{20},^{21}\) developed his theory of closed "self-re-exciting chains" according to which when a given cell discharges, the impulses go toward the effector system through multiple efferent paths but also travel through fibres which loop back and re-excite the first cell. This cyclical process continues until some cell in the loop fails to discharge. Ranson and Hinsey\(^{22}\) in 1930 independently suggested reverberating neurone circuits to account for flexor after-discharge in the hind-limb reflexes in cats.

Histological evidence for such loops is plentiful. Ramon y Cajal\(^{23}\) demonstrated many such recurrent paths in the human cerebellar cortex and also in the cerebral cortex and olfactory bulb. Lorente de Nö\(^{20}\) has worked them out in detail for the vestibulo-ocular reflex in rabbits, and Pitts and McCulloch\(^2\) have published studies of the nervous nets involved in eye movements in mammals. And there are many examples of self-re-exciting neuronal loops in other phyla, as for example, the cyclical pathways demonstrated in the cuttlefish by Young\(^6\), section of which disturbs the capacity for "learning".

The concept of feed-back mechanisms as applied to the nervous system has recently been brought into prominence by Wiener,\(^{24}\) a pre-publication copy of whose book entitled "Cybernetics or Control and Communication in the Animal and in the Machine" I have been privileged to read. As mentioned above, in any
system displaying negative feed-back, some of the output of the system returns to limit and control its further output. In a voluntary movement some message goes back to the brain informing it of the amount by which the movement has failed in its objective. If this return message is over-adequate, that is, if the negative feedback is excessive, the system will be set into oscillation. An example of disturbance of feed-back systems in pathological states given by Wiener is cerebellar tremor, where the proprioceptive input is intact but the output response is so disturbed that the resulting movement swings into oscillation. But one does not need to go into the diseased states to find examples of feed-back swinging into a "hunting" oscillation as anyone knows who has tried to carry a shallow oblong tray of water (such as an ice-tray) across the room.

A detailed study of clonus in the cat has been made by Rosenblueth and Wiener.** By calculations based on the number of incoming impulses per unit time necessary to achieve the required summation to pass the threshold of synapses, and from the conduction time for single impulses in other parts of the neuromuscular arc, they have been able from the technique of servomechanisms to derive mathematically the frequency of clonic contraction. This calculated result is found to be in reasonable agreement with the observed frequency of clonus, experimentally induced by stretch stimulation of the myotatic receptors.

Wiener has given an interesting example of "informative" feed-back. When driving on an icy road "one gives the steering wheel a succession of small, fast impulses, not enough to throw the car into a major skid, but quite enough to report to our kinaesthetic sense whether the car is in danger of skidding and we regulate our method of steering accordingly. We superimpose on the incoming message a weak high-frequency input, and take off the output of the effector a partial output by an appropriate filter. We explore the amplitude-phase relations of the high-frequency output to the input in order to obtain the performance characteristics of the effector. On the basis of this, we modify in the appropriate sense the characteristics of the compensator."

The importance of self-re-excitation is the influence it has on the thresholds of the synapses; it may so facilitate the incoming sensory impulses (which alone might be ineffective) as to make them now effective. This describes training. And the reverberation once started, can continue indefinitely provided the necessary energy for nerve cell metabolism is maintained, so that impulses are retained and persist through time. This last sentence is a description of one type of memory — memory, the old puzzle of the Dualists who met the difficulty by allotting it to a non-material, non-physiological mind.

In this context the concept of scanning takes its place. Wiener has drawn attention to the close analogy which may be made between computing machines and the brain; both consist of consecutive switching devices in which a choice between two alternatives is made at each synapse in the nervous system (on-or-off at each switch in the machine, all-or-nothing at each synapse in the nervous system). Wiener solved the problem of representation of functions of more than one variable in computing machines by introducing scanning, and McCulloch and Pitts have introduced it into the design of an apparatus to enable the blind to read the printed page by ear. By its use they have been able to make automatic selective readings of type imprint for a set of different magnifications; that is: the variable tones pro-
duced by the agency of the photocell are specific for the pattern of letters and independent of the size of the print. This work led them to their application of scanning circuits to physiology.

They have recently presented some anatomical diagrams based on known neuro-anatomical micro-structure which describe how a scanning mechanism consisting of impulses sweeping up and down in nonspecific and associative afferents can furnish a basis for recognition of universal form when a particular specific stimulus arrives over sensory pathways. One example is the recognition of chords regardless of pitch. The network they present, and for which they have completed the mathematical analysis, is based on the cytoarchitecture of the transverse temporal gyrus with its spatially arranged arrival stations for afferents from the medial geniculate; low tones excite the outer and forward end of this cortical strip, high tones the inner and posterior. The neurones excited by these afferents lie in vertically arranged columns of fifty or more, and relay the message to the associative afferents. Pitts and McCulloch suggest that the arriving sensory impulses in the specific afferents are inadequate to pass the synaptic threshold at this level except at the moment when the particular level of the column of nerve cells is facilitated by a simultaneous impulse from the scanning circuit. The sweep passes (and facilitates) each layer of neurones in turn. Any chord which has come in as impulses to a spaced set of neurones in the auditory cortex will be found in its turn by the periodic sweep, the impulses will summate, and discharges will descend in the associative fibres. "The level in the column, facilitated by the non-specific afferents, moves repetitively up and down, so that the excitement delivered to the depths moves uniformly back and forth as if the sounds moved up and down together in pitch, preserving intervals". The chord would thus be recognized regardless of pitch.

These authors also have described an anatomical net for Area 17 of the visual cortex based on Cajal's drawings from Golgi preparations, in which scanning through non-specific afferents would result in the recognition of shape regardless of size. Another spatial dimension has been gained by this temporal scanning mechanism. Were there indeed to be a ceaseless rhythmic sweep of impulses in non-specific afferents up and down through the cortex one would reasonably expect there to be some smoke from all this fire. That the alpha-rhythm may be this smoke has recently been suggested. Evidence that efferents to as yet undifferentiated nuclei in the thalamus and non-specific afferents from them back to the visual cortex are the neuronal pathways of the alpha-rhythm has been brought forward by Morison and Dempsey and it is to them that the rhythmic scanning mechanism has been tentatively assigned by McCulloch. The time-relationships are possible, for the number of synaptic delays in the circuit would result in a total sweep-time approximately the periodicity of the alpha-rhythm (10 cycles per second).

When the sweep has nothing else to do but follow its cyclical sequence (i.e. when we are awake with our eyes shut) the electrical rhythmicity is recordable in its purest form. When the scanning circuit is busy facilitating the transmission of specific impulses from the visual cortex (as when we open our eyes) the periodicity disappears. It is in keeping with the known facts of electroencephalography to recognize the close association between the alpha rhythm and form perception. But it is very generally accepted that the alpha-rhythm slows in the normal person on
overbreathing, and the critical experiment to determine whether the rhythm slows in these particular circuits between the visual cortex and the thalamus has not yet been made. It is of the utmost importance for this theory that experiment should establish whether the slower rhythms seen on overbreathing originate in some other part of the brain and spread elsewhere or whether they are truly a slowed form of the normal rhythm. Were the latter the case it would be odd that so gross a change in the scanning rate could take place without disturbance of perception.

In the opening sentence of this paper reference was made to the impact of these developments in the neurophysiological field on psychology, philosophy and sociology. A neural mechanism which can “detect the equivalence of apparitions related by similarity and congruence, like those of a single physical thing seen from various places” without the necessity for depicting it as a constellation on neuronal mosaics, will interest the Gestalt psychologists. A neural mechanism involving a net into which an impulse can enter and persist through time to influence a response at a later date must interest the Behaviourist school. The traditional theories of neuronal paths passing into, through and out from the nervous system by non-circular connections, paths where the “cerebrum itself may be indeed regarded as the ganglion of the distance-receptors”, provided no mechanism for retention of impulses; the signal passed through and perished. A self-re-exciting loop of neurones, sharing neurones with other loops, in which reverberation can be set up by the entry of afferent impulses from different sense receptors gives and preserves the association between different particular events and allows the recognition of a universal to be sparked by the receipt of a particular. Thus the sight of a cat whatever its colour or size, the written or spoken word for it in any of the languages known to us, the sound of its voice in the night, the feel of its fur in the dark, and, alas, its smell, will inform us of the same universal.

Without the circular paths in the nervous system the incoming impulse would enter an “empty brain” and could inform it only of what happened at that particular instant; the response elicited would be merely to that particular. As McCulloch has put it “a train of impulses in a regenerative loop preserves the form of the fact without reference to the one particular moment when it was experienced”. The uniformity of the nerve impulse, the unique form of the nerve action potential makes possible this blend of stimuli, specificity having been left behind at the receptors. The number of neurones in the human brain, approximately 10,000 million, makes possible a vast number of intercommunicating nervous nets.

Northrop in a recent symposium has emphasized the import to philosophy of these recent advances in neurophysiology. He states that the description by Pitts and McCulloch of neuronal nets by which nervous systems may know universals is “of revolutionary significance for natural science, moral as well as natural philosophy, and for one’s theory of the normative factor in law, politics, religion, and the social sciences.” “In other words, the basic premise of both the traditional philosophical dualists and idealists, and the traditional, supposedly scientific naturalists and mechanists, to the effect that natural and biological systems can have neither knowledge of universals nor normatively defined and behavior-controlling purposes, must be rejected.” The dualism of mind and matter which began with Plato has been much buffeted through the years. The Cartesians increased it to a triad, of God, mind and matter. Spinoza admitted only God. Berkeley eliminated matter. Eddington advocated “mind-stuff”. The nagging problem was how to
account for purpose, for memory and for the knowledge of universals. For the
mechanists and Behaviourists these were epiphenomena of no causal significance,
rationalizations after the fact.

Northrop also stresses that neurophysiology has now found a possible mechan­
ism for purpose, for teleological purposeful activity in the correlate of negative
feed-back systems by which signals from the goal can alter the behaviour after it
has been initiated so that it reaches its goal. As Northrop points out, this is the
requirement of any mechanism in order for it to be teleologically goal-directed, and
“a teleological system can be — and in human nervous systems it is — a mechanical
system. It is a mechanical system in which the behaviour of the system is controlled
by a negative feed-back over the goal.”

In the field of sociology we as human beings react to universals, to ideas which
persist through time, impulses which were initiated into reverberation by stimuli
received in the past: perhaps at our mother’s knee, from the teacher in the school­
room or the church. Later data arriving from outside us through our sense organs
may not find any path leading into the reverberating circuits of these socially pre­
scribed universals nor any common loop, but may enter some different regenerative
loops set up by other informative impulses from the physical world. In the light
of the information carried by these new impulses some of us may reconstruct our
universals in new circuits, but others will stick to the universals demanded by the
social pressure of their culture.

The conflict between universals of one social theory and those of another is
the stumbling block to world order. Northrop has quoted the current example of
the capitalistic and communistic theories as typical incompatibles. The brain is
faced with a choice between these universals.

The individual as he matures is continuously faced with this conflict between
universals and it seems that the nervous system must surely embody the possibility
of choice. McCulloch has suggested that since many paths share nervous parts,
conflicts may be barred by inhibitory links from one circuit to another so that when
both are excited only one works.

That these are problems which concern the psychiatrist is inescapable. The
analogy to many conditions in the neuroses is clear. The disturbances of associa­
tion, with the suggestion of inefficiently working inhibitory links; the continuously
circulating worry with the failure of effective discharge in anxiety; the absorption
into inappropriate association of stimuli from particulars in paranoia; the profound
disturbances of memory in some neuroses, and the common experience, for which
one does not have to go to the neuroses, of the conflict between intellectually estab­
lished universals and emotionally conditioned ones; all these suggest themselves as
pertinent for study in this light. That these may have their correlates in the
neural nets of the brain is now a possibility; that such nets may be involved in
certain states has been indirectly recognized by the introduction into therapy of
prefrontal lobotomy.

The test remains to be made: whether these ideas in fact prove fruitful, “for
experiment will serve to eliminate those which do not fit the facts.” But at least
we may take a more hopeful outlook than that expressed in 1946 by Gerard when
he said “It remains sadly true that most of our present understanding of mind
would remain as valid and useful if, for all we knew, the cranium were stuffed
with cotton wadding.”

Cambridge, September, 1948
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BIBLIOGRAPHY (Continued)


THE ELECTRICAL FIELDS AT THE SURFACE OF THE HEAD DURING SLEEP

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These studies were undertaken as part of an investigation of the action of sedatives. Since one of the effects of sedatives is to induce sleep, some objective test was sought to determine whether or not a person was asleep. A second objective was to search for information as to the neuronal pathways carrying the electrical activity of the brain to the surface during sleep. With these aims a study has been made of the electroencephalogram during the night throughout periods when the subject was awake, drowsing and sleeping.

That slow potentials appear in the record when the subject is asleep was one of the first observations to be established in electroencephalography; and since Berger's (1932, 1933, 1935) original demonstration of this change, it has been plentifully confirmed by subsequent workers. In general these workers have not studied the locus at which these slow waves appear on the skull but have concerned themselves mostly with the frequency changes. By inference, the slow potentials have been regarded by some as a slowing of the synchronized beat of the same neuronal systems which are responsible for the waking alpha rhythm. The waking alpha rhythm is well-known to be principally localized to the parieto-occipital region in man but there is good evidence that there may be more than one source of these potentials in some individuals since we have confirmed Jasper and Andrews' (1938) observation of independent foci of alpha waves in other regions of the head. Only Bakuradze and Narikashvili (1945) and Liberson (1944) (1945) have made at all detailed studies in man of the locus of the slow waves seen in sleep. Liberson found several foci of slow waves and showed that the region of the vertex was among the first to show localized 'paroxysmal' 3-6 per sec. waves at the beginning of sleep but believed that this selective localization did not persist during deep sleep; that in deep sleep even slower waves (1/2 to 3 cycles per sec.) appeared and that these waves originated, not at the vertex but from the frontal and temporal regions. Further mention of Liberson's careful studies will be made later in this paper when our data have been reported. Bakuradze and Narikashvili (1945) found foci in the central and frontal regions, but not in the temporal lobes. Gibbs (1935) in an early paper commented on the change in frequency but used an electrode placement which was not designed to give information as to localization.

The earlier studies of Blake and Gerard (1937 a and b) were made with one amplifier and were not concerned with localization. From their later work (1939) they reported maximal amplitude of the slow activity at the vertex, but they concluded that "similar patterns of delta waves are clearly simultaneous at the parietal, occipital, frontal, and temporal regions". They did not relate this finding to a spread of activity from a single focus.

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Davis, Loomis and their co-workers (1935, 1937, 1938) at first used not more than 3 or 4 electrodes which gave them inconclusive data as to the origin of the slow waves. In a later work (1938b) they used more electrodes and 6 amplifiers. Their published records show slow potentials centering at the frontal electrodes. Although they commented on the fact that the slow activity was most prominent on the 'top' of the head and could be recorded elsewhere, they did not relate this to electrical spread but emphasized their opinion that the cortex acted as a whole. Adrian and Yamagiwa, (1935) surprisingly, did not find the focus of slow activity in their studies using 5 midline electrodes from front to back of the head.

**TECHNIQUE**

In the present work multichannel Grass inkwriting oscillographs were used for permanent recording, with simultaneous monitoring by a double-beam cathode ray oscilloscope. Photographic records of the cathode ray traces were used to prove the identity of electrical signals appearing in more than one pair of leads, since by this method the waveform could be studied on a much broader time scale and with greater accuracy. For the same reason many of the inkwriter records were run at a speed of 6 cms. per second and at a higher amplification than is standard for clinical electroencephalography. In some stages of sleep it was, of course, found necessary to reduce the amplification to avoid blocking of the amplifiers by waves of high voltage. Electrodes were applied *ad hoc* in order to surround and confirm the foci when found. In some subjects a nasopharyngeal electrode was also used.

All recordings were made with amplifiers incorporating 'push-pull' operation and connected in the standard manner so that an electrically negative signal on the input of grid 1 of each amplifying system gave an upward deflection of the recording pen, whereas a negative signal on grid 2 gave a downward deflection.

**RESULTS**

In all of the 32 experiments on the 16 subjects so far studied there has been alpha activity localizable to the parieto-occipital regions when they were awake.

In figure 1 two samples of the EEG of an individual are shown: that on the left taken while he was awake, and that on the right while he was asleep. In this particular case electrode 5 was 2 cms. below the inion, and the distance between each pair of electrodes was 6 cms. This brought electrode 2 to a position just anterior to the vertex on this head. In the sample shown the spatial phase-reversals indicate that the alpha activity is originating in an area in the occiput nearest electrode 4. From this position forward all the alpha waves are synchronous and in phase and show a falling gradient of voltage, indicating that they have a common origin at the occiput and that the tracings recorded from the electrodes anterior to the occiput are of the electrical spread of this activity. This is the classical distribution originally described by Adrian (1934) (1935). A single line of electrodes thus placed along the midline gives a localization only in the anterior-posterior direction and
does not of course give any information as to the transverse plane or as to whether there are separate foci in each hemisphere. The work of Adrian (1934) (1935), Jasper (1938) and of Cohn (1948) and others has firmly established the existence of separate foci in the two hemispheres so that, since our results are in general confirmation of their findings, the evidence will not be restated here.

**THE FIELD of a DIPOLE in an INFINITE CONDUCTOR**

![Diagram of voltage distribution along a surface YY, 3 cm. from center of dipole.](image1)

Field lines around a dipole in an infinite medium. Voltage gradients on an axis parallel to the dipole (YY), and on an axis normal to the dipole (XX).

The well-known slow activity of high voltage seen during normal sleep has quite clearly defined foci, not in the occiput, but in other parts of the head. Contrary to the suggestion of some workers, these slow potentials are not equally represented all over the head. In the present work it has been found that the principal foci of the most prominent of these slow potentials of deep sleep are in the frontal region. The usual focus is somewhat anterior to the vertex on the part of the skull which, as far as one can tell, probably lies over area 6. This point will be taken up again later.

With the same electrode placement and linkages as were used for the waking record depicted on the left of figure I, the focus of the slow activity in sleep, shown in the re-
whether there is a single focus at the midline or two synchronously fired foci, one in each hemisphere.

We have found that the electrical fields on the surface of the head resemble those of a dipole-like field such as, for example, the great average of a double-layer with its axis oriented perpendicularly to the skull. In theoretical physics a double-layer can be represented as a plane consisting of many dipoles of infinitely small length, perpendicular to that plane. Figure 2 shows a standard diagram of the fields of voltage distribution around a dipole with the voltage on the axis parallel to the dipole (YY), and on an axis normal to the dipole (XX). Our data show that it is to a field on the latter axis that the EEG voltage gradients conform in sleep.

When electrodes are placed across the head in a line through the point where the A-P focus is found, the type of record obtained is generally similar to that shown in figure 3. In this illustration a schematic diagram has been made of the electrical voltage field which would fit the data at the moment in time marked by the arrow on the sleep record. Such a sketch can be only approximate for many reasons, among which are that the curvature of the head is foreshortened in the drawing and that the number of phase relationships and measurements of voltage gradients that can be made for any one moment is limited by the number of channels of the electroencephalograph in use. Also the fact that in the head the volume conductor is a finite one, producing distortion of the field at the surface. The effect of the
boundary on the field is to give a greater voltage on the surface in the vicinity of the dipole than would occur in an infinite medium at a similar distance from the source. A more complete mathematical study of the fields of these potentials is the subject of another communication.

In figure 3 the field has been plotted to fulfill the following voltage relationships for the slow transient marked by the arrow, namely: electrode 1 strongly negative to electrode 2; 2 rather less negative to 3; 3 and 4 approximately isopotential; 4 positive to 5; and 5 strongly positive to 6. The voltage lines of the field have been spaced in proportion to the height of the deflection at the point marked by the arrow in each channel. The data from the small sample shown justify only those parts of the field drawn in solid lines. The broken lines are inserted from inference and by deduction from other parts of the same EEG record in which other electrode linkages were used. The fields would in fact be circles only in the theoretically ideal situation of complete symmetry in an infinite conductor. This of course is never the case on the human head so that the sketch must be regarded as highly schematic.

For using this method of representing fields it is clearly of the utmost importance to have the pens in exact alignment and the channels equally calibrated. It is, of course, also important that the amplifiers should not be allowed to block since this would mask the waveform and hinder the identification in different channels of an individual signal. Phase-distortion by the amplifiers is another hazard.

Such a focus of slow wave activity as is shown in figure 3 might suggest a single midline focus were it not for the fact that any localization found by scalp electrodes is the recording at a distance (at least the distance of the skull and scalp) from the electrical event presenting at the cortex; the fields surrounding a generator fall away very steeply in voltage when recording electrodes are close to the source and then more gradually as the distance is increased (see figure 2). In the EEG recorder from the scalp the sharp fall of potential is always lost since the electrodes never come close enough to the source. Usually the curve is already flattening before the closest positioning of electrodes can register a potential difference. Thus one is always recording on the far outer surfaces of potential fields.

It follows that if two bilaterally homologous areas of the cortex are being triggered to discharge synchronously, and if these lie very closely together, the scalp leads will usually be unable to record these two foci as anything but a plateau, an area of isopotential value. Physiologically, since man develops bilaterally it seems likely that this is the explanation of the plateau found at the midline in sleep, and in fact we have in a few of our subjects, been able to obtain records of two discrete foci, one in each hemisphere lying very close to the longitudinal fissure (see figure 4).

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In the case of the two simultaneous foci illustrated in figure 4, the data are consistent with two generators each presenting its field at the surface. At the moment in time marked by the arrow, electrode 1 is nega-
tive to electrode 2, 2 is positive to 3, 3 is negative to 4. 4 positive to 5 (and the midline electrode 3 is also, but less positive to 5 and is slightly negative to 1). Thus two reversals are clearly seen, one in each hemisphere. These data would suggest a common triggering of activity reaching the cortex of each hemisphere in approximately area 6 (Brodmann).

![Image](image)

**Fig. 5**
Far-frontal focus of slow transients during sleep. For explanation see text.

This is not the only focus of slow activity we find in sleep. Another focus is often found farther forward on that part of the skull which would appear to be over area 9, although to make a definite localization to this area through the skull would seem unjustified. An example of this far-frontal focus is shown in figure 5. In this record 8 electrodes were placed in a line from front to back of the head at the midline and each in turn was connected to a distant electrode, R (shown in the diagram). The amplitude of the change in potential in the time between the two vertical lines was measured in millimeters for each midline electrode referred to the distant electrode. This represents the negative slope of the slow transient marked by the arrow. These measurements are entered on the EEG record and are also plotted on the ordinate of the graph. On the abscissa is plotted the length in centimeters of a line from the nasion to the inion and the placement along this line of the electrodes. These measurements were made on the arc of the head and their projection onto the plane of the paper carries the error familiar to map-makers. The peak of the amplitude difference is seen to be near electrode 2, which was 10 cms. from the nasion and 9 cms. forward of the vertex in this individual.

![Image](image)

**Fig. 6**
Precentral focus of slow waves during sleep. For explanation see text.

In the schematic drawing of the head in figure 5, the simplest fields which would fit these data are sketched diagrammatically. For demonstration purposes one contour line has been drawn for each millimeter of pen excursion measured on the EEG. This is the same linear relationship as plotted on the ordinate of the chart. The head is also drawn to the scale of the abscissa of the same chart.
For purposes of comparison an EEG is shown in figure 6 which is from the same individual at another moment during the same period of sleep. This sample has been subjected to the same method of measurement, charting and sketching of fields as that in figure 5. The focus is clearly near electrode 4 which was 17 cms. from the nasion and 2.5 cms. forward of the vertex. This lies approximately over area 6, and most likely represents the same activity as was previously illustrated in figures 1, 3 and 4. In our experience the far-frontal focus does not only occur in the later stages of sleep, as suggested by Liberson, but during the same period as the precentral focus. Frequently the two different foci of slow activity are found within a few seconds of each other. They appear to be the same foci as those suggested by Davis (1939a) for the non-specific electrical response of the brain to external sensory stimulation.

In our experience these would appear to be the two principal areas giving the most prominent waves during sleep. Superimposed on these slow transients many other types of faster activity can be seen. In a search for foci at the base of the brain we have in two subjects recorded from nasopharyngeal electrodes; these were electrodes designed by Dr. Paul MacLean (1949) and the experiments were carried out with his help. As yet we have been unable to find evidence for a focus at this site during sleep. The result of a typical recording with the nasal electrode is shown in figure 7.

We have been interested also in localizing the 14 cycle spindles which are as characteristic of sleep as are the slow waves. Experiment shows these frequently to have the same field as the slow activity and to vary in frequency through a range of at least 12 to 15 cycles per second in different individuals. Because of the faster frequency, identification of these waves is more difficult than that of the slow waves. The recording in figure 8 was made with two of the linkages run simultaneously on the cathode ray oscilloscope to determine whether or not the waves were indeed identical. This example shows a focus similar to that which we have called the precentral focus when describing the slow activity. This appears to be the same location for these spindles as that described by Jasper and Andrews (1938) who...
traced the progressive change in frequency of the normal beta activity in the precentral region to a 14 cycle rhythm as the subject fell asleep.

We have also found these spindles in the occiput and have not yet exhausted the possibility that they may also appear elsewhere. These are not the only rhythms found in sleep. A fast rhythm of approximately 25-28 c/sec. not present in the waking record, has been prominent in some of our subjects and is now being studied.

**DISCUSSION**

In the records discussed in this paper two foci of slow activity have appeared more prominently than others during sleep. These have been referred to descriptively as a pre-central focus and a far frontal focus. As yet we have found no evidence for a major focus in the temporal lobe, such as has been described by Liberson (1944) (1945) in schizophrenic patients. Our evidence is contradictory to the opinions of early workers that the 'cortex acts as a whole'.

We have not specifically studied the so-called 'K' complex, but our data are in agreement with Davis' (1939a) observations as to localization. It may be remarked that these disturbance patterns may be set up by any external sensory stimulus and not solely by an auditory one, and that they are similar in waveform, frequency, and localization to activity occurring during sleep in the absence of any stimulus consciously applied by the observer. This is of interest in view of Davis' (1939a) hypothesis that these non-specific responses to sensory stimuli are analogous to the secondary discharge of Forbes and Morison (1939). This would suggest that the electrical activity of the brain during sleep is not the electrical concomitant of 'resting' cells, or of a quiescent brain, but the signal of activity in certain sub-cortical networks. Our data suggest that the projection areas involved may possibly be areas 6 and 9. To confirm this suggestion experiments are in construction for checking these localizations by animal experimentation, both by surgical methods and with reversible deafferentation by drugs.

Further conjecture is not justifiable from experiments on the intact human head and further identification of the structures involved must await the results of the animal experiments.

We have found the plotting of our data in the form of fields an aid to clear localization of the electrical activity we are studying. All our data from experiments on sleep conform to dipole-like fields oriented perpendicularly to the surface of the head. They are therefore more in keeping with Adrian's (1934) (1935) proposal (made for the waking alpha rhythm) of dipoles with their axes mainly perpendicular to the scalp, than with that of Beevers (1944) who suggested a system of dipoles with their axes parallel to the surface of the cortex. It may however be noted parenthetically that there are some data from this laboratory (as yet unpublished) indicating that a certain type of electroencephalographic activity can be recorded from the brain which creates a field consistent with that of a dipole effect parallel to the scalp. This is the activity to which Kennedy (1948) first drew attention and which he named the kappa rhythm. There is also a hint that some sources of alpha activity may be oriented in this way. In these cases, where more than one source is apparent in the records, the concept of dipole sources and the plotting out of the fields has helped us to sort them one from the other.

**SUMMARY**

(1) A method of charting the electrical fields at the surface of the head has been described which has proved useful in the localizing of EEG activity during sleep.

(2) A shift of focus of maximum activity from the parieto-occipital region when awake to the frontal lobes when asleep has been described.
(3) More than one focus, both of slow potentials and of spindles, have been demonstrsted.

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CHAPTER 12

ELECTROENCEPHALOGRAPHY

By

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The twentieth anniversary (1949) of Berger’s first publication on the EEG of man, has been marked by three events of the greatest importance for electroencephalographers: the formation of an international federation of electroencephalographic societies, the founding of a journal especially devoted to this branch of electrophysiology, and the holding of the second International EEG Congress in Paris in September. It is impossible to overestimate the influence of these three events, not only in cementing friendships between workers in many lands but in familiarizing those from this continent with the great postwar growth of the centers across the Atlantic.

Three books on electroencephalography have been heralded for 1949 but have, at the date of going to press, not reached this reviewer. They are: Electroencephalography, a volume of contributions by several authors (Hill, Walter, Cobb, Whitteridge, Greville, Heppenstall and Parr); a new edition of the Atlas of Electroencephalography by Gibbs and Gibbs, and Clinical Electroencephalography by Cohn. An excellent and comprehensive review of papers which appeared in 1946-47 has been published this year by the Walters, and of those for 1948 by O’Leary. Assessments of the scope and value of electroencephalography have appeared during the year and it is good to have a reminder from Bremer of the basis of physiological knowledge on which any of our hypotheses must rest. A fascinating biographical study of Berger has been published which reveals his strange personality, and a Berger Festschrift has appeared in Germany.

Electroencephalography is a field of many controversies, which is stimulating in effect, for in general it is not the data that are called in question but the interpretations deduced. As Claude Bernard maintained, the fact that a controversy can exist shows that no theory yet advanced is sufficient to explain all the data. To the old familiar controversies (bipolar versus ‘unipolar’ technics, automatic analysis versus the unaided eye, etc.) have now been added new ones. Is the standard voltage-time graph the best equipment for localization, or should one use toposcopic display in addition? And exactly what is presaged by strange activity in the temporal
lobe? And what is the role of thalamocortical circuits? All these and many others have become prominent questions in 1949.

First as regards apparatus: Designs for a nonblocking amplifier have been presented by Goodwin and for a direct-coupled amplifier with short blocking time by Offner; a very neat new oscillograph with a frequency response faithful from 1 to 150 cycles per second has been designed by Rémond, who has also produced a tripod electrode which is a modification of the type of silver-silver chloride electrode introduced by Walter. This electrode ensures more even contact and hastens the application of many recording points for localization. Studies of electrode characteristics and of the virtues of nonpolarizable electrodes have been made by Grass and by Rouvray. The disadvantages of the interconnected ear electrodes have again been stressed (McAvoy). The search for a truly indifferent electrode continues, (Stephenson, Goldman, Fuster) although most workers now believe it to be a siren song.

More and more workers are employing nasopharyngeal electrodes and a new design eliminating the need for local anaesthesia has been brought out by MacLean. A bipolar pharyngeal electrode which is introduced through the mouth has been designed by Gastaut, and an electrode which can be inserted in the external auditory canal has been made by Arellano and has added considerably to the technics available for recording from the base of the brain. Types of electrode for recording from the exposed surface of the brain in man have been demonstrated by Marshall and by Geddes. Depth electrodes for recording subcortically have been used by Spiegel, Hayne, Bickford, Epstein and Gastaut.

Recording from the depths of the brain has drawn attention to the electrical sign of the discharges recorded. A discussion of the electrical signs of remote events in the central nervous system has been given by McCulloch. The orientation of the discharging neurones relative to the electrodes is decisive for the form of recorded activity. Gibbs interprets negativity at the exploring electrode (when referred to a relatively indifferent area) as indicating that the electrode is on or in the discharging area, and positivity as indicating that the discharging area is at a distance. This is not the usual experience of the physiologist when recording the electrical fields about a group of discharging nerve cells, for the orientation of the cells themselves determines the distribution of the field potentials. In the quite different case of travelling impulses in white matter, which conducts discharges but never originates them, the reversals of sign have been fully elucidated by Lorente de Nó in his classic monograph on nerve physiology. A clear exposition of the fields around discharging nerve cells has been published this year by Bishop.

Stereotaxic instruments and headholders for use with inserted elec-
trodes, in addition to Spiegel's apparatus, have been designed for man by Baudouin, Jasper, Monnier, Uhlein, and Lorimer, and for small animals by Kaufman, Monnier, King, and Rosenberg. New technics in electroencephalography include remote recording by radio transmission (Blinn, Breakell) and a wave correlator (Goodwin) for giving information as to the phase relations of activity from two different regions of the head.

When one comes to the principles and methods of localization one enters a field in which all are equally interested: the clinical electroencephalographer and the neurosurgeon who want to know where, the physiologist who wants to know why, and the electronic engineer who wants to know how. Walter advocates many simultaneous recordings of different linkages from a few (eight) widely spaced electrodes for the traditional voltage-time curves that most electroencephalographers use, but recommends the additional use of a toposcope in which the intensities of multiple light spots vary as a function of the potential changes between the electrodes on the head which form their input. Many electrodes, each pair having its amplifying system and separate light source with a suitable scanning device, thus can give information as to localization, frequency, phase relations and harmonic relations, but sacrifice waveform. Instruments for toposcopic display have been designed by Lilly, by Walter, and by Goldman. Lilly's records show patterns of two types, those which are fixed in position and oscillate with respect to time and those which travel over the cortex. Among the latter are the 'spindles' found in nembutal anaesthesia, as well as some normal patterns in the anaesthetized animal. Among the users of the standard oscillographic methods are many who prefer far more electrodes for localization purposes and as many channels as they can get. Among these are the Montreal school who advocate 15 as a minimum, Rémond who uses at least 27 and prefers 48, Aird who uses many electrodes and attaches clinical significance to minor differences in homologous tracings. Bagchi has pursued his studies of phase reversal, which should be interesting material for studies of surface electrical fields.

The signs for which one searches when making a localization have been the subject of study in several laboratories. Carvalho finds absence of activity between two electrodes a trustworthy localizing sign for tumors. As a sign of the depth of the tumor, Walter's observation that lesions far from the cortex produce theta waves, whereas lesions near to or invading the cortex cause delta waves, has had fresh confirmation from Cornil and Gastaut in a study supported by histological data. O'Leary finds the differentiation less simple. Bohm finds theta rhythms common in tumors of the brain stem. Types of electrical disturbance which arise at a distance from a tumor and which may be misleading have been discussed by Fisch-
gold, and Drumheller and Bickford have studied tumors in children, giving especial attention to posterior fossa tumors.

A detailed analysis of EEG changes in 70 cases of verified brain lesions in which the basic knowledge of electroencephalography has been applied to the findings has been published by Courville. This paper especially examines the apparently aberrant records sometimes found in these cases and draws attention to transmission over long association bundles and to dislocation of brain mass. Kershman's summary of results in 100 cases of brain tumor should prove a useful guide to clinical electroencephalographers. The EEG findings in a series of 40 cases of verified brain tumor have been reported by Cuneo and Sjaardema who express some disappointment as to the aid given by the EEG in localizing these tumors. Possibly part of this failure may have been due to their use of the triangulation technique which most workers have now jettisoned.

Studies of head injury have progressed. Hoefer has recently summarized the EEG findings in these cases. Kaufman has compared the EEG abnormalities in head injury cases which developed seizures with those that remained seizure-free. Jasper from his long experience of neurosurgical cases concludes that the EEG is of great importance in evaluating the severity of cerebral damage following head injury. Molin reaches the same conclusion from his examinations of children with head injury. Good agreement on the EEG changes in cases of subdural hematoma is seen in the publications of Sullivan and of Marsh.

The addition of automatic analysis to the armory of the electroencephalographer is proving its worth. The flurry which greeted it in its early youth has now subsided. Many automatic analyzers are now in constant use in several different countries; the majority of these incorporate the original design of Walter, but not all. Four others have made their appearance this year: of these, that of Hoefer and Markey uses 20 tuned filters without integrator circuits, and chooses a short period of analysis at the expense of selectivity; that of Minot incorporates a multiplier so that the frequencies 1 to 40 become 40 to 1600 and therefore within the hearing range, making auditory methods of detection possible. Another type of analyzer, based on measurement of wave duration, is under construction at Randolph Field (Prast), and the Japanese school (Imahori) have developed an automatic frequency analyzer consisting of a series of resonating reeds.

The additional information gained from frequency analysis has given great impetus to research on photic stimulation—a subject very appropriate to the Walter type of instrument since the waves produced by flicker have a continuous periodic function. In animals, the response of different cortical areas to photic driving in the rabbit has been mapped by Buser. And with Fessard he has studied “doubling”—the appearance of the second har-
monic of the fundamental flicker frequency—and has established, by the use of colored lights, its dependence on the intensity of the light. Fields, King and O'Leary\textsuperscript{64} find that, with repetitive electrical stimulation in the thalamus, wave frequencies of double and triple the frequency of the stimulus appear, after a variable period, in the cortex. All their results support the hypothesis that the neural mechanism responsible for these harmonics is not the same as that of the alpha rhythm. The differentiation of two related but functionally distinct neuronal systems in which cortical and thalamic activity both take part, the specific response system and the alpha rhythm mechanism, has been made by Bishop.\textsuperscript{16} But it is the clinical application of flicker that has attracted the greatest number of workers, for this is the era of activated electroencephalography. A normal resting record is not, of course, acceptable as evidence for the absence of epilepsy. Further technics must be used to rule it out. Of these there are many: overbreathing, sleep, barbiturates, metrazol (cardiazol), other biochemical activators, flicker, and combinations of these. The activation most commonly used and the least effective is overbreathing. Even when the degree of overbreathing is assessed by some such method as that devised by Bickford,\textsuperscript{14} or the alveolar CO\textsubscript{2} studies of Asmussen and Buchtal\textsuperscript{15} and of Blinn,\textsuperscript{17,18} interpretation of the EEG changes is still difficult. Careful studies by Vigoroux\textsuperscript{248} on 1400 subjects have confirmed that overbreathing gives no differential diagnosis between epileptic and nonepileptic subjects under the age of 15 or over the age of 60. A similar assessment of overbreathing as a diagnostic procedure for children has been made by Debré and Lefebvre.\textsuperscript{59}

Insulin as an activator has been used by Heuyer\textsuperscript{111} for children and by Hertz\textsuperscript{106} who concludes that it is not of diagnostic value. Baisset\textsuperscript{7} has used it in an attempt to bring out foci in head injury cases, but with disappointing results. Hypoglycemia has a more differential effect in schizophrenic patients owing to their high insulin resistance (Hill\textsuperscript{115}). The chemical activator which has received the most attention recently is metrazol (cardiazol). Kaufman\textsuperscript{139} using a rapid intravenous technique has found the method useful in bringing out electroencephalographic foci in symptomatic epilepsy but considers this method inconclusive for differential diagnosis between epileptic and nonepileptic individuals. Paillas\textsuperscript{208} has reported a case in which metrazol brought out a very precise focus on the surface 2 cm. from a subcortical tumor. Roger\textsuperscript{221–223} is more successful with a technique of slower injection especially for bringing out foci, and comments on the diagnostic value of abnormal electrical patterns persisting after the end of the injection. Colombati\textsuperscript{43,44} has found Benzedrine and Pervitin useful activators in some cases of latent epilepsy.

The comparative values of the various methods of chemical activation
have been reviewed by Rémond who emphasizes the diagnostic importance of the threshold at which the abnormalities are provoked, rather than their actual appearance (since they can be provoked in nonepileptic subjects also).

Normal sleep, in the hands of the Gibbs has proved an excellent activator, as has also sleep induced by barbiturates. In the hands of some others it has given less satisfactory results; Merlis found positive results in only 10 per cent of his epileptic cases in contrast to Gibbs' 82 per cent. In a small series of 13 epileptic cases Heuver and Rémond found only two activated by pentothal sleep, but have found the drug useful in refining the localization of cerebral tumors, as have also Euzière and Passouant. Negrin has found that recordings made during and following pneumoencephalography reveal hidden abnormalities which may be of diagnostic value. The same method has been used by Duplay. The use of intermittent sound (Gastaut, Hamoir) to provoke fits has also been studied; Teglbjaerg reports a case in which focal phase reversals were evoked by Chopin's Prelude in A major; Forster has reported a case in which tapping the left shoulder evoked a cortical potential and precipitated an attack. But intermittent light is undoubtedly the more common activator among epileptics.

The technic and effects of photic stimulation have been very fully described by the Walters who, following up their earlier work, have found this method applicable to a wide range of conditions. The simplicity of this method for routine use has been demonstrated by Gastaut who has also used it when recording at different depths in the exposed cortex of man. As a basis for assessing the responses of patients to flicker, Bickford's study of normal subjects is most valuable. Opposing opinions have been recorded as to whether a facile response to photic driving is indicative of immaturity (Walter) or physiological maturity (Ostow).

Among epileptics photic stimulation appears to be an especially potent activator in the petit mal cases and several striking instances of its use in these patients have been published. A striking advance is in the detection of thalamic factors in certain types of epilepsy by a combination of the two activators, Metrazol and photic stimulation, a technic evolved by the Marseille laboratory. In brief, it consists of the very slow intravenous injection of Metrazol with frequent application of photic stimulation; no subject, healthy or epileptic, is unaffected if the injection is pushed far enough, but the threshold of reaction to flicker is reached at a far lower dosage of Metrazol in the epileptic than in the normal subject. The Metrazol alone being so far below a convulsive dosage, complete control of the patient's reaction can be maintained by the application or removal of the stroboscope, and the test need not be carried to the stage
of a convulsion. For the patient the advantages are obvious. Confining the seizure pattern to threshold level in this way also brings out localizing signs which, if present, might be lost in the general turmoil of a full seizure. Studies of the reactions of nonepileptic subjects to this method of activation have been made and interesting results have been found in cases with lesions in the optic radiations, thalamo-cortical connections and in the motor pathways.

Consideration of these many methods of activation reveals how meaningless is any statement as to the percentage of epileptic patients who give normal records. Any such figure merely reflects the intensity of the search that has been made for the activator appropriate to each case (though a record which is normal without activation may have prognostic value). Activation has undoubtedly raised the percentage of abnormal records in epilepsy very greatly and in the opinion of some this figure may soon be 100 per cent. What is more important is that the number of records specifically diagnostic of epilepsy has been raised by these methods.

The focal signs of epileptic discharge, whether evoked or spontaneous have received considerable study (Gastaut). The Montreal school from their very wide experience have lately modified their criteria from those listed earlier in the year. It is now recognized that the random spike discharge is not the only sign of a local epileptogenic lesion of the cortex. High voltage slow waves have been found, upon occasion, to have a local cortical origin, as have also paroxysmal discharges of rhythmic form. The distinction between abnormalities of local cortical origin and those transmitted over fiber systems from disturbances at a distance from the cortex is thus less easily drawn. O'Leary finds no distinguishing differences between focal cortical and focal subcortical lesions causing seizures. But for the electroencephalographer the classification of the epilepsies is still more satisfactorily described on a basis of localization than of waveform alone (Kershman and Jasper). Even the wave-and-spike is sometimes found in traumatic cases (Derbyshire), (Jasper). This particular waveform however retains its fascination and both receives and merits engrossing attention. Its clinical correlates have received further study by Lennox and by Subirana, and its waveform further analysis by Cohn.

The origin and spread of the epileptic discharge is of absorbing interest because of the implications. Jasper has followed up the earlier studies made with Fortuyn by further animal experimentation. Rhythmic electrical stimulation, at a critical frequency, of midline thalamic nuclei in the anterior portion of the massa intermedia—though not apparently strychninization of the nuclei of this area (Cohn) has been found to produce in cats bilaterally synchronous wave-and-spike complexes, closely analogous to those seen in petit mal epilepsy. It is now shown (Hunter and Jasper)
not only are the electroencephalographic signs elicited by localized stimulation of the intralaminar nuclei of the thalamus, but also, in unanaesthetized animals, they are accompanied by a petit mal type of seizure. The hypothesis of a diencephalic pacemaker for petit mal discharges thus receives strong support, although whether in these patients an abnormal pacemaker triggers a normal cortex, or a normal pacemaker triggers an abnormal cortex (as Bremer has suggested) remains to be demonstrated. Wyceis and Spiegel\textsuperscript{269} have been able to record in man from the thalamic regions in cases suffering from grand and petit mal attacks. They found random spike discharges at various levels in the thalamus but these were not maximal in the region of the internal medullary lamina. M. Lennox,\textsuperscript{186} on the other hand, finds that the symptoms evoked in animals by electrical stimulation of the cingulate gyrus are similar to the clinical symptoms of petit mal, akinetic and myoclonic epilepsy.

Darrow\textsuperscript{49} has suggested that there may be different mechanisms involved in the spread of different types of epileptic discharge, the grand mal seizure being favored by any agent which lowers the threshold of cortical excitation, and petit mal by any condition which limits the intrinsic activity of the cortical cells rendering them more susceptible to synchronization. Evidence for a different mechanism in the grand mal type of seizures from Jasper’s thalamic pacemaker of petit mal is found in McCulloch’s\textsuperscript{379} experiments where the epileptic discharges spread through the white matter immediately below the cortex (and after thalamic removal). An excellent account of the electrophysiology of the epileptic discharge has been published by Droogleever Fortuyn.\textsuperscript{53}

The location of the structures stimulated in some of Jasper’s experiments is of interest when compared with those which Hess\textsuperscript{107} has found to evoke sleep, another condition in which the EEG indicates a general synchronization of cortical neurones. Hess’s electrode placements are in the inferior half of the thalamic massa intermedia (there may be some differences of anatomical nomenclature between the Zürich and the Montreal schools) and his stimulating frequency is 4 to 6 per second. As a corollary to this are the arousal reactions resulting from stimulation of the reticular formation of the cat’s brain stem and basal diencephalon which have been studied by Moruzzi.\textsuperscript{198–201} This “arousal” is evoked by stimulation of pathways other than the classic sensory paths, impulses in which are known to disrupt the EEG diffusely. Hess,\textsuperscript{109} in unanaesthetized and unrestrained animals, has found areas quite near to each other which give different responses on stimulation.

These animal experiments in which stimulation of subcortical centers has resulted in sleep or its opposite have aroused interest in localization of EEG activity during sleep in humans. Liberson,\textsuperscript{163} R. Hess\textsuperscript{109} and Brazier\textsuperscript{33}
agree in finding the main foci in sleep at positions on the skull which appear to lie over areas 6 and 9. R. Hess finds the pattern during narcoleptic attacks to be that of normal sleep whereas there is no EEG change in cataplexy. Use of a depth electrode in man by Meyers and Knott\(^\text{188}\) reveals that the typical EEG changes with sleep appear in the thalamus and corpus striatum several minutes before they are recordable from the cortex. R. Hess has used displacement of the normal sleep foci as localizing evidence in cases of brain tumor, and Grossman\(^\text{100,101}\) has used the response pattern to auditory stimulation during sleep for a similar purpose. Calvet\(^\text{55}\) has studied electroencephalographic responses to sound during Pentothal “sleep” and Marcus\(^\text{172}\) has used them to detect hearing loss in very young children.

Lindsley\(^\text{166}\) finds destruction of the brain stem activating system intensifies the synchrony of cortical activity. This result is interpreted as the release of synchronized activity in thalamo-cortical pathways isolated in this way, and it is suggested that such a mechanism may account for the synchronized activity in the EEG in normal sleep and under barbiturate anaesthesia. If the lesion is restricted to the ventromedial hypothalamic nuclei there is no EEG change cortically although as a result of the lesion the animals show typical savage behavior (Wheatley and Knott\(^\text{255}\)). Horsten and ten Cate\(^\text{129}\) have examined the effect of temperature changes on the rhythms of the cortex, thalamus and hypothalamus in rats. The action of barbiturates on the EEG in man has been studied by Wulff\(^\text{259}\) and by Tucci and Brazier.\(^\text{246}\) In human subjects large doses of barbiturate may produce periods when no cortical activity can be recorded; these cases do not necessarily end fatally and the records appear very similar to those found by Swank\(^\text{242}\) in his experiments on dogs. Cohn\(^\text{42}\) finds the EEG changes in barbiturate intoxication to be so consistent that they are of diagnostic value. For anaesthesia with either barbiturates or ether, Bickford\(^\text{12}\) has developed a dosage regulator controlled by brain potentials; as the potential output of the cortex drops with deepening anaesthesia, the supply of drug is cut down by a feed-back circuit operated by the integrated EEG potential.

The problem of psychomotor epilepsy has been admirably reviewed by Hill.\(^\text{114}\) From his extensive survey some specific facts emerge. A common interseizure pattern is, as Gibbs has shown, a spike focus in the anterior temporal area, but in fact spike foci are also common in other areas (the early confusion in which the intervals between the spikes were interpreted as ‘square-topped waves’ has now been cleared up). This type of EEG abnormality is not however specific to this kind of epilepsy, nor is it the only type of abnormality correlated with psychomotor attacks. When the other kinds of abnormality (focal slow waves, etc.) are also taken into account the temporal lobe emerges clearly as the favorite site. O’Leary\(^\text{208}\)
has reached the same conclusion. Hill suggests that this may be due to a greater readiness with which impulses are conducted from the temporal cortex to some deep central pacemaking mechanism where they disturb the activity of the thalamocortical system. Fuster confirms the high incidence of temporal lobe foci in this form of epilepsy as also does MacLean using nasopharyngeal and tympanic leads. In this context it is interesting that M. Lennox finds spontaneous spikes common in the exposed temporal lobes of monkeys and finds stimulation of these areas the most productive site of seizure discharges. Cases of borderline or larval epilepsy with minimal symptoms such as dizziness or blurring of vision (or rare seizures in some cases), have been followed over a course of years by Kershman. All have abnormal electroencephalograms between attacks, which differentiates them from cases of syncope.

The electroencephalogram is still used by some workers to assess the effect of anticonvulsant drugs. Lennox finds that clinical and EEG improvement follow only a broadly parallel course during drug therapy. In the case of mesantoin, Little has shown that EEG abnormalities may even increase while the clinical state is improving. Jewesbury finds that the clinical response of cases of petit mal to treatment with Tridione is not necessarily paralleled by changes in the EEG. But Melin, on the other hand, finds the EEG changes a guide not only in the Tridione therapy of petit mal but also in the treatment of grand mal epilepsy with Dilantin. Kaufman reports a parallelism of response when using Paradione. Toman points out that any correlation between clinical and EEG improvement varies widely from patient to patient.

Dalsgaard, Nielsen and Hertz in a study of headache find dysrhythmia frequent in cases of migraine between the attacks but the dysrhythmia is not increased when headaches are induced by nitroglycerine or histamine, from which they conclude that vasodilation is not the cause of the dysrhythmia. On the basis of the EEG findings, Delay, like Lennox, considers some cases of migraine as epileptic equivalents.

In the field of psychiatry an interesting contribution has come from the Maudsley Hospital group (Pond, Rey). By giving their attention more to location of activity than to a search for abnormal frequencies, they have established in a study of a great many records from neuropsychiatric patients that in cases with abnormal potentials localized in the temporal region, immature or schizoid personalities are common. The authors suggest that in those cases where the EEG abnormalities are confined to the temporal lobe there may be some local defect of maturation resulting in immaturity of personality.

An approach of this kind brings one closer to understanding the persistent reports of abnormal EEG’s in schizophrenics, psychopaths and
children with behavior disorders. Kennard\textsuperscript{41} found 67 per cent of her group of child schizophrenics and 72 per cent of those with other behavior problems had abnormal EEG's, but she stresses that the EEG's are not merely those of a younger age group, for they would be abnormal at any age. Jus\textsuperscript{94} from his study of 82 schizophrenics was led to the conclusion that the scarcity of alpha rhythms in their records was due to extreme tension in persons incapable of relaxation. Honke\textsuperscript{118} has found slight dysrhythmias in 35 per cent of a large group of psychopaths but found them also in 12 per cent of his normal group. He has contrasted the type of abnormalities found in these cases with the more severe dysrhythmias of epileptics. He has found no evidence for a genetic factor for this type of dysrhythmia.

In the psychoneuroses, Faure\textsuperscript{63} has made an attempt to determine whether the modifications of the EEG in these cases (low alpha content, etc.) are permanent bioelectric characteristics or merely due to the reaction of the patient to the experience of the test. By the use of Rorschach cards and the Murray thematic apperception test he established a correspondence between the transient changes in the EEG and the degree of emotion aroused by the cards. Cain\textsuperscript{34} in his study of boys with behavior troubles confirmed that a strong rhythm in the 4-7 cycle band (theta), usually present only in the subdominant hemisphere, is a fairly consistent abnormality. Bert\textsuperscript{13} finds theta rhythms common also in hysteria and regards them as a sign of immaturity not necessarily specific to hysteria.

In the field of pediatrics electroencephalography of the newborn has been studied in some detail by Surean\textsuperscript{259,260} who found electrical activity even in the occiput within a few hours of birth, a result which contrasts with that of Hughes\textsuperscript{222} who found no activity worthy of the name in newborn infants unless they were drowsy. Some early studies made with a Grass frequency analyzer have now been published by Gibbs\textsuperscript{92} and cover not only the newborn but older children and adults to the age of twenty-nine. Jasper\textsuperscript{137} has published a valuable guide to the electroencephalographic findings in the records of children with various neurological diseases. Larsson and Melin\textsuperscript{134} have followed the change in alpha frequency over a period of ten years in 60 normal cases and find a more regular increase than in mongoloids, spastics and mentally deficient children. Mozziconacci and Lefebvre\textsuperscript{202} find the EEG useful in the differential diagnosis of convulsions in infancy. Shinners\textsuperscript{331} has followed up the EEG's in encephalitides following some of the common diseases of childhood. Cobb\textsuperscript{39} has described a specific periodic slow wave complex in sporadic subacute encephalitis unlike the EEG abnormalities seen in the common type of encephalitis. In tubercular meningitis Euzière and Passouant\textsuperscript{49,60} and also Lichtenstein and Melin\textsuperscript{164} find the EEG changes to be useful prognostic indicators during streptomycin therapy. Brissaud and Levebvre\textsuperscript{31} from their cases of men-
ingitis reached the same conclusion. They also studied the EEG in acute poliomyelitis.

The question of the role of thalamo-cortical circuits in determining the rhythmicity of the "spontaneous" electrical activity of the brain has attracted a great deal of attention this year. Bremer\textsuperscript{26,27} has restated his opinion that the spontaneous electrical activity of the cortical grey matter is only a particular manifestation of the general tendency to synchronized autorhythmicity common to all central neuronal aggregates and that it is not dependent on rhythmic activity of the thalamus or on activity reverberating in thalamo-cortical circuits. In his experiments on unanaesthetized cats with the "encéphale isolé" technic, he found that sectioning of the thalamo-cortical fibers greatly attenuated and modified the electrical activity of the undercut cortex but did not abolish it. From this and other experiments he concludes that, although cortical neurones receive thalamo-cortical impulses (not necessarily rhythmic) and although their activity may sum with these impulses (and also with outgoing pyramidal cell discharges), their rhythm is not paced by them. The synchronizing of the beats he attributes to direct electrical interaction as well as to synaptic connection between the cortical neurones.

This view is in agreement with earlier findings of Spiegel\textsuperscript{22} who, in 1936, was the first to describe the persistence of rhythmic discharges from the cortex (sigmoid gyri) after the connections with the thalamus had been completely cut. Kristiansen\textsuperscript{18} also found traces of very low voltage rhythmic activity surviving in portions of completely isolated cortex provided an adequate blood supply was maintained. Swank's\textsuperscript{24} experiments on barbiturized dogs may perhaps be interpreted in the same way. Some clinical reports of EEG changes following frontal leucotomy have also been regarded as supportive evidence for this viewpoint (Kershman,\textsuperscript{149} Henry,\textsuperscript{105} Lennox\textsuperscript{155,156}) although not all workers have interpreted the results in this way (McCulloch,\textsuperscript{180} Levin\textsuperscript{161}). Gellhorn's\textsuperscript{67,68} animal experiments, in which he injects strychnine into the hypothalamus and thalamus, suggest that it is only when the cortex is in an abnormal state of activity that its rhythms are paced by subcortical centers.

On the other hand, another hypothesis as to the origin and nature of the alpha rhythm has its equally enthusiastic supporters. The concept which envisages the alpha rhythm as a sweep scanning the cortical projection areas for activity arriving from the sense receptors, as suggested by Marshall and Talbot in 1942, receives support from Walter\textsuperscript{294} and from McCulloch.\textsuperscript{181} This is a very attractive hypothesis from a theoretical point of view since it is easy to envisage a scanning mechanism behaving as does the alpha rhythm, and models have been made\textsuperscript{294} which act in this way. The physiological evidence is however as yet indirect. There has been a growing
tendency in several laboratories to study the brain as a transmission system and Prast\textsuperscript{21} has suggested consideration of the brain as a transmitter of transient signals with a relatively narrow band-pass filter.

The hypotheses of autorhythmicity and, on the other hand, of a scanning mechanism, that is, of impulses passing periodically through the cortex, whether their path is thalamo-cortical or entirely intracortical, do not to this reviewer appear mutually exclusive. Less compatible is the hypothesis that the rhythm is set by the conduction time of impulses circulating round a multineurone loop between the thalamus and the cortex.

The role of the alpha rhythm not only in afferent inflow but in efferent discharges, raised again by Bremer,\textsuperscript{28} has interested other workers. Bates\textsuperscript{8} in a study of voluntary finger movement recorded by multiple superimposed electromyograms and EEG's finds that when alpha activity is present there is a significant tendency for the voluntary movement to be initiated always at the same point in the phase of the alpha wave. Kibbler and Boreham\textsuperscript{21,150,161} made simultaneous recordings of the alpha rhythm and eye-opening in response to an auditory stimulus and found that the probability of the occurrence of a motor discharge depended on the phase of the alpha rhythm. These experiments follow directly from the classic observation of Adrian and Moruzzi. Two attempts to evaluate in man the influence of spino-cerebral discharges on the EEG have been made by studies of the effect of spinal injury (Merlis\textsuperscript{138}) and spinal disease (Kaplan\textsuperscript{125}) but the conditions, as the authors point out, were not critical nor are the results unequivocal.

The inter-relationships between the alpha rhythm and other rhythms is little understood. Masland\textsuperscript{178} has described 6 cases of occipital lobe removal in which the postoperative EEG showed the interesting finding of increased activity (sometimes of alpha frequency, sometimes rather slower) in the temporal area of the operated hemisphere. This activity waxed and waned independently of the occipital alpha activity of the opposite side. He has suggested that this may be a release phenomenon. Kennedy\textsuperscript{142,143} has reported further on the activity in the temporal area evoked in some subjects by fixating the eyes and diverting attention from visual sensation to mental tasks. Whether this too is a release phenomenon remains for further work to decide. It seems unfortunate that this activity, which was described by Liberson in 1937, should have been given a new name, since it is not yet clear that it is a separate rhythm.

Another question is the role of reverberating circuits, not in the resting alpha rhythm, but in the cortical responses evoked by sensory stimulation. Bremer's contributions\textsuperscript{28,33} continue to lead the field in study of the auditory cortex. In the unanaesthetized animal he finds both the components of the diphasic response to a click to be cortical in origin, the initial positive
wave being the reaction of cortical interneurones with short ascending axons, and the slower surface-negative wave being the postsynaptic corticofugal discharge of large pyramidal cells; he finds no evidence for corticothalamic reverberation.

In the visual sensory system Monnier's studies of the electroretinogram and its relation to the cortical response established that the long-lasting surface positive potential which follows the earlier diphasic potential is the most constant response recordable in man. Its latency varies from 90 to 115 msec. The initial positive response is more difficult to obtain, but when found has a latency of 40 msec. The long interval between the time of arrival of visual impulses at the cortex and the first blocking of the alpha rhythm (215 msec. after the stimulus) leads Monnier to the conclusion that reverberation in thalamo-cortical circuits must play some part in the alpha response. The short latency time for the evoked response in man has also been found by Cobb using the technique of superimposed sweeps on a cathode-ray tube.

From their results obtained with flickering light most workers have been led to the conclusion that some reverberation must take place. Gastaut evoking myoclonic attacks by this method is convinced of thalamic participation since the discharges occur bilaterally in the receiving areas of projection tracts from the thalamus. Perhaps a clue to the underlying mechanism may lie in the hypothetical schema suggested by Forbes to account for the refractory phases in cerebral mechanisms. Evidence for reverberation is contributed by Walter who reports a case of myoclonic epilepsy in which the evoked rhythmic response persisted in the EEG after the stimulus was cut off. Chang's studies of the repetitive discharges set up by an afferent volley in the monkey's thalamus and cortex show them to behave like a reverberation rather than an afterdischarge.

Some fuller understanding of the organization of the thalamus and its relationships with the cortex is clearly essential for electroencephalographers, and we have been helped in this by several excellent papers. Rose and Woolsey's studies of degeneration of thalamic nuclei after removal of cortex has shown that each dorsal thalamic nucleus has its specific projection area in the cortex; in the ventral thalamus only the reticular complex degenerates. In the dorsal thalamic nuclei of higher primates, in contrast to lower animals, they find more nuclei whose afferents originate within the thalamus than outside it. Drooglegover Fortuyn using the same technic found little evidence for interneurones in the thalamus in rabbits. One's immediate thought is to use caution in drawing too close an analogy between animal experiment and observations in man, but in the case of thalamic projection to the cortex, Gerebtzoff has found remarkable constancy in his studies of comparative anatomy. Minkowski has con-
continued his detailed studies of thalamic-cortical connections in the monkey and the cat, and McLardy\textsuperscript{182} has worked them out in man from postmortem specimens with primary lesions of the frontal lobe. He found point-to-point projection from the dorsal medial nucleus to the prefrontal cortex, from the anterior nucleus to the anterior cingulate gyrus, and from the ventralis anterior to the premotor cortex.

The electrical potentials recorded directly from the thalamus in man are difficult to interpret. Williams\textsuperscript{258} has studied them in a variety of conditions. Spiegel and Wycis\textsuperscript{234} have made cortical and thalamic recordings before thalamotomy; after the operation the chief cortical change is a transitory slowing of rhythm in the frontal leads. Shinners\textsuperscript{229} has recorded rhythmic activity from the thalamus in an infant with agenesis of the neopallium, and has studied the results of stimulating in that area.\textsuperscript{230}

With so much discussion of reverberation in neuronal systems, it was inevitable that electroencephalographers would be stimulated by the growth of interest in cybernetics since the publication of Wiener's\textsuperscript{256} book. Essays in this field have been published by Walter,\textsuperscript{262} by Hoagland,\textsuperscript{116} by Gastaut\textsuperscript{72} and by Brazier.\textsuperscript{24} A somewhat different approach has been followed by Ashby.\textsuperscript{4} The implications for neuropathology have been reviewed by McCulloch\textsuperscript{181} whose contribution is a major one.

If one attempts to summarize the progress in electroencephalography in 1949 the most striking feature is that it has emerged from being a merely descriptive science (what Gerard has called "the simple description of pen wiggles"). The era of the statistical study of empirically established relationships is also behind us, as is evidenced by the scant number of this type of report.

The electroencephalographier of 1949 is concerned with experiment, induction and application of the findings to clinical medicine, and it is here that a reverberating circuit between the laboratory worker and the clinician becomes indispensable.

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ELECTROENCEPHALOGRAPHY

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A study of the electrical fields at the surface of the head

**The electrical fields at the surface of the head**

The concept to be discussed is not new; in fact, it has been lifted whole from theoretical physics. It is its application to electroencephalography that will be described here. Most of our work in human electroencephalography is a study of the voltage distribution on the surface of a volume conductor — the brain. We would like to know what kind of generators inside this volume conductor could give us the voltage distribution which we find experimentally. This is not quite as im-

possible as it sounds: it is a similar problem to that which the geophysicist has who attempts, from the behavior of his instruments on the surface of the earth, to detect what lies below. We have one advantage over him — we have our knowledge of the projection pathways to the cortex.

Although we have only the electrical events at the surface to study, if we are able to localize any specific type of electrical change to a given area of the surface we can, by applying our knowledge of projection tracts to the cortex, approach the question as to where it is coming from.

Working with this concept we have studied some of the several components of the human EEG with this in mind and the results will be outlined here. This work includes studies of potentials of the normal brain, waking and sleeping, working and resting, and under the abnormal conditions of anoxia. Some examples of EEG from cases with brain lesions will also be shown.

Adrian and his colleagues in 1934 studied the distribution of current of the alpha rhythm with the skull intact, and trephined, and stated their conclusion that the potentials were due to structures close to the surface of the brain and directed at right angles to it,

**Figure 1.** Lines of current flow proposed by Adrian and Matthews for the alpha rhythm. *(Brain, 1934; 57: 355).*

This figure is reproduced from Adrian and Matthews original paper and shows the lines of current flow they proposed for a generator close to and at right angles to the surface of a sphere: of an intact skull, and of a skull with an opening at the vertex. These authors concluded that the active region must cover a fairly large area in the occipital lobe and thus it must be close to the surface of the brain. If it were deeply situated the short-circuiting by inactive tissue would be too great to allow the potentials to be recorded through the skull.

In this diagram the source of current has been sug-
Fig. 2. — Schema suggested by Beevers. (Edinburgh Roy. Soc. Proc., 1944-7, 62 B, 43-50)

Fig. 3. — Classic field of a dipole in an infinite conducting medium. (Lloyd: In Howell's Textbook of Physiology).
THE FIELD of a DIPOLE in an INFINITE CONDUCTOR

Voltage distribution along a surface YY, 3 cm. from center of dipole.

Figure 4. — Voltage distribution for planes parallel to, and at right angles to a dipole.


gested in the form of a double-layer of equal and opposite charges and these dipoles are oriented with their axes perpendicular to the surface.

In 1945 Beevers made a new approach to this question and as a result of his studies concluded that a complex of dipoles with their axes lying parallel to the scalp gave a field more closely analogous to that found in the EEG. Figure 2 shows the type of schema he suggested.

Figure 2.

We have been interested in re-examining these concepts of dipole-like fields in relation to the EEG.

Figure 3.

In Figure 3 is an example of a classical field of a dipole in an infinite conducting medium, taken from Lloyd. The picture shows the positive and negative poles of an electrical source and the flow of current in the arbitrarily accepted direction from the positive to the negative pole. The lines of equipotentiality lie, of course, at right angles to the current flow and are shown here as broken lines. Any pair of electrodes lying on the same contour line will register no potential difference.

Figure 4.

In Figure 4 we have calculated the voltage distribution for planes XX and YY at a distance 3 cm. from a point dipole. We have plotted the potential difference since this is the information our EEG gives us, rather than the lines of current flow which Adrian used. They are, of course, at right angles to each other. These fields are really three dimensional, as also in the last figure, and the lines should be thought of as surfaces.

This is a diagram of a typical dipole-field which shows on the left the calculated voltage distribution along an axis parallel to the dipole and 3 cm. from its center. This would be the field to expect in the EEG, were the generator lying parallel to the scalp. It is an approximately S-shaped curve. In this case a row of electrodes along plane YY would give two simultaneous foci for a single source of current, one on the positive side, one on the negative. The formula from which the curve was derived is the one shown on the figure, where \( V \) = the potential difference, \( P \) = the dipole moment, \( K \) is a constant, \( Y \) is the linear distance along this plane drawn 3 cm. from the center of the dipole.

If we took the plane through the origin of the dipole, the potential differences would of course be maximal, and the change from positivity to negativity would be instantaneous.

Now let us take the other case in which the dipole is oriented perpendicularly to the surface: the voltage distribution is shown along the plane XX in this diagram. It is quite different. This curve has been plotted
THE EFFECT of BOUNDARIES on the FIELD of a DIPOLE

INFINITE CONDUCTING MEDIUM
Voltage distribution along a surface XX, normal to a dipole and 3 cm. from its center.

CONDUCTING MEDIUM LIMITED to a SPHERE
Voltage distribution along the surface of a sphere 10 cm. in radius, due to a dipole 3 cm. below the surface and oriented perpendicularly to the surface.

Fig. 5. — Effect of boundaries on electrical field

Fig. 6. — Fields of a focus of slow potentials in sleep
from the formula shown above it. A string of electrodes along this plane gives only one focus — no electrode on this plane records from the opposite half of the field.

It is approximately to the latter distribution that the fields of many of the components of the EEG most commonly conform. But in the case of the head we do not have an infinite conducting medium; the volume conductor in this case is confined by its surface. This makes the voltage distribution quite different.

Figure 5.

This figure shows the voltage distribution we saw before, along an axis normal to the dipole and 3 cm. from it in an infinite conducting medium.

Under this is shown the voltage distribution along the boundary of a sphere in the vicinity of the dipole inside it oriented from the center to the surface and also 3 cm. from the surface. Although the head is not a true sphere this approximates more closely to the conditions we are concerned with in the human head. The boundaries have a marked effect on the voltage. The fields are distorted in a way which gives a greater voltage on the boundary in the vicinity of the dipole than would occur at a similar distance from the source in an infinite medium. The fields fall away very steeply in voltage when recording electrodes are immediately over the source and then more gradually as the distance is increased. This is a point of some importance which will be discussed later. This figure has been derived theoretically, but it is a simple matter to confirm it experimentally.

The first EEG illustrations are from a sleeping subject. A sleep record has been chosen to begin with because here the foci are very well localized and, what is more, they occur with great consistency at the same places on the scalp.

Figure 6.

One of the common foci of slow potentials in sleep as we know not only from our own work but also from that of Davis, Liberson and others, is just forward of the vertex. Here is an example of a sleep record showing this focus. It is our practice to use very many electrodes in this work, applying them ad hoc to surround and confirm foci when found, but for the sake of clarity each example given will show only those electrodes whose tracings are shown in the sample in the figure.

This sample of tracing was obtained from a string of electrodes along the midline, each connected to an electrode sufficiently remote to contribute nothing which could confuse identification of the particular signal we were studying. We find the practice of monitoring our remote electrode very helpful in deciding whether it is really ‘indifferent’ in respect to the particular activity in which we are interested: we often use an electrode on the cervical spine as a remote lead and give one channel of our EEG to the recording of the potentials between this neck electrode and one elsewhere far out on the body. This, of course, usually gives us a heartbeat but since we run most of our records at fast speed (6 cm. per second) we get ample space between beats for recognition of any competing potentials.

In this illustration a schematic diagram has been made of the voltage field which would fit the data at the moment in time marked on the sleep record. Such a sketch can be only approximate for many reasons, among which are that the curvature of the head is foreshortened in the drawing and that the number of relationships and measurements of voltage gradients that can be made for any one moment is limited by the number of channels of the electroencephalograph in use. Any faults in alignment of the pens, or in the calibration of the channels or phase distortion by the amplifiers would contribute errors.

In the chart on the upper right the amplitude of the change in potential in the time between the two vertical lines was measured in millimeters for each midline electrode referred to the distant electrode. This represents the positive slope of the slow transient marked in the EEG. These measurements are entered on the EEG record and are plotted on the ordinate of the graph. On the abscissa is plotted the length in centimeters of a line from the nasion to the inion and the placement along this line of the electrodes. These measurements were made on the arc of the head and their projection onto the plane of the paper carries the error familiar to map-makers. The peak of the amplitude difference is seen to be near electrode 4, which was 17 centimeters from the nasion and 2.5 centimeters forward of the vertex in this individual.

The resultant curve is similar to that which we have just demonstrated to be the field of a dipole oriented perpendicularly to the scalp. It is not an S-shaped curve, and it shows only one focus.

In the schematic drawing of the head in this slide the simplest fields which would fit these data are sketched diagrammatically. For demonstration purposes one contour line has been drawn for each millimeter of pen excursion measured on the EEG. The head is drawn to the scale of the abscissa of the same chart. These are, of course, not the only foci found in sleep.

Another type of record in which one can make a simple study of a stationary field is often found in cases of brain lesions.

Figure 7.

The slide shows two EEG’s taken a month apart on one of D’Schwab’s patients with a lesion in the left post-frontal region, the position of which was confirmed by operation. The electrode placement was different on the two occasions and was not designed with this sort of study in mind, but the same field diagram fits both lots of data. The first test did not include electrode placements 1, 2, and 3 and the record showed most disturbance at 5. In the next test by using more electrodes it was possible to pin down the localization more exactly, but the same field held for both tests.

This is, of course, essentially what any electroen-
Fig. 7. — Field of a focus of a lesion (for details see text).

Fig. 8. — Schematic diagram to demonstrate the data used in plotting a field.
Fig. 9. — The original EEG from which the schema in Fig. 8 was drawn.

Fig. 10. — Field which fulfills all the data given in Fig. 9.
cephalographer is doing when he searches his record for localizing data. He does not usually graph the fields of the activity he finds, but we would suggest that were he to do so he would be able to extract yet more information and this we hope to be able to demonstrate in later examples.

Figure 8.

Here is a schematic diagram showing what we all look for in our records when making a localization. We look for the sign and amplitude of the pen deflection resulting from each combination of electrodes at the same moment in time. Here a lesion at the darkened spot, is at the moment shown, negative to all other areas of the head. Actually two electrodes are over the lesion and are therefore isopotential. Not only are the electrodes over the lesion negative to all others but any electrode which is nearer to the lesion is negative to any one which lies farther from it.

Figure 9.

This is the actual record with the moment we are analyzing marked by the arrows. In the top channel the left temporal electrode is seen relatively positive to one on the lesion. Then the electrodes string along the forehead with, in every case, the electrode nearer the lesion being negative to a more distant one. In the 4th channel, the electrode on the extreme right frontal region is linked to the right temporal electrode and shows normal activity because both electrodes are outside the field of the disturbance. In the 6th channel both electrodes are over the lesion and are equipotential. They do not record any disturbance. The 7th and 8th channels record the spread of disturbance on the left side of the head. One field, and only one fulfills all the data.

Figure 10.

These recordings have been made on an electroencephalograph with eight channels and the data obtained are less likely to be equivocal than with fewer channels. As soon as one is restricted to four or fewer channels the plotting of fields becomes invaluable in revealing apparently hidden foci. For example, in this case supposing one had two electrodes recording from the dark spot, there could be no potential difference between them. Another two might be on the next contour line and again no potential difference would be registered, and again if they were both on the further contour or on any other which one cares to sketch consistent with the data. It would be quite possible to miss entirely this episode of abnormal waves. They would not of course, be missed if each electrode were referred to an indifferent electrode, say one on the cervical spine for this when plotted reveals the degree of negativity at each exploring electrode. This has been done at the upper left of figure 11. In this particular example we established that our remote electrode was equipotential with the right temporal electrode in respect to this par-

![Voltage plot (upper left) drawn from the field established in Fig. 10.](image-url)
particular slow wave disturbance. Therefore one may use this same EEG strip to demonstrate the voltage plot. Electrode 1 and 2 show zero potential (as seen in channel 4) and are so plotted on the graph. In the 3rd channel we see that electrode 3 is 60 uV negative to electrode 2 and is plotted as 6 in the voltage graph. In the second channel electrode 4 is negative by 40 uV to electrode 3 and this added negativity is plotted in the graph. Channel 6 shows electrodes 4 and 6 equipotential and on the other side of electrode 4 the voltage plot begins to go downhill.

Figure 11.

This particular case came to operation and a rather deep-lying lesion was found in the left frontal lobe. The fact that it was likely to be deep-lying was predicted by the shape of this voltage distribution curve, a statement which will be defended in a moment. It is in fact only a detailed description of standard EEG practice. The shape of this voltage distribution curve takes the form of a plateau with rather gently sloping sides.

When we come to examine the fields of the alpha activity we find a more complex situation. The source of maximum activity is not nearly so stationary when the subject is awake as when he is asleep, nor is it as stationary as a lesion.

Figure 12.

This example shows the type of field very commonly found for the alpha rhythm, plotted for the moment marked on the record. The first two channels show the anterior-posterior reversal at electrode 3, and the next two the lateral reversal at three. The last 3 channels give the voltage gradient of three of the occipital electrodes to a frontal electrode which is relatively inactive as regards alpha activity. The highest amplitude is seen in the 6th channel, and comes from electrode 3. This is the familiar voltage distribution of alpha. But it is, of course, a very great oversimplification of the real situation. As Adrian pointed out, the distribution of current flow of the alpha rhythm shifts from time to time and the area of maximum activity moves over a fairly wide area.

Not only does the source shift in position but dipole-like fields are sometimes found which give a distribution of voltage such as one finds on a surface parallel to the axis of a dipole. In other words, there is an apparent effect in which both ends of a dipole-like field are found on the scalp, one in the occiput, one in the frontal regions. In these cases the frontal alpha rhythm has the same frequency and opposite polarity to the occipital alpha and sums with it in a linkage using a frontal with an occipital electrode, thus giving an apparently abnormally high voltage. The voltage in these cases is, in fact, not abnormal, it is merely doubled by an electrode placement which records a situation similar to the summed potential difference at both ends of the same dipole source. An alpha source such as this blocks light simultaneously in the frontal and the occipital

THE SURFACE POTENTIAL DISTRIBUTION OF AN ALPHA RHYTHM

![Diagram](image-url)
regions unlike the alpha sources of purely frontal origin which have been described by other authors.

Figure 13.

This figure shows two samples of alpha activity giving this kind of distribution. They are from the same EEG within half a minute of each other and are shown in this way only because the eight channels to which we were restricted were insufficient to show all the leads simultaneously.

In both these samples the remote electrode was on the neck, which accounts for the muscle potentials you see in the record. In the top channel of each sample this electrode on the neck is linked to the wrist to check whether it may justifiably be regarded as indifferent. The placement of the other electrodes is shown in the diagram of the head. The sample on the left takes in all the scalp electrodes except the two most posterior on the occiput. It also shows the spread of the field to electrodes 2 and 3 which were on the cheeks. An electrode on the chin was too remote to pick up the field. In the far left strip the maximum amplitude is from the 2 frontal electrodes numbered 4 and 5, with only slightly less amplitude in the parietal electrodes at 6 and 7. These values are plotted on the graph below the diagram of the head. The second strip takes in these two occipital electrodes as well as the frontal ones. Now we see maximum amplitude in electrodes 8 and 9 on the occiput but it is of different polarity and is so plotted on the voltage graph. One area of maximum voltage can be seen in the frontal regions in the plane around electrodes 4 and 5, the other area of maximum voltage, of opposite polarity is seen in the occiput (electrodes 8 and 9). Both these foci are blocked by opening the eyes, as is shown in the strip on the far right.

The S-shaped voltage graph with its two foci of opposite sign will be recognized as comparable to the diagram, shown earlier, of the voltage distribution on an axis parallel to a dipole. We have not enough experience yet to say how commonly this type of field occurs. We would not even care to hazard whether it should be regarded as normal or abnormal. This happens to be the record of a patient of Dr Schwab’s with a diagnosis of epilepsy.

We are in the early stages of our study of the detailed application of this concept to our data and are therefore wary of making generalizations until we have more experience. We know, though, that it is a common experience to find more than one field for waves of alpha frequency, and that dipole fields in their simplest form do not cover the very complex phenomenon of the alpha rhythm.

Figure 14.

In this EEG, a sample taken from an anoxia experiment in which the subject had been breathing a mixture low in oxygen (approximately 9 per cent oxygen) there is a change within this time interval of 11 seconds from an area of maximum voltage at electrodes 3 and 4 to

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**SURFACE POTENTIAL DISTRIBUTION OF AN ALPHA RHYTHM**

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Fig. 13. — An example of a dipole-like field with its axis parallel to the surface of the head. (For details see text).
VARIATION OF VOLTAGE FIELD FOLLOWING ANOXIA

Fig. 14. — Fields of alpha in a subject breathing low oxygen. (For details see text).

CHANGING VOLTAGE FIELDS FOLLOWING ANOXIA

Fig. 15. — Enlarged sections from Fig. 14.
one at electrodes 2 and 3. It will be noticed that it is the latter focus which shows the slowing due to the anoxia. The next figure will show an enlargement of two sections from this same record.

Figure 15.

On the left is the section showing maximal voltage around electrodes 3, 4 and 6 with negligible activity at 2. These are 10 per second waves. On the right is the section showing maximal voltage around electrodes 2 and 3. These are 7½ cycle waves.

It is essentially when we try to isolate different types of activity from a medley of potentials of approximately the same frequency bands that we have found this method useful. The next figure illustrates the activity...
which appears so prominently in electrodes over the temporal lobes in some subjects when engrossed in difficult mental work. Kennedy and his co-workers have recently named this the Kappa rhythm.

Figure 16.

This shows some plots of voltage distribution for a burst of Kappa waves. As you see, the voltage distribution is similar to a dipole-like field lying across the head parallel to the surface with two maxima of different sign, one in each temple. At the moment in time when electrodes 8, 7 and 6 are negative to the remote electrode, numbers 1, 2 and 3 are positive.

Now one of the familiar features of the EEG which is revealed by any detailed study is that many of the rhythm components show a temporal phase shift in different parts of the head. This is not in reference to the phase reversals which we all use for localization studies but about the slight time-lags of a wave component in different parts of the head. This is one of the reasons why the dipole field in its simplest form does not adequately cover the complex distribution of the alpha activity.

There has been so much interest in the last ten years in hypotheses as to the alpha rhythm in terms of activity in circuits between the thalamus and the cortex,
either moving up from below and bombarding the cortex, or moving up and down to the cortex in a circular pathway, that we have been interested to examine the data available from the field theory.

Let us for a moment briefly review the subject of the fields around a travelling nerve impulse in a conducting medium, for in the head we very surely have a conducting medium. This subject has been studied extensively by Bishop and O’Leary and by Lorente de Nó.

Figure 17.

This figure contrasts the record we get from a nerve in air when an impulse passes, and the record we get from the nerve in situ or in any other conducting medium. The simple monophasic action spike is now preceded by a positive phase and is also followed by a positive phase. These are due to the fields surrounding the active region of the nerve.

Figure 18.

This figure illustrates very diagrammatically the potential changes recorded by a pair of electrodes, one of which, the exploring electrode, is on the nerve, and the other, the indifferent electrode is on some remote inactive tissue in the same conducting medium. As the impulse travels towards the recording electrode a source of current precedes it (making a positive deflection) then the impulse arrives at the electrode (making a negative deflection) and finally it passes and again a source moves past the electrode (giving a final positive swing to the recording).

Now if the alpha rhythm were activity in many nerve fibers moving up to the surface it would be as though we were recording on a plane at right angles to the ends of the nerves as depicted here, in other words, positivity followed by negativity followed by positivity.

Figure 19.

This figure is constructed from the physical laws governing the voltage distribution on the surface of a sphere due to dipoles at various depths below the surface. For purposes of the present discourse it is probably justifiable for us to regard the skull as an approximate sphere.

Curve 1 is the calculated voltage distribution for a dipole at depth 1, curve 2 for depth 2, and curve 3 for depth 3.

At a glance one can see how very great an influence the depth of the source has on the field at the surface. In the case of one of the brain lesion records discussed earlier it was predicted that the lesion would lie deep. The prediction was based on the voltage distribution which showed a plateau with gently sloping sides, very similar in fact to curve 1.
In the case of a cortical scar, a surface injury giving focal cortical spikes, these have a field which resembles curve 3. That is, the electrode which is actually over the focus gives a spike of very high amplitude whereas moving the electrode only a very small distance from the focus reduces the amplitude very greatly indeed. In fact, if all channels are being run at the same gain, that is, a gain suitable for recording the spike without blocking the amplifiers, the field of the spike may be lost at the other electrodes. This point has not always been clear to those who have been interested in studying fields some of whom have been bothered by the fact that a spike of considerable amplitude may appear from one situation of the electrode and no trace of it be visible in neighbouring electrodes. Curve 3 is the reason, and such a finding indicates a very superficial source of the abnormality. The shape of the voltage curve when graphed in this way is of great help in giving information as to the depth of the source of activity.

Figure 20.

This is a figure showing cortical spikes and as a matter of fact in this case there is some trace of the outer field. The record shows a focus of cortical spikes found on the skull before operation and confirmed later on the open cortex. The numbering is different in the 2 recordings but as a matter of fact electrode 2 is very close to the source in both records. The amplification was reduced to one-third in the operation room; the spikes are six or eight times as high in the tracing from the exposed cortex. Note also that the electrodes were more closely spaced in the record from the exposed cortex.

But to return to the alpha rhythm and the problem of the travelling source. We can see from Figure 19 what the changing field at the surface would be like were the source to be moving up and down from the depths. The field would change from 3 through 2 to 1, and then back through 2 to 3, and so on. We can see that at the center of the field, that is at the central focus of the alpha as the dipole moved towards the surface, there would be an increasing negativity. In the periphery of the focus, however, there would be an opposite change of potential with decreasing negativity as the dipole moved towards the surface but the change is of extremely low amplitude. At the periphery curve 1 is more negative than curve 3, whereas in the center the opposite is true. The evidence from this method of treatment of the data is difficult to reconcile in any simple way with the view that the alpha rhythm represents the arrival and departure as such of impulses from below the cortex. It does not exclude a less direct influence of corticopetal discharges.

In summary it may be said that the alpha rhythm gives more complex fields than can be regarded simply as a point-dipole generator in the cortex, or by a moving dipole travelling rhythmically towards and away from the cortex.

**BIBLIOGRAPHY**


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The turn of the half century has seen a spate of new books on electroencephalography. Following Cohn's book which appeared at the end of last year has come the collected volume from the English workers. This book, although a little uneven in quality, will be invaluable to those training students of electroencephalography, especially the chapters by Walter on epilepsy and by Cobb on tumors. Hill, on the EEG in psychiatry, gives an excellent treatment of a complex subject. One searches in vain in this volume for any discussion of morphology, but the basic electrophysiology of the nervous system is ably dealt with by Whitteridge, who gives a masterly compression of this wide field. In view of the importance of neuroanatomy and neurophysiology for any true understanding of the EEG, it will perhaps be regretted that more space was not given to them and less to the sections on pharmacology and biochemistry, excellent as these are. A textbook on electrophysiology has appeared this year which gives a more detailed account of some of the underlying neurophysiology, but the bias of this reviewer makes it inappropriate for discussion here.

A review which will be of interest to electroencephalographers is that of Fessard and Posternak on synaptic transmission. This carries a comprehensive reference list, and the fact that these authors reach a pluralistic hypothesis for this most fundamental of neurophysiologic processes forms an accurate commentary on the present state of our knowledge. A volume of the British Medical Bulletin has been devoted to neurophysiology and contains much basic information.

The long-awaited second edition of Gibbs' Atlas has still not made its appearance as this review goes to press. It is perhaps unfortunate that two of the books mentioned above are outside the reach of the student's purse.

In contrast to the above volumes written especially for the electroencephalographer, Schwab has written a book addressed also to the referring doctor; this messianic work, which deals, not only with the scope, but also with the limitations of the EEG, may be expected to bring a more enlightened form of cooperation. It should also be of help to anyone newly setting up an EEG department. Heralded for the near future is a collected
volume from the French workers with a biophysical section to be written by
Baudouin, technic and the normal EEG by Rémont, epilepsy by Gastaut,
brain tumors by Fischgold, and a chapter on psychiatry by Verdeaux. The
French edition of Moruzzi’s monograph on experimental epilepsy will be
out before this volume but a copy has not yet reached this reviewer.

The International Federation of EEG has brought out two new publica­tions: a symposium of the principal reports given at the 2nd Interna­tional EEG Congress in Paris last year, and a classified and cross-indexed
bibliography of all papers on EEG published between the years 1875 and
1948. Several reviews have appeared during the year including ones on the application of EEG to neurosurgery to psychiatry, to pediatrics, to epilepsy and an excellent account for the intelligent layman has been written by Cobb. We have been given reports of the EEG in the prizefighter and in the genius.

A small symposium of fifteen workers from eight different countries meet­ing in Marseille included methods of display described by Walter and photographs shown of results obtained with the latest development he and Shipton have made in their toposcope. By adopting from radar the device of a rotating beam in each of the cathode ray tubes, not only frequencies but phase reversals can be detected and localized with a clarity of display which is most revealing and instructive. Lilly’s instrument is of a different design and has been planned for a different purpose. He has made, for implantation through animal skulls, a multiple electrode in which in an area of 1 sq. cm. there are twenty-five electrodes, each about 1 mm. in diameter set in a plastic insulator. The electrode holder is left in place for chronic experiments lasting as long as ninety days. The intensity of glow from a set of twenty-five neon tubes, each connected to one of the cortical electrodes is the indicator of the relative activity at these points. The reference electrode is provided by an electronic feed-back system giving the mean of the activity at all twenty-five electrodes. Evoked responses at the cortex can be traced, not only in their locus of maximal intensity, but also in the course of their travel over the sq. cm. of cortex under observation, while concurrent events in the rest of the area can be studied simultaneously.

Cohn has designed a simpler type of toposcope, employing six or more split disc neon lamps, one-half of the disc lighting up at the peak of each wave and the other half at the trough, brightness being a function of the voltage. The polarity of discharges can be detected by this method which has also indicated a fluctuating DC component in addition to the usual “alternating” one.

Another method of display has been designed by Shipton for the Walter analyzer which allows one to see a nearly instantaneous analysis instead of a 10-second epoch. Use is made of a cathode follower and a neon
tube for each of the frequencies under inspection. These neon tubes have an anode running the full length of the tube and a cathode in the form of a ring around the base. The length of the tube which lights up is linearly proportional to the voltage applied. For the study of frequency changes during an evoked response at the cortex this method should prove most informative.

On the technical side, the indifferent electrode, that will-o'-the-wisp, is still being chased. Oeffner urges the use of a reference electrode averaging the potentials from all the scalp leads. This would seem theoretically correct only if the sources of potential inside the head were distributed and oriented in a truly random fashion, and, as its designer points out, it could possibly be confusing in the case of a focal high voltage discharge. Goldman has however used it in clinical work and finds it valuable. It is, of course, preferable to the use of the ear as a reference. This system is often loosely referred to as a Wilson electrode but the latter averages fewer points and does not include the “active” electrodes in the average. Grezes-Rueff notes an increase in accuracy of localization of frontal lobe tumors since abandoning the ear as a reference in favor of the chin or nose. M. Lennox has made an experimental study in dogs (in whom the location and size of the lesions were known) of the variety of results obtained by the use of alternate ears as reference points. She found considerable shifting of the apparent focus and, in the case of deep lesions, the EEG focus would appear in different hemispheres according to the ear used. Gammon recommends a metal collar (in contact all round the neck) as a reference lead devoid of ECG interference.

An EEG incorporating a 4-channel CRO as well as 4 pens has been constructed by Horsten and a new type of calibrator has been designed by Gordon by which detection of pen resonances is possible; it has the same accuracy at 1.0 cycle per second as at the higher frequencies. Bickford has further developed his servomechanism for automatic control of anesthesia by the EEG and has been able to demonstrate a relationship between the EEG pattern and depth of nitrous oxide-ether anesthesia which is sufficiently constant to be used as a practical guide. When the patient is unconscious he finds a maximal discharging focus in the same location as that found in natural sleep (the precentral region).

Only one paper has been devoted to analysis per se (Knott’s description of the analyzer he has built), but automatic analysis, having served its apprenticeship, is now becoming a familiar part of the illustrations of EEG publications, particularly those of Walter, Gastaut, Martin, Corriol, Fischgold, Hess, Bickford, Schwab, Ingram, and Braziere. Esser has used the Walter type analyzer to study the reactivity of individual frequencies in the alpha band and has shown independence of
components in response to overbreathing, eye opening, photic stimulation and mental activity. It is interesting to compare these observations with those of Gastaut (see below). Bates and Kibbler have given further reports on the relation between phase of the alpha rhythm and initiation of a voluntary movement and Contamin has described a characteristic EEG change immediately before a movement in non-anesthetized rabbits.

The July number of the Semaine des Hôpitaux has been devoted to the EEG work at the hospital of Ste. Anne in Paris. (The occasion is a sad one, this being a memorial volume to Dr. Puech.) A careful appraisal of the EEG signs of verified cerebral neoplasms has been made by Fischgold who considers not only areas of electrical silence and phase reversals, but such signs as failure of alpha suppression. He again emphasizes that phase reversals more often localize the activity marginal to a tumor than its center and he finds the plotting of fields a useful aid to localization. He also discusses the correlation between x-ray and EEG findings. The causes of erroneous localization have been analyzed by Dow and by Fischgold; both warn against false foci introduced by somnolence and coma. Passouant has made a study of the EEG in coma induced by insulin and notes that the voltages of the slow waves are maximal anteriorly, as they are in sleep. The coma of barbiturate poisoning has on the other hand been differentiated by Cohn by the presence of fast activity superimposed on the slow waves. In the reviewer's experience with these cases, this differentiation is clear-cut but can be made only if the patient can be tested in the early stages, for in long persisting coma the fast activity disappears before the slow. Those who are concerned with the measurement of eye movements in cases of suspected frontal delta rhythm will be interested in the techniques discussed by Lord and Wright.

Cuneo has further analyzed his series of 40 verified tumor cases, and it is interesting to compare his results with those of Paillas. These authors agree on the rarity of unilateral EEG signs in posterior fossa tumors as do also Pampiglione, Martin and Fischgold. Little does not find the EEG a reliable indicator of speed of growth of a neoplasm. In an analysis of a large number of verified temporal lobe tumors, Tamalet found the EEG a guide of high fidelity. In cerebral abscesses the EEG is more abnormal in those of recent onset than in longstanding cases. An interesting report on the EEG in vascular diseases has come from Noel.

The problem of secondary foci of abnormal rhythms appearing at a distance from a cerebral lesion is one that has interested many workers. Fischgold, Rémond and Brazier have all reported on this problem. Fischgold finds a high incidence for these anomalies (1 in 5 of his cases of neoplasm, and most frequent in those deep in the posterior regions, a point also stressed by Longo); Fischgold regards their phase reversals as ex-
Extreme misleading and recognizes three principal types of rhythm in these cases: burst of sinusoidal slow waves, continuous hypersynchronous waves and theta rhythms. Rémond\textsuperscript{188} has assembled ten varieties of rhythm seen at a distance from a verified tumor and has drawn up thirteen parameters by which to judge them, and Brazier\textsuperscript{24} has presented cases in which such anomalies were present after, as well as before, surgical removal of the primary lesion.

The temporal lobe received a great deal of attention this year, being given special billing at the International Congress of Oto-neuro-ophthalmology at Barcelona,\textsuperscript{148} and at the annual meetings of the American EEG Society, and of the International League against Epilepsy. At Barcelona detailed studies were reported on its anatomy and physiology as well as clinical studies of symptoms and treatment, and Gastaut\textsuperscript{71} reported on the EEG. He gave data which indicate a source of alpha-type activity in the temporal lobe separate from that of the occiput and blocking more readily during mental arithmetic than on opening the eyes. Automatic analysis revealed theta rhythm to be commonly present, even when the alpha frequencies masked it in the primary trace. In Gastaut's hands the EEG has been successful in localizing 82 per cent of temporal lobe tumors, a figure in excellent agreement with that previously published by Kershman. In those with spike foci he confirms Gibbs' finding that sleep helps to evoke these discharges.

In psychomotor epilepsy, a thesis by Dell\textsuperscript{46} and a paper by the Gastauts\textsuperscript{73} confirm the high incidence of foci of negative spikes in the temporal regions; the latter report 1 in 4 of their 100 cases as having these spikes bilaterally. Vercelletto\textsuperscript{185} has searched for a clinical differentiation between cases with bilateral temporal spikes and those with unilateral, but finds these EEG signs difficult to predict. Penfield\textsuperscript{181} concludes from experience with 65 operations for removal of the temporal lobe that this is an encouraging method of therapy for seizures produced by focal lesions in this area. He considers EEG localizations in these cases of great help. On the other hand, M. Lennox\textsuperscript{112} and her colleagues' confirmation of their earlier finding of unelicited spikes in the temporal pole and orbital cortex of normal monkeys throws doubt on whether these necessarily indicate epileptogenic tissue. (One wonders whether amplitude of the discharge may not be the critical differentiation.) In a study of head wounds in 100 cases, Bartschi-Rochaix\textsuperscript{12} emphasizes that the epileptic focus is not always found in the region originally injured.

A new report has come through on the use of depth electrodes at brain operations. As a result of their findings, Knott\textsuperscript{139} and his collaborators suspect that epileptogenic firing points may lie in the deep nuclei and they therefore question the concept of a cortical epileptogenic focus as the only
primary factor in the production of seizures and are wary of using a focus of cortical spikes as indicative of an epileptogenic focus. For users of depth electrodes Bishop’s \cite{16} critique of Gibbs’ “law” will prove an invaluable aid in the interpretation of polarity (as will also Chang’s commentary \cite{18}). A report from Williams \cite{19} on discrepancies between the surface EEG and recordings with a depth electrode may also be interpreted in the light of basic precepts as to the role of electrode orientation. A modification of the depth electrode has been designed by Rouvray. \cite{20}

A study of electrocorticography has come from Ectors \cite{22} in Brussels, with control experiments on animals for such factors as the epileptogenic influence of antibiotics applied to the exposed cortex. In man he has found a transient effect on the EEG on lifting the bone flap and opening the dura mater; this effect lasts about fifteen minutes and should be taken into account before judging the record. For the localization of epileptogenic foci his experience leads him to place more trust in the phase reversals (in two planes) of spike discharges than in the after-discharges following electrical stimulation. Guillaume \cite{23} shares this opinion, but does not limit surgical section to the center only of the spiking focus; his series shows a comparatively low incidence of postoperative seizures. Ectors \cite{22} reminds us that the epileptogenic focus may be in normally appearing cortex at some distance from the visible scar. Rémond \cite{24} has also stressed the abnormalities introduced into the EEG by events incidental to the operative procedures, such as hemorrhages of the pia mater and cortical hyperemia. Another localizing sign in focal epilepsy has been stressed by Mme. Mazars \cite{25}: i.e., the phase reversal of the high voltage fast activity occurring during the actual convulsion. This, of course, demands high speed recording.

Studies of recordings from the basal and temporal regions have recently been reviewed by MacLean. \cite{26} From their experience with naso-pharyngeal and tympanic electrodes he and Arellano \cite{27} conclude that these basal electrodes are especially valuable in detecting spikes in cases of epileptic automatisms. A new type of basal electrode consisting of an insulated fine gage needle inserted under local anesthesia between the zygoma and the sigmoid notch of the mandible has been designed by Jones \cite{28} and has been found of localizing value.

Sleep as an activator has been reported on again by the Gibbs \cite{29} who find it invaluable in the diagnosis of epilepsy. Kellaway \cite{30} is equally enthusiastic, as is Hawkes. \cite{31} The Gibbs have also studied sleep in a large number of normal persons \cite{32} and Nekhorocheff \cite{33} has published much needed data on normal infants and children. Fischgold \cite{34} has used it in children under 10, and takes a rather guarded stand; in his series of known
epileptic children who had normal records when awake, less than two-thirds gave clearly diagnostic records when asleep. Brandt found that sleep brought out or exaggerated abnormalities in a series of 47 children, but that in 18 children with abnormal waking records normal sleep patterns were obtained. He does not comment on the diagnoses in these groups. Melin does not find sleep as useful as photic stimulation for activation in children. Wayne finds sleep helpful but does not give us statistics. Some electroencephalographers will question her interpretation of one illustration as "generalized positive spike seizure discharges," since the recording is a "unipolar" one. Gastaut has published this year an extremely clear demonstration of this particular polemic. Wayne stresses the similarity which exists between the EEG in sleep and in narcolepsy, as also does Titeca. Delmas-Marsalet has made basal lead studies of patients with nocturnal seizures, using somnifaine and pentothal. Delay advocates a mixture of scopolamine and chloralose as a hypnotic activator, as this does not produce any change in the record of a normal person. Leroy reports a case which could be activated equally by overbreathing and by sleep and notes vagotonia as the common factor. One wonders whether the hypersynchrony of the delta waves in sleep may trigger the release of the epileptic discharge; some observations point this way. This might account for some of the conflicting reports, for delta waves do not occur in all stages of sleep.

The use of sound as an activator has been further explored by Arellano, who reports 2 cases of audiogenic epilepsy. That physical and mental stress may also play the role of activators has again been stressed by Kershman in an interesting follow-up study of 11 patients with larval epilepsy.

Photic stimulation has received a great deal of study. A long thesis on the subject has come from Thiry from the laboratory at Salpêtrière, analyzing the results in 100 subjects. Definite activation was found in 35 epileptics but never in normal controls. The most potent frequency for activation was found to be 15 cycles per second. Evoked responses following the frequency of the flicker could be found as high as 70 per second in normal subjects. A method for using the subject's own EEG to trigger the flash has now been published. Flicker has also been used by Hutchinson in an attempt to localize cerebral lesions; he finds a failure to follow the flicker frequency in the area of a cortical lesion and a tendency to respond at double the frequency in lesions of the deeper layers. Hodge has tried photic stimulation with a multiple flash using 4 independently operated stroboscopes and finds interesting subjective effects. Melin finds it an especially useful method with children, among whom photogenic epilepsy is more common than in adults. He recommends it as a routine
procedure in EEG laboratories, as does also Weil.\textsuperscript{169} Lerique-Koechlin\textsuperscript{115} stresses that a paroxysmal response to photic stimulation is not specific for epilepsy in children.

Gastaut's method of combined photic and metrazol activation has now been published in full,\textsuperscript{70} together with figures for the thresholds in normal subjects, and corroborative material has been published by Schwab.\textsuperscript{166} Gastaut's hypothesis that a low threshold for the myoclonic response indicates a sensitivity at the diencephalic level is supported by the animal experiments he has published with Hunter\textsuperscript{74}; these indicated that the leakage of the discharge (normally confined to the visual pathways) to the precentral regions was due to an abnormal permeability of thalamic synapses. New work by Gastaut\textsuperscript{76} reveals that paired flashes are efficacious activators over a range of frequencies provided that the interval between the paired flashes is about 60 to 70 msec. This suggests a facilitatory mechanism and would explain the efficacy of 15 per second single flashes (i.e., flashes with intervals of 67 msec.). Gastaut's\textsuperscript{70} statement that the myoclonic threshold is low in hysterics is supported by the results of Gallais,\textsuperscript{69} and that it is low in some schizophrenics by the observations of Corriol,\textsuperscript{59} who found this to be so in 14 of 30 adult schizophrenics examined. This is interpreted as an activation of a cerebral circuit having perhaps only one point in common with the circuit which is active in idiopathic epilepsy, i.e., a point in the diencephalon. He does not tell us how many of these patients had previously had shock therapy.

Taking advantage of Gastaut's discovery that intermittent photic stimulation lowers the threshold to metrazol, O'Flanagan\textsuperscript{146} has used this as a substitute for metrazol convulsions in shock therapy. EEG control allows the physician to keep the activation at a level where spikes appear and myoclonic movements are minimal. The therapeutic results compare favorably with E.C.T. and the method is naturally preferred by the patient.

Metrazol used alone as an activator has received further study from Merlis,\textsuperscript{138} who, using slow injection, found seizure discharges (not always accompanied by a convulsion) in 47 per cent of an epileptic group with previously normal records, and in none of his controls. This is in contrast to the results of rapid injection which Greenblatt\textsuperscript{171} found to evoke EEG changes of a petit mal type in 36 per cent of a group of 57 nonepileptic patients. Intravenous trimethadione has been found useful by Gastaut\textsuperscript{73} in averting seizures in metrazol activation, but this reviewer's personal experience does not inspire confidence. Animal studies by Marsan\textsuperscript{2} show that the direct convulsive effect of metrazol is cerebral and not spinal.

The role that the EEG can play in elucidating the organization of the brain is now receiving the attention which was its due 20 years ago. Further work has come from the laboratories of Jasper and of Magoun on the
regulatory effect of the thalamic reticular system, and the current knowl­
dge may be summarized as follows: stimulation of the centre median,
intralaminar, anterior, ventralis anterior and anterior reticular nuclei by
low frequencies produces an extensive (but not ubiquitous) recruiting
response; higher frequencies cause desynchronization, or “activation,”
to use Magoun’s term; this arousal effect can also be evoked by stimulation
of the hypothalamus and of the brainstem reticular system but it is not
totally abolished by destruction of the hypothalamus; stimulation of
certain nuclei, such as the intralaminar nuclei and the habenulo-peduncular
system facilitates cortically induced movements and segmental spinal
reflexes; stimulation of the caudate nucleus, the septal nuclei and centre
median on the other hand causes inhibition. These facilitating and in­
hibitory effects survive cortical ablation (Austin). Frequency of stimu­
lation appears to be critical. In a study by Lindsley of the sensory paths,
only those which interrupted the ascending reticular system were followed
by chronic somnolence.

Fortuyn has investigated further the anatomic problems raised by
the effects of stimulation of the intralaminary system and has drawn atten­tion to the role of the basal ganglia. The long latency (35 msec.) be­
tween the stimulus and cortical response (too long for a direct pathway)
may well be due to stimulation of the caudate nucleus which, having no
direct route to the cortex, has to send its impulses to the globus pallidus
and back to the anterior ventral thalamic nucleus and hence to the cortex.
The paramedian region of the ventral nucleus projects to that part of the
premotor cortex where the face and particularly the eye movements are
represented. In petit mal these are the muscles in which myoclonus is most
often seen. Last year’s report by Gerebtzoff on the connections of the
thalamus has now been published in full.

Spiegel has attempted to check in man Jasper and Fortuyn’s identi­
fication of the internal medullary lamina as the focus of origin of spike-and
wave discharges. In studies of thalamic recordings in epileptics he found
that the spike discharges were maximal, not in the internal medullary
lamina, but in the dorsal medial nucleus. Rose points out that the intra­
laminar nuclei, unlike the thalamic reticular nuclei, have no direct cortical
projections. The recruiting response has received more study in Moruruzzi’s
laboratory. Arduini has shown that the gradually increasing amplitude of
the cortical responses is mainly due to recruitment of thalamic neurons
rather than facilitation at the cortex, although variations in excitability
do occur within the cortex itself.

The earlier findings of Bremer and of Kristiansen that the cortex retains
its rhythmic activity after isolation have been seriously challenged by
Burns, who finds no sign of spontaneous activity (once injury currents
have subsided) in the cortex isolated from the rest of the CNS, even when it retains an undisturbed blood supply and still responds to surface stimulation. His earlier experiments were made on animals under light anesthesia, but to rule out this factor he has now repeated them on unanesthetized animals. From his results he concludes that the cells of the cortex cannot discharge unless they are excited from an outside source but that since the excitability of the cells responsible for the surface-positive response is very high, a single stimulus can evoke a prolonged repetitive discharge. A hypothesis is advanced that this repetitive response is due to self re-excitation in closed chains and a calculation is made of the mean circumference of a cortical neurone circuit which could give such time characteristics as have been found empirically. Evidence that the repetitive discharge following stimulation from an outside source is not a simple after-discharge of local neurones but the activity of a cortico-thalamic reverberatory circuit has been advanced by Chang, who has shown that not only does it depend on all components of this circuit being intact, but it can be evoked by stimulation of any point in this neuronal circuit. Moruzzi in a discussion of the physiology of sleep draws attention again to the role of thalamo-cortical impulses in the synchronization of cortical neurones.

Stimulation of the anterior thalamic nuclei and of the fornix in the cat evokes attacks similar in appearance to temporal lobe fits in man (Hunter); these are accompanied by bilateral discharges in the posterior ectosylvian gyrus, a region presumed to be homologous to the tip of the temporal lobe in man. The subcortical connections of this gyrus have been worked out in cats by Ajmone-Marsan and Stoll by three different methods: strychnine neuronography, electrically evoked responses, and electrically induced after-discharges. Direct two-way paths have been demonstrated connecting the tip of the temporal lobe with the lateral posterior thalamus and also with the septum via the fornix, and indirect ones between the temporal tip and the anterior thalamic nuclei and the centre median. These experimental studies may provide a clue to the appearance of local temporal EEG abnormalities in the absence of cortical epileptogenic lesions. It is interesting to compare this work with that of Pribram, who has by strychnine neuronography worked out the connections of the orbital and medial surfaces of the frontal and temporal lobes in monkeys. This paper is excellently diagrammed.

In some quarters the concept of localized suppressor areas has this year come under a cloud. Sloan's experiments bring strong evidence that "suppression" is the same phenomenon as the spreading depression of Leão and that it is not localized to special areas. It is characterized by a long-persisting reduction of EEG activity spreading out very slowly from...
the point of stimulation and a rise in threshold of the cortex (including the motor strip so that cortically induced movements are abolished). There are many characteristics of this depression of EEG activity which suggest that it may be not a neuronally conducted effect, but a vascular one. The inhibition of motor movements may be a different story. Its propagation is certainly different from that of after-discharge, which is much faster (Whieldon). Marshall also could find no specific suppressor areas (in cats) and postulates that spreading EEG depression involves a neuro-chemical reaction which is nonphysiologic, for only when the pia-arachnoid was inadequately protected from exposure to air or unduly cooled could he demonstrate spreading depression. The effect could not be elicited if the cortex was protected with mineral oil but could be mimicked by internal dehydration producing decrease in subarachnoid fluid. This would appear to rule it out as an explanation of the 'phenomenon of extinction' seen just before a seizure in the EEGs of some patients. Sloan found that surface drying of the cortex augmented the response but was not a prerequisite for its appearance. (The response is evoked more easily in rabbits than in cats or monkeys). There is no evidence that the depression of EEG activity is correlated in any simple manner with the change of the observed DC potentials, but absence of the effect is correlated with highly negative cortical baseline voltages.

The anterior limbic cortex which has in the past been regarded as a suppressor area, not only produces spreading depression when stimulated electrically but evokes generalized cortical activity which suggests that impulses from this area have triggered centers in the thalamic reticular system and in the brainstem reticular formation. Thus both facilitatory and inhibitory effects may be obtained from this "regulatory" center in the limbic cortex. However, M. Lennox reports a suppression produced by electrical stimulation of the supracallosal anterior cingulate gyrus in monkeys which bore no relation to the spreading depression of Leão. She also on rare occasions found an increase in electrocortical activity from similar stimulation, i.e. a facilitatory effect.

In some interesting studies made by O'Leary's group with thalamic as well as cortical leads it was demonstrated that coincident with the slowly spreading cortical depression of Leão there is a similar and simultaneous spread in the thalamus. Histologic checks showed the spatial correlation to coincide with the anatomic connections between the cortex and related thalamic nuclei. Their evidence pointed to a cortico-thalamic neural transmission but gave no indication of spread to the cortex by a return pathway.

Slow potential changes (too slow for recording by the usual condenser-
coupled amplifiers commonly used in EEG work) have received considerable study this year. The St. Louis group surprisingly finds that in electric shock the principal change in DC potential does not occur during the passage of the current but follows one to two minutes later and after the period of maximal spiking in the EEG. They are alive to the question as to how much of this DC potential may be due to the skin and how much truly neuronal in origin, and have made observations on the exposed human brain at operation which indicate at least some neuronal component.

Knowledge of the effects of prefrontal leucotomy on the EEG is beginning to accumulate. Greenblatt and his collaborators have recently summarized their extensive experience of this subject and have given a useful review of the work of others. Seizures were more common in patients who had received preoperative electric shock treatment. In a five-year follow-up of 16 cases Greenblatt found only 3 to have EEG’s which had reverted to a normal pattern, although 13 were seizure-free. It is interesting in this context that the only cases other than epileptics in whom Spiegel found spike discharges in thalamic recordings were schizophrenics who had been subjected to repeated electric shocks.

As for electric shocks themselves, the effect on the EEG, although initially great, is apparently transient. Calloway in a study of extremely intense shock treatment (four a day for seven consecutive days) found that although the slow activity increased for some days after the end of the treatment none persisted longer than five months. He found the transient slow activity to be more prominent in frontal leads but not clearly localized. Gibbs, however reports the right frontal area to be the most vulnerable for slow activity irrespective of the placement of the stimulating electrodes. Roth has advanced a hypothesis that the mechanism behind such changes is a progressive augmentation of activity in the diffuse projection systems from the thalamus.

The high voltage slow activity so commonly found in the frontal regions immediately after prefrontal lobotomy is not seen when the technique of transorbital lobotomy is used (Henry); Spiegel and Wycis have used electrocautery of the dorsal medial nucleus of the thalamus as an alternative for frontal leucotomy and found little subsequent change in the EEG.

At the Pediatric Congress in Zürich it became clear that electroencephalographers feel themselves on firmer ground, since many studies have now established the normal standards. At this congress, both Hill and Melin gave discussions on convulsive disorders in children. Melin stressed the importance of serial EEG’s not only for diagnosis but for control of medication. Courjon finds the EEG helpful in differentiating the type of epilepsy in children and hence the appropriate therapy. The relationship
between failure of maturation and types of behavior disorder is becoming clearer. Melin\(^8\) on examining children with persistent (in contrast to periodic) enuresis found only 23 per cent of these children had normal EEG's, and he reached the conclusion that immaturity of the nervous system was the important factor in the etiology of this symptom. Another long and careful study\(^31\) of children with behavior disorders unfortunately omitted to use temporal leads and therefore probably lost some pertinent information. The electrical activity of the newborn has received further study from Sureau,\(^178\) who finds clearly marked EEG activity within the first few hours of birth, even in the prematurely born. The predominant frequency is usually 5 or 6 cycles per second but faster frequencies are also present.

The EEG has been carried into other fields of medicine by Melin.\(^129\) At the Congress of Internal Medicine at Ostend he reported on the use of the EEG to detect brain damage after angiocardiology. EEG abnormalities persisting for more than 2 days were far more common after arterial than after venous injection of diodrast. He points out the dangers of this technique. The value of the EEG in assessing the course of tubercular meningitis during treatment by antibiotics has been stressed by Euzière\(^67\) and by Enell et al.\(^84\)

Verdeaux\(^160\) has been impressed by the frequency with which the EEG reveals latent epilepsy in psychoneurotics. Faure’s\(^69\) results would suggest that the EEG changes found in these patients may reflect mainly their disquiet during the test. He found no correlation between clinical diagnosis and EEG changes but was able to demonstrate\(^69\) great lability of the EEG (especially in the basal leads) in states of slight emotion induced by projection tests in patients with anxiety neuroses. Taking this finding together with that of an absence, in many of these cases, of any change in the tracing on opening or closing the eyes,\(^61\) he postulates that in these patients there is some dysfunction of the alpha regulating mechanisms, possibly of the reticular systems of the thalamus and brainstem.\(^62\) His search for and study of parallel conditions in dogs whose behavior and reactions were observed for many months is an extremely interesting approach,\(^63\) and reminds one of Pavlov’s categories of dog behavior. Barker\(^10,11\) has experimented with the induction of paroxysmal waves in the EEG of epileptics by stress in order to test the hypothesis that the epileptic fit is a defense mechanism, while Higgins suggests that the seizure serves a repressing function. In neither case are the data presented critical tests for the hypotheses as framed.

Iwama\(^100\) has attempted to correlate EEG changes with stages of conditioned reflexes in man, but his interpretation of the results ignores recent views on the causes of alpha suppression, possibly because of the difficulties in obtaining current literature. The same comment applies to his paper\(^101\)
on the influence of oxygen lack on the EEG. His results confirm those of earlier workers and differs only in that he used more heroic levels of hypoxia than others have used for man. The hypothesis that hypoxia rather than hypocapnia is the cause of high voltage slow waves during overbreathing is supported by the work of Lloyd-Smith,\textsuperscript{124} who finds them recurring if the apnea following overbreathing is voluntarily prolonged; during this period the arterial $O_2$ is falling and the $CO_2$ rising. Dogs held in apnea by an overdose of pentothal\textsuperscript{89} and kept alive by diffusion respiration with $O_2$ show a depression of the EEG followed by electrical silence. By this technic, $CO_2$ mounts rapidly while the $O_2$ remains for a long time unchanged. Dogs recover normal EEG's after periods of electrical silence as long as 26 minutes.

Kreer\textsuperscript{109} has continued his study of alpha frequency and I.Q. in adults with mental deficiency. The hints of correlations found were not statistically significant. Nor was any correlation between degree of EEG abnormality and intelligence found by Aird\textsuperscript{1} in children with cerebral palsy. It is interesting that although spastics have slightly more abnormal EEG's than athetoids, the difference is not significant.

An observation has been reported by Gordon\textsuperscript{48} of an EEG change in multiple sclerosis; this consisted of short bursts of high amplitude theta activity in the frontal areas. Studies\textsuperscript{106} from the Mayo Clinic and from the Montreal Neurological Institute mention paroxysms of low voltage waves in this range but note them as only one of the abnormalities found in the acute phases of this disease. In essential or malignant hypertension, in spite of the disturbances of cerebral physiology which accompany this disease, Bagchi\textsuperscript{9} found distinctly abnormal EEG's in only 25 per cent of 84 patients. The degree of EEG abnormality did not correlate with the blood pressure per se; it was of some help in predicting postoperative complications after splanchnicectomy.

With the wide interest in ACTH it is not surprising that we have some studies of its effects on the EEG. Hoefer\textsuperscript{95} reports changes in the EEG in 13 out of 15 patients receiving this drug for various complaints, but Ulett\textsuperscript{84} in a smaller series found no significant changes, although in the resting record of 2 cases there was a greater facility in following the frequency of a photic stimulus. Klein\textsuperscript{167} after testing the therapeutic effects of ACTH in epilepsy reports a marked improvement in the EEG in 4 out of 6 patients, but most of his illustrations compare the EEG during a seizure with an EEG between seizures and therefore mostly reflect only a fall in the incidence of seizures rather than a change in the interseizure EEG.

D.F.P. in dogs\textsuperscript{89} produces EEG abnormalities proportional, within limits, to the decrease in cholinesterase activity in the brain. In man, the EEG changes do not correlate with red cell cholinesterase activity.\textsuperscript{164} A secondary
vasomotor effect is perhaps the operative factor here. The action of synthetic curare on the EEG has been studied by Bertrand.14

As reports come in from the many fields in which the EEG now plays its part, the pieces of the puzzle begin to fall into place. Perhaps the most forward-looking of the papers published this year is the Maudsley Lecture given by Walter,187 which presages a crumbling of the barrier erected by man between the brain and the mind.

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PHYSIOLOGICAL PERFORMANCE FOLLOWING A HYPNOTIC DOSE OF A-BARBITURATE

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PHYSIOLOGICAL PERFORMANCE FOLLOWING A HYPNOTIC DOSE OF A BARBITURATE

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GENERAL AIDS. The work recorded here is part of a continuing effort to develop criteria for appraising the sedative agents, both narcotic and hypnotic. Our primary goals are to evolve methods of study that will (1) permit accurate comparisons of therapeutic power from one agent to another and (2) allow measurable comparisons of toxic and other side effects, when doses of equal strength are administered.

We already have described a method (Denton and Beecher, 1949a, b, c; Keats, Beecher and Mosteller, 1950) for quantifying pain relief in terms that allow accurate comparison of analgesic agents. We also have described in those same papers methods for precise comparisons of side effects in the group (narcotics) where these effects are not very subtle: nausea, vomiting, drowsiness, and so on.

In the study reported here we have attacked the more difficult problem of discovering side actions that develop inconspicuously and that have potentially grave effect: impairment of neuromuscular function, auditory reaction time, attention, memory, association, and in so far as possible, critical judgment. Again, our interest has been to elicit these in terms that permit accurate comparison of the subtle effects of one agent with another.

SPECIFIC PURPOSE. The use of pentobarbital sodium is widespread and increasing. Although generally employed as a hypnotic agent, other studies in this laboratory (Denton and Beecher, 1949a, b, c; Keats, Beecher and Mosteller, 1950; Keats and Beecher, 1950) have shown that it is also effective in the alleviation of pain. Notwithstanding an extensive literature on this agent, little exact information is available concerning the nature and duration of the neuromuscular effects of the usual hypnotic dose, 0.1 gram. Study of these is the specific purpose of this work.

We had hoped to correlate blood levels of the barbiturate with the after-effects, but in two years of effort we have failed to develop a satisfactory method for measuring the blood levels in man following the usual clinical dose. Particular effort was directed toward adaptation of the ultraviolet absorption method for barbiturates to the small doses used here, but without success. The “blanks” were always as large as the anticipated blood levels of the drug. Our failure in this is perhaps not surprising since at the drug’s greatest concentration one would have to expect a dilution of about $1:700,000$ (0.1 gram in a 70 kgm. man). The method

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has in any case come in for considerable criticism (Maynert and van Dyke, 1949). However, the fact that hours after administration the effects of the agent are still detectable physiologically in impaired performance is of interest.2

**Method.** The first step in this work was to try out a considerable number of physiological and psychological tests to find which would reveal persistent effects of the barbiturate. By means of these tests we then proposed to investigate the duration of the effects and the range of variability of reaction within a group of normal young men, all of whom were college students. Preliminary studies of modes of testing carried out by Drs. M. Verzeano and O. H. Straus in this laboratory gave us a starting point on which we have built the experimental plan described below.

Performance in most psycho-physiological tests is not only a function of the physiological condition of the subject but also a function of variables such as practice effect, learning, motivation, and under the present conditions, the subject's anticipation of the effect of an unknown medication. An experiment which attempts to measure the effects of small doses of a barbiturate must carefully control these variables in its design and analytic procedures.

![Fig. 1. Scheme of experimental design](image)

Control of variables was obtained by means of experimental design in the following plan:

Each of 30 normal young men was studied twice, in two test sessions. Each session lasted a day, a night, and a day. The first day served to standardize the activities of all subjects prior to medication and before the experimental night. It also provided a practice period for the tests.

At the end of the first day (1:45 a.m.) half of the subjects received orally, 0.1 gram pentobarbital sodium. The other half got a similar appearing lactose placebo. The drugs and placebos were always given as "unknowns". On the second day the post-medication testing periods started at 6:00 a.m. and continued until 11:00 p.m.

After five days the subjects returned for a second session identical with the first except that the subjects who had previously received the barbiturate were given the placebo and *vice versa.* The following scheme shows the sequence of events (fig. 1).

The battery of tests was administered at 9:00 a.m., 1:00 p.m., 4:00 p.m., 7:00 p.m., and 10:00 p.m. on each of the four days and also at 6:00 a.m. on the second and fourth mornings (the days after the medications had been given). The barbiturate or placebo was given at

2 This supports the view that legislation concerning the easy distribution of barbiturates needs tightening.
1:45 a.m., fifteen minutes before the subject went to bed. The sleep period was limited to three hours, a compromise to permit recording of electroencephalographic activity during sleep and administration of the tests while the barbiturate was still maximally effective. Results of the electroencephalographic findings have been published elsewhere (Brazier, 1949).

The subjects were all male college students, between the ages of 18 and 26. They were paid for their time. They were screened by a physician for physical fitness, allergies, and any previous history of abnormal reactions to drugs. They were also interviewed by a clinical psychologist who rejected those who showed symptoms of personality maladjustment.

Tests Employed. The battery used consisted of ten psychological tests. These were selected from several studies of fatigue and of drug effects (Bartley and Chute, 1947; Spragg, 1941; Jones et al., 1941; Tyler, 1947; Halstead, 1947). A survey of these investigations led to the conclusion that the likelihood of obtaining meaningful results would be greater if the tests could be repeated at frequent intervals over a relatively long period of time. The tests selected covered a range of functions from relatively simple ones such as reaction time and tapping speed to tests of higher mental activities such as memory. The tests which were tried out included an arithmetic test, a letter-crossing test, a coding test, a static steadiness test, a visual choice reaction-time test, and a determination of critical flicker frequency. These tests failed to show with statistical reliability the effect of the barbiturate. Because of the known (Kleitman, 1939) effects on performance of body temperature, rectal temperature was taken at each test period. The following four tests showed statistically reliable effects of the barbiturate.

Tapping Speed, the most sensitive indicator of the drug effect, was a measure of the number of taps a subject could make in ten seconds using a telegraph key. The test was given in three ten-second runs which were separated by intervals of fifteen seconds. The subject sat at a table with the key before him. He rested his forearm on the table and tapped with the fore and middle fingers of his preferred hand.

Auditory Reaction Time, the next most sensitive test, was a measure of the speed with which the subject could react to an auditory stimulus by pressing a key. Each run consisted of two practice trials followed by twenty test trials. The intervals between trials were varied at random around three seconds. Before each trial a ready signal was given which preceded the stimulus by 4 to 2 seconds. The subject's position was the same as for the tapping speed test.

Naming of Opposites, third in order of sensitivity, was a measure of the time required to name the opposite of a common word of one or two syllables. Each run consisted of ten words given orally by the experimenter. Twenty-two equivalent forms of these sets of ten words were developed for the purposes of the experiment.

Memory for Digits, the fourth test which indicated sensitivity with statistical reliability, was the number of digits a subject could recall in reverse order after a list of digits had been read to him. The examiner read in a monotone, at a rate of one digit per second, the lists progressively increasing in length until the subject failed twice on a list of a given length.

Results. As mentioned earlier, the assessment of the effect of the barbiturate upon test performance requires the isolation of the barbiturate effect from the effects of other variables such as changes in motivation and practice. Part of this isolation is accomplished by the experimental design in which half the subjects received the barbiturate on their first experimental night, and half on their second night, without knowledge of which was given. Further isolation of the drug effect was accomplished by the statistical analysis employed. This will be described.

Since factors like the effect of continued practice produce a gradual improvement in the performance of a test, the relatively small differences in performance
(either improvement or deterioration) produced by the barbiturate will not appear significant if a score after lactose is compared directly with a score after barbiturate. It is necessary to correct for the practice effect. This is accomplished by expressing the score after barbiturate in terms of the increase or decrease in score from the average of the immediately preceding day, when the subject had received no medication and had had a normal night of sleep. Similarly the score after lactose is expressed in the same manner—an increased or decreased score from the average of the day before. The effect of the barbiturate then is determined by finding the difference between these derived scores. Expressed algebraically the procedure is:

\[(X_{bi} - X_i) - (X_{bp} - X_p) = \text{effect of barbiturate, where}\]

- \(X_{bi}\) = mean score of day before lactose was given,
- \(X_i\) = score for any given test period after lactose,
- \(X_{bp}\) = mean score of day before pentobarbital was given,
- \(X_p\) = score for any given test period after pentobarbital.

These differences for each of the six test periods after medication were computed for each of the thirty subjects. They were then added and the mean difference was submitted to a Fisher “\(t\)” test of significance as described in Snedecor (Snedecor, 1946). Table 1 shows the “\(t\)” scores for each of the tests at each of the test periods. (An example of individual performance on each of these tests is given in Table 2.)

A minus sign indicates less efficient performance after the barbiturate and a plus sign indicates more efficient performance. More efficient performance is assumed to be indicated by a greater speed of tapping, shorter auditory reaction

<table>
<thead>
<tr>
<th>TEST</th>
<th>TIME OF TESTING</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6:00 a.m.</td>
</tr>
<tr>
<td>Tapping Speed</td>
<td>-5.13†</td>
</tr>
<tr>
<td>Auditory Reaction Time</td>
<td>-3.33†</td>
</tr>
<tr>
<td>Naming of Opposites</td>
<td>-3.07†</td>
</tr>
<tr>
<td>Memory for Digits</td>
<td>-2.37‡</td>
</tr>
<tr>
<td>Body Temperature</td>
<td>-1.56</td>
</tr>
</tbody>
</table>

* In this Table the figures in the vertical columns represent the Fisher “\(t\)” scores indicating the degree of significance of the differences found between the effect of placebo and that of pentobarbital on the subjects’ performances in four different tests. The figures given are the means of “\(t\)” values for 30 subjects.

† Significant at 1% level (i.e., if there were no difference in performance, values this large or larger would arise only one time in 100).

‡ Significant at 5% level (i.e., if there were no difference in performance, values this large or larger would arise only five times in 100).
time, more rapid response in accurately naming opposites, and a larger span of digits remembered. For rectal temperature a minus indicates a lower temperature after the barbiturate.

The results for the thirty subjects were broken down into three groups of ten subjects each. As a check, the same kind of analysis was carried out on these subgroups.

An inspection of the table reveals that all four psychological tests satisfactorily demonstrate a deterioration in performance at 6:00 a.m., one hour after being awakened and four hours after medication. At 9:00 a.m. all four tests show negative “t” values—and using Fisher’s method of pooling significance tests, the four together are highly significant (strictly this statistical test is not applicable because of lack of independence of the psychological tests, but further work not shown indicates that the correlations are small enough that the significance so computed is not badly distorted). Again at 1:00 p.m. all four tests are negative,

<table>
<thead>
<tr>
<th>Test</th>
<th>Mean of Day Before Placebo</th>
<th>Mean Score Day After Pentobarbital</th>
<th>Mean of Day Before Placebo</th>
<th>Mean Score Day After Pentobarbital</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tapping Speed (Taps/ten sec.)</td>
<td>65.2</td>
<td>62.7</td>
<td>68.2</td>
<td>55.0</td>
</tr>
<tr>
<td>Auditory Reaction Time (Milliseconds)</td>
<td>167</td>
<td>175</td>
<td>170</td>
<td>214</td>
</tr>
<tr>
<td>Naming of Opposites (Time in seconds)</td>
<td>.71</td>
<td>.60</td>
<td>.82</td>
<td>.91</td>
</tr>
<tr>
<td>Digit Span (Number of digits recalled in reverse)</td>
<td>6.4</td>
<td>7.0</td>
<td>7.0</td>
<td>6.0</td>
</tr>
</tbody>
</table>

but not as radically so as at 9:00 a.m. At 4:00 p.m. (14 hours after medication) three of the four tests continue to show negative “t” values, one of them significant at the 5 per cent level.

All of the tests, as well as body temperature, showed a marked diurnal trend on all of the four days—a sharp rise in efficiency from a low point at 6:00 a.m. through 9:00 a.m. and 1:00 p.m., a small drop at 4:00 p.m., a rise again at 7:00 p.m., and a final drop at 10:00 p.m.

Prior to the experiment the subjects had been informed that they would receive a “pill” before going to bed each night and that one or both might contain a very mild dose of a sedative. At the end of the last test session each subject was asked to guess whether he had received a sedative. Twenty of the subjects guessed the correct night, two guessed both nights, three guessed neither night, and five guessed the wrong night. The right and wrong guesses were submitted to a chi-square test of significance (Snedecor, 1946). Assuming an equal probability of the occurrence of right and wrong guesses, the differences between the expected and observed values produced a chi-square value of 9.0. For one degree of freedom
this value is significant at the 1 per cent level (i.e. there is one chance in 100 of obtaining a value of chi-square as large as that observed by chance alone).

Since responses were correct more often than would occur by chance, it is concluded that the "morning-after" effect of the barbiturate was recognized by the subjects as well as being demonstrated by the tests. The cues used by the subjects in detecting the drug effect were various and difficult for them to describe. They generally included "greater difficulty in getting up" on the morning after the drug, and "greater lassitude" and "drowsiness" during the day. Difficulty in performing the tests, however, was seldom reported. Indeed, several subjects expressed surprise when they were later told that their test performance had deteriorated after the barbiturate had been taken. Loss in critical judgment, although difficult to measure, is evident in the subjects' surprise.

Performance was significantly less efficient after the barbiturate in the four tests described above when the sample of thirty subjects is considered as a whole; but not all subjects were affected to the same degree in all of the tests. The subjects were therefore ranked for degree of barbiturate effect at 6:00 a.m. on the Tapping Speed and on the Auditory Reaction Time tests, and a rank order correlation was computed. It was found that the correlation was +.19. The low correlation is to be expected since the tests were purposely selected to represent a variety of functions involved in performance. The Tapping Speed test seems to be primarily motor and is probably the simplest test. Auditory Reaction Time is a relatively simple test combining sensory and motor function. Memory for Digits and Naming of Opposites, on the other hand, involve more complex functions of attention, memory, and association. It is not to be expected that these should be equally affected in all subjects. The important observation is that the whole range of functions spanned by these tests is significantly affected to some degree when the group of subjects is considered as a whole.

SUMMARY

1. The after-effects of 0.1 gram pentobarbital sodium administered by mouth were investigated by means of psycho-physiological performance tests. Four tests, representing a range of functions, Tapping Speed, Auditory Reaction Time, Naming of Opposites, and Memory for Digits, showed a significant deterioration in performance at 6:00 a.m., four hours after the barbiturate had been taken.

2. The effect observed at 6:00 a.m. diminished after breakfast but was found to continue in a highly suggestive (qualitative trend) but not statistically significant degree until after 4:00 p.m., 14 hours after medication.

3. Although previous studies had been unable to demonstrate the effects of small doses upon test performance, the present findings were made possible by controlling many of the sources of variability, by means of the experimental design and analytic procedures.

REFERENCES

CROSSCORRELATION AND AUTOCORRELATION STUDIES OF ELECTROENCEPHALOGRAPHIC POTENTIALS

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at the Massachusetts General Hospital, Boston

For some time it has appeared clear to us that some of the recent techniques and new developments in communication theory have applications in the field of electroencephalography. In studies of the electroencephalogram we are concerned with nearly periodic functions (e.g., the alpha rhythm); with truly periodic functions (e.g., the cortical response evoked by rhythmic photic stimulation); with aperiodic transients; and with what, within the limitations of our recording apparatus, appears to be random activity (i.e., it appears to be unpredictable). These are the same classes of time functions as those in a communication system.

From among the many tools of modern communication theory one of the most applicable to our field is the autocorrelation function. For an understanding of the theory of autocorrelation the reader is recommended to Wiener's book (1949) on stationary time series and to the publications of Lee (Lee 1950; Lee, Cheatham and Wiesner 1950; Lee and Wiesner 1950). The applicability of correlation functions to problems in a field such as electroencephalography derives from the new statistical approach to these problems, and the introduction of statistical prediction theory (Wiener 1949). The concept of the statistical character of noise and signals can be directly applied here as can the techniques for determining how predictable a signal is from its own past. The characteristic by which this is calculated is known as the autocorrelation function, and its mathematical definition is given below.

\[ \text{Autocorrelation function} \]

This, in the simplest possible terms, is a method for comparing one time series (in our case an electroencephalogram) with itself displaced in time. This comparison is made at a great number of given delay periods. Thus, if there is a repetitive event present in the EEG (such as a response evoked by periodic stimulation), the correlation of the EEG with itself will be high when it is displaced by a delay which is equal to the interval between stimuli. This will be so even if the evoked response (the "signal") is of considerably lower amplitude than the background activity (or "noise") present at the same time, and even though this may completely mask the response in the original tracing.

Another function borrowed from communication theory that is applicable to the analysis of electroencephalograms is the crosscorrelation between two periodic functions of the same dominant frequency. In this case, instead of comparing the EEG with itself for autocorrelation, two EEGs occurring simultaneously are compared for crosscorrelation. One is familiar in electroencephalography with tracings which reveal waves of apparently the same frequency in different locations on the head, often having an apparent shift of phase. Frequently such bursts of activity are periodic within the limits of the sample chosen.

It is an example of such activity in the electroencephalogram that we have chosen for our first analysis by this method, and for determination of the crosscorrelation curve. A return to the subject of autocorrelation will be made later in this paper and an example will be given to illustrate its application.

1Aided by a grant from the Office of Naval Research Contract NS-ORI-76/VIII. N. R. — 113-141.
Electroencephalographic Data for Crosscorrelation.

The observation that changes take place in the electroencephalogram when the subject concentrates on mental work goes back to the early history of this science and is to be found in Berger's publications (1931). These changes are many and varied. Some workers who have studied only the occipital alpha activity have been disappointed in the lack of correlation between problem solving and changes in rhythm (e.g., Hadley 1941, Toman 1943). Such changes as were found in the alpha activity were: a decrease in the time during which alpha was present (Martinson 1939), a dropping out of certain frequencies (Esser and Bickford 1950), or a depression of their amplitude (Gibbs, Davis and Lennox 1935). Recently Gastaut (1950) has demonstrated rhythms in the temporal regions having frequencies in the alpha band (i.e., 9 and 10 c/sec.) which disappear during mental arithmetic although rhythms of the same frequencies persist in the occiput. In strong contrast to these rhythms which are depressed, are those which are evoked or at least augmented by mental concentration.

In 1937 Laugier and Liberson described a temporal rhythm which, on opening the eyes, was less depressed than the alpha rhythm, and which increased markedly during mental calculation. Their records show a more regular rhythm of higher amplitude when the subject is doing mental calculation than when he is relaxed with his eyes either open or closed.

If many electrodes are placed over the scalp, it is found that many changes take place in the EEG during mental effort, of which that described by Liberson is only one. Another striking one is the appearance of rhythms in the frequency band of 4-7 c/sec., usually localizing in the midline just anterior to the vertex. These vertex rhythms have received recent study from Arellano and Schwab (1950).

There is great individual variation in these changes, the temporal rhythm appearing more prominently in some subjects during mental work and the vertex rhythms more so in others. In some subjects both rhythms appear, and in some neither seems elicitable. Figure 1 shows a sample of three rhythms recorded simultaneously from a subject engaged in mental calculation. The electrodes are on the vertex, the temporal area and the occiput respectively, and each is referred to a distant electrode on the seventh cervical vertebra. The rhythm from the vertex is approximately 6 c/sec., that from the temple 7-8 c/sec. and that from the occiput is 10 c/sec. The subject's eyes are open and fixated.

In 1948 Kennedy and co-workers independently made some further study of the temporal rhythms evoked by mental arithmetic. These they recorded from a bipolar linkage with an electrode on each temple "just back of the external canthi of the eyes". They noted that this placement of electrodes with bitemporal linkage gave the record the highest amplitude. This latter observation was of interest to us in relation to some studies we were making at that time of the electrical fields at the surface of the head, since this rhythm appeared to have a voltage-gradient distribution similar to that of a dipole-like field lying across the head parallel to the face, with two voltage maxima of different sign, one in each temple. Our own studies (Brazier 1949) established that such a field could be demonstrated in that small fraction of the population who exhibit this activity, but we found the foci of maximal voltage at electrode placements closer to those of Laugier and Liberson than to those of Kennedy, i.e., on the temporal regions just anterior to the pinnae.

These rhythms appeared to be identical in both hemispheres except that they looked 180° out of phase. On the ordinary ink-writing oscillographs and cathode ray oscillograph records this phase displacement can only be judged approximately. Since the inference from a truly 180° displacement would have considerable physiological interest we have submitted this problem for
calculation of the crosscorrelation function, for here we appear to have two nearly periodic functions of the same fundamental frequency. Or at least they are approximately periodic within the limits of the sample chosen for analysis. Various mechanical and electronic methods have been devised for determining these functions.¹

The digital electronic correlator at the Massachusetts Institute of Technology was made available to us for these studies.

The questions to be answered are whether all frequency components in the two EEGs have the same phase shift and whether all phase angles are 180°; or whether, as an alternative, it is merely the apparent dominant frequency (usually 7 or 8 c/sec.) that has this opposition of phase in the two EEGs.

In order to answer these questions we need as full a spectrum of this activity as our recording instrument will give us, as well as the phase relations of all the frequencies common to the two temporal lobe activities.

Outline of Procedure.

The electrodes used were placed as follows: electrode 1 was put on the left anterior temporal region in front of the pinna, electrode 2 was in a similar position on the other temporal region, and electrode 3 was on the chin and was used as a reference for both the temporal leads. The mental task given was the subtraction alternately of 17 and 23 from an odd number in the high thousands.

Electrode 1 was connected to grid 1 of a Grass amplifier and electrode 2 to grid 1 of a second matched amplifier. The reference electrode was connected to grid 2 of each amplifier. Each of the outputs from the two power amplifiers was led into one of two channels of a frequency modulated tape recorder. The playback from this tape recorder formed the input for the electronic correlator.

In figure 2 is shown a sample of the EEG actually used for the input of the correlator in the first of the experiments about to be described. This was recorded simultaneously on the inkwriter and the tape. In this

¹ For details of instruments capable of performing the mathematical operations necessary for the determination of correlation functions, see references: Lee 1950; Lee, Cheatham and Wiesner 1950; and Lee and Wiesner 1950.
sample the ink recording was made at a paper speed of 6 cm. per sec. and shows quite clearly that when the dominant activity at one temporal lobe gives a negative deflection that in the other gives a positive one when they are connected to the same reference. The consequent summing when the temporal electrodes are linked is seen in the third channel.

The tape recorder used was designed and built especially for this purpose by Mr. Paul Green, the frequencies with which one is concerned in electroencephalography being considerably lower than those common in communication engineering. The tape recorder was designed to play the EEG back into the correlator at five times the speed at which it was originally recorded (e.g., when a 5 min. sample of EEG was taken, the total playback time was 1 min.) The two channels of the tape recorder (one carrying the recording from the left temporal lobe and the other that from the right) were played back as input into the correlator simultaneously. A full description of the tape recorder with details of the circuit has been published by Green (1950). It is of the utmost importance that phase distortion should not be introduced by the tape recording and for a discussion of this point the reader is referred to the original paper (Green 1950).

The first action of the correlator is to note the amplitude of one EEG at a given moment and to multiply it by the amplitude of that of the other at the same moment, i.e., with no delay time in this case \( \tau = 0 \). In other words it takes a function of the first time series, \( f(t) \), and multiplies it by a function of the other, \( g(t + \tau) \), (where in this case \( \tau = 0 \)) to get a product \( f(t) \cdot g(t + \tau) \). It obtains this product at 12000 points throughout the EEG sample, so that we now have one curve (the product) where we previously had two (the two EEGs). The area under this curve is then integrated and, since the sample does not extend from infinity in the past to infinity in the future, but from a time \(-T\) to a time \(+T\), the average, over the complete period, of the integral of the product is obtained (by dividing by \(2T\)). The function so obtained is in this case the crosscorrelation function of the two EEGs at that particular delay time (in this first case, for a delay time of zero).

\[
\lim_{T \to \infty} \int_{-T}^{+T} f(t) \cdot g(t + \tau) \, dt
\]

The integration of the products in an EEG sample taken from its beginning at \(-T\) to its end at \(+T\) is shown by the integral sign and the averaging by the expression \( \lim_{T \to \infty} \). The term \( \frac{1}{2T} \) represents the limit of the function as \( T \) approaches infinity.

The correlator has at this stage made 12000 calculations and has given us the crosscorrelation between the two EEGs when they are compared simultaneously, i.e., with zero delay. The tape record is now played back in such a way that one EEG is displaced in time in relation to the other. Different values of delay time, in steps of 8 msec. between the extremes of minus 300 msec. and plus 300 msec. are used. For each of these steps (about 80 in number) the correlator calculates again the crosscorrelation function \( (\rho(\tau)) \). Figure 3 shows two delay steps for a single EEG to illustrate the type of time function used for this analysis.

With these data we can now plot the crosscorrelation function of our EEGs at each delay time against this delay time. In figure 4B the curve obtained for the crosscorrelation between the left and right temporal lobe recordings of a 5-min. sample of the EEG illustrated in figure 2, has been plotted.

Had there been no correlation between the activity from the two hemispheres, the graph would have been a straight line parallel with the abscissa since there would have
been no positive correlation to swing it upwards and no negative correlation to swing it downwards. At the other extreme (see fig. 4A), had the two EEGs been purely sinusoidal and identical in both amplitude and phase, the resultant curve would have been another sine wave which would not decay to zero however long the delay time, activity being, although briefly periodic, not continuously so (as is, for example, a pure sine wave) and hence the likelihood of the relation holding, as time is extended, approaches zero.

When we examine the curve in figure 4B, we find that it does not fall in any of the three categories just discussed. It does for sine waves being truly periodic would hold this relationship to infinity. Were the two EEGs identical in frequency and phase but not truly periodic in character they would be maximally positively correlated when superimposed (i.e., with zero delay time) and the crosscorrelation curve would be symmetrically distributed around zero \( \tau \), the curve on each side of this mid-reading eventually approaching zero correlation. This decay to zero correlation is due to the EEG not show zero correlation, it is not a sine wave, and it does not indicate identical original traces. It does have a reasonably symmetrical distribution about zero delay time, it shows the gradual decay to zero correlation with increasing time, indicative of an imperfectly periodic function, and it shows maximum negative correlation close to zero \( \tau \). This last is what was evidenced in the original tracings as a 180° difference in phase between the two hemispheres —
when the wave in one EEG was at its peak, that in the other was in its trough, and therefore the correlation is a negative one.

At a delay time which on the average places the peaks of one EEG coincident with the peaks of the other, the correlation is positive. In the particular instance shown in figure 4B this is seen to occur maximally when the delay time is either minus approximately 60 msec. or plus approximately 60 msec. This is the duration of one-half of an 8 per sec. wave (the dominant frequency of this activity in this subject) and hence the maximum positive correlation in this case for the duration of the sample, the EEG was highly periodic.

In figure 5 an example of the crosscorrelation between the two temporal lobes during mental calculation is shown for another subject. At actual zero delay a positive correlation is present in all cases because some noise in the system is unavoidable — such as tube noise, or in our case, muscle potentials; but since this is random, the correlation will not hold at delay times much distant from zero. In figure 4A and 4B this has not been included, but in figure 5 plots at and close to zero delay time have been

occurs when one EEG is delayed behind, or advanced in front of, the other by half the duration of its dominant cycle. This would not necessarily be evident in all such curves and would only appear in those cases where, graphed and illustrate the presence of random noise as explained above.

The frequency spectrum of an EEG record is familiar to electroencephalographers who use automatic analysis, but
analyzers such as the Walter instrument give the amplitude parameter only and give no information about phase. In such a comparison as we are attempting to make, however, phase cannot be neglected. It is for this reason that we go through the step of finding the crosscorrelation curve, since it retains the phase difference between the two EEGs. The next step is to find the value of this phase difference, and for this we calculate the Fourier spectrum of the crosscorrelation curve (i.e., of the curve shown in figure 4B). Any curve of this type can be compounded of cosine and sine terms which can be found by standard methods of derivation. The degree of symmetry around zero \( \tau \) determines the absolute values of the cosine and sine terms.

When such an analysis was applied to figure 4B several things became apparent. In the first place the sine terms were very small, indicating that almost all frequencies were either approximately in phase, or approximately 180° out of phase. The small deviation from exactly 0° or exactly 180° we lay to our experimental error. Its size was not a function of frequency.

The integer frequencies whose angles approached 180° were 2, 3, 4, 7, 8, 9, 11, 12, 15 and 16, and when the curves for the cosines and sines were plotted the cosines were found to be maximally positive at 7.6 c/sec. and 3.3 c/sec. These frequencies corresponded to the fundamental and the subharmonic of the dominant frequency during mental calculation in this individual. The deviation
vary from person to person as of course do those of the occipital alpha, but in each subject examined we have found almost all frequencies present to be either 0° or 180° out of phase (with a small deviation presumably due to experimental error).

An attempt at the full neurophysiological interpretation of this result is outside the scope of this report, and in any case must await an increase in our knowledge of the interdependence of the two temporal lobes: work from many laboratories is bringing this more and more into prominence. We believe that these results do, however, rule out one mechanism: i.e., that a neuronal delay (of tract conduction and synaptic delay) is responsible for impulses from a single source reaching one temporal lobe before the other, for no delay of this kind could result in the same phase displacement for so many frequencies.

To return now to the subject of autocorrelation, we are applying this characteristic to electroencephalography for the detection of an evoked response of low voltage (i.e., a signal) in a fluctuating background of EEG activity (i.e., “noise”) which may be of far greater amplitude.

An example of a “mock-up” experiment in which a known signal was mixed with random noise to demonstrate the possibilities of this method is shown in figure 6. These are the data of Dr. Y. W. Lee of the Research Laboratory of Electronics at the Massachusetts Institute of Technology. At the bottom of this figure, in section (e), is shown an amplification of the signal used. For input to the autocorrelator its amplitude was drastically reduced to that shown in (a), the uppermost trace, and it was mixed with the noise shown in (b) which, as can be readily seen, was of markedly greater amplitude. Consequently the resultant input to the autocorrelator was that of the two as seen in (c).

The autocorrelator, finding no correlation in the random noise component at the longer delay times, reports only on the periodic one, i.e., the signal; its output (d) is found to reproduce with extreme faithfulness the original signal.

This technique is being applied by us to the study of cortical responses (in different locations in the brain) to repetitive photic stimulation of the eye. The correlator technique has the advantage over a narrow-band filter in that it can detect the periodic signal.
irrespective of its frequency components. A
description of this work will form the subject
of a further report.

Another method (Casby) for achieving
this when no correlator is available is to use
narrowly tuned resonating circuits (i.e.,
circuits with a very high Q). In our case
we have used those of the Walter analyzer
(Baldock and Walter 1946) but have tuned
them especially for this purpose as will be
described below.

Twelve resonant circuits have each been
tuned sharply to a harmonic of 2 c/sec., i.e.,
2, 4, 6, 8 . . . . . . 24 c/sec. (All frequencies
above 24 c/sec. were cut out, since we were
limited in the number of circuits we had
available). Each is adjusted with great care
so that the output is as nearly as possible
in phase with the input at the center fre-
quency. The outputs are added together
electrically and the sum is traced out by
a pen. (The integrator circuits of the Walter
analyzer are not used.)

The concept of crosscorrelation is also
implicit in this method, for the filters may be
considered not only as devices selective to
frequency, but as storage systems. The
characteristic of the long decay time of each
filter, produced by the narrow tuning re-
results in the reconstructed response to a
single impulse being repetitive (so that a
trace of it is stored for several seconds). If
the original impulse does not recur this
response decays after 6 or 7 repetitions. If,
however, the impulse is repeated at the fun-
damental of the frequencies to which the
resonators are tuned, each new one will
coincide and sum with the stored signals
from the previous ones, whereas the back-
ground EEG, lacking this periodicity, instead
of summing will tend to cancel. The cross-
correlation of the evoked response is high
in comparison with that of the background
EEG. The reader is referred to the original
thesis for further elaboration of this state-
ment.

In the laboratory application of this tech-
nique the eyes of the subject are stimulated
photically at a frequency of 2 per sec. while
the EEG from the occipital region is record-
ed directly on an inkwriting oscillograph
and at the same time is led from the power
amplifier into the twelve resonating circuits.
The EEG presents to the filters (after the
initial transients have abated) a complex
wave with a fundamental frequency of 2
c/sec. Each filter extracts its own harmonic

1This method has been developed by one of us
(J.U.C.) and the mathematical justification for it has
been the subject of a thesis available for reference in
the thesis library at the Massachusetts Institute of
Technology ("A Comb Filter for the Study of the
Evoked Response of the Cerebrum to Peripheral Sti-
of the response plus a small portion of the background EEG. The aggregate output of the filters gives back the first twelve harmonics of the evoked response together with a greatly reduced part of the background EEG as explained above. In this way the signal-to-noise ratio of the evoked response is greatly increased. In practice we have reduced the square of the voltage of the background EEG to 1/7th that of the evoked response. Were more stable circuits available, this could, of course, be cut more.

Experience with the circuits available to us has lead to a choice of a maximum $Q$ of 150 for all 12 circuits ($Q = \frac{\tau}{2\pi f}$, where $\tau_n$ is the time constant of decay of the $n^{th}$ harmonic). With circuits tuned in this way the following results were obtained.

In the first place the results produced with a known artificial input were examined; these are shown in figure 7. As can be seen from the first column, every resonator responds to a repeating pulse with equal amplitude. In the samples shown in figure 7 the first channel depicts the input pulse, the second is the reconstruction from the electrical addition of the 12 harmonics and the remaining channels display six of these harmonics singly.

In figure 8 examples of EEGs from a normal subject are shown; in the upper section the eyes are open and in the lower they are closed. In each case the subject is being stimulated with flashes at a rate of 2 per sec. The uppermost trace in each sample is the original EEG; the middle one is the photocell and the lowest is the reconstructed evoked response.

The previously undetectable response to the light flash is now clearly apparent. The repetitive waves following each flash when the eyes were closed was a consistent finding in all subjects examined.

As noted above, because their number is limited, the use of narrowband filters has the disadvantage that they can be used only for detection of signals whose periodicity is related to their frequency, unlike the autocorrelator which is not bound in this way.

In electrical studies of the brain where output alone is recorded (i.e., the EEG) one is constrained by the fact that an almost infinite number of combinations of electrical events within the brain could contribute to produce similar outputs, and little can be said about the possible generators or circuits responsible for it. The recent development in this field of techniques of activation in which a controlled input (for example, a
visual stimulus tagged in time (Walter, Dovey and Shipton 1946) is used, has opened up new possibilities. One can study the output in the presence and absence of the sensory stimulus, and by crosscorrelation studies obtain information as to what effect the input has had on it. One can by response and some information gleaned as to how transmission through the brain has modified it. The opportunity for examining the influence on the impulse response of other activity of the brain taking place between input and output (such as, for example, occupation with mental calculation) is also open to study.

It is with this goal of developing methods suited to this approach to the study of the brain that the above techniques have been explored.

SUMMARY

With the purpose of demonstrating that some additional information can be brought into the study of brain potentials by techniques developed in communication engineering, an application of crosscorrelation analysis to a problem in EEG has been reported, and an application of autocorrelation analysis has been outlined. A practical method for applying these concepts when no automatic correlator is available has been described.

We wish to express our gratitude to Professor J. B. Wiesner for making the electronic correlator at the Massachusetts Institute of Technology available to us; to Dr. Y. W. Lee for permission to publish figure 6; to Mr. Paul Green for his work on the tape recorder and for his help and interest; and to Dr. Robert Schwab for his interest and encouragement.

REFERENCES


EXPANDING CONCEPTS IN NEUROPHYSIOLOGY

MARY A. B. BRAZIER, PH.D.

In 1748 Albrecht von Haller, the Swiss physiologist and physician, found himself the unwilling recipient of the dedication of an anonymous pamphlet entitled "L'homme machine." Nothing could have been more at variance with his pious philosophy, and the controversies aroused by its theme burned with a white heat.

The message carried by this pamphlet, which was almost certainly written by the French physician, La Mettrie, was that man's sole guide to the universe is the observations he makes and that preconceived deductions are valueless. Nearly two centuries later Einstein gives us the same warning against metaphysics: "In order that thinking might not degenerate into 'metaphysics' or into empty talk, it is only necessary that enough propositions of the conceptual system be firmly enough connected with sensory experiences."

The author of "L'homme machine" expresses himself in terms which for his century are strongly neurophysiological. The "faculties of the soul" are held to depend on "the proper organization of the brain," for, he says, "so far then am I from thinking that thought is inconsistent with organized matter, that I look upon it to be a property as much belonging thereto as electricity, impenetrability, extension etc."

In spite of semantic difficulties with the word esprit (the French language having no exact equivalent for "mind") and in spite of the author's innocence of what Galvani, Lavoisier, Darwin, and Cajal were later to reveal, anyone who has followed the recent developments in neurophysiology cannot fail to hear the echo of this voice from the 18th century.

One is reminded of it when reading a paper which appeared in 1947, nearly 200 years later, entitled "How We Know Universals: The Perception of Auditory and Visual Forms," by Pitts and McCulloch. This paper is the logical development of

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"If we have any insight into mind, or any eye for human history, we must confess at the same time that the oracular substitutes for knowledge to which, in our perplexities, we might be tempted to fly, are pathetic popular fables, having no other sanctity than that which they borrow from the natural impulses they play upon. To live by science requires intelligence and faith, but not to live by its folly."—Santayana.

1. L'homme machine, anonymously published, 1748.
some earlier work evolving a mapping of nerve nets which, by virtue of reverberating circuits and branching connections, would determine the order of choice between incompatibles. The choice between ends was thus put on a possible neuronal basis.

In the 1947 paper designs are presented for neuronal nets based on known neuroanatomical structure which could furnish a basis for recognition of universal form when a particular specific stimulus arrives over sensory pathways. Here for the first time is a suggested mechanism for a neuronal apparatus by which the organism may know universals and respond to symbols of these universals, rather than to mere particulars. It is by the introduction of scanning circuits into the postulated network that these workers have been able to formulate a system by which impulses (which are particulars) arriving in any sensory nerve, at any moment in time, may evoke, not merely the reflex response to that particular, but the universal of which it is a part. One example is the recognition of chords regardless of pitch. The network they present, and for which they have computed the mathematical analysis, is based on the cytoarchitecture of the auditory cortex. Another example is the recognition of shape regardless of size. This is an ability shared in some degree by animals lower than man; rats, for example, can learn to differentiate a square from a triangle regardless of the actual size.

The line of argument develops from the concept of reverberation in chains of neurones as a basis of recognition of universals. A neural mechanism involving a net into which impulses can enter and persist through time, to influence a response at a later date, is a comparatively new concept. The traditional theories of neuronal paths passing into, through, and out from the nervous system by noncircular connections provided no mechanism for retention of impulses; the signal passed through and perished. A self-reexciting loop of neurones, sharing neurones with other loops, in which reverberation can be set up by the entry of afferent impulses from different sense receptors gives and preserves the association between different particular events and allows the recognition of a universal to be sparked by the receipt of a particular. The first taste of the *madeleine* dipped in tea was sufficient to evoke in Proust the full setting of his lost childhood happiness. The sight of a bird, whatever its shape, size, color, or orientation, the written or spoken word for it in any of the languages known to us, the sound of its song, the feel of its wings in the dark, and sometimes even its smell, will inform us of the same universal.

The uniformity of the nerve impulse, the unique form of the nerve action potential, makes possible this blend of stimuli, specificity having been left behind at the receptors. The number of neurones in the human brain, approximately 10,000 million, is sufficient for a vast number of intercommunicating nerve nets.

Man has a far greater ability than animals to extract the factors common to many different sense impressions received at different times and to synthesize them into a universal. Köhler's apes could, however, achieve a combination of two, and sometimes more, experiences occurring in isolation and at different instants in time, and not related in time as are conditional reflexes. There must, in these apes, have been some retention of components of each separately occurring experience and an integration of them, which they later used. Where could be the nets in which these essentials are retained and integrated? Are they perhaps in the cortical association neurones, Parker's "internuncial apparatus," which has twice as great a mass in
man as in ape? Where man is alone in his achievement is in the construction of symbols by extraction from his experiences and the use of these later for semantic formulation, such as language, or the symbols of logic or mathematics.

Not only does the new orientation towards neurophysiological mechanisms suggest (and this is the first time it has been done) a neuronal basis for choice and for the knowledge of universals; it also implies a mechanism for purposive behavior. The postulation of feed-back mechanisms introduces the possibility not only of self-regulating processes (with which physiologists are familiar) but also of self-directing systems. That such a system may have a neuronal structure brings goal seeking out of the clouds and into the nervous system. The first move in this direction was made in a paper published in 1943 by Rosenblueth, Wiener, and Bigelow \(^3\) entitled "Behavior, Purpose and Teleology." Here, and again for the first time, a possible neural mechanism has been suggested for purposeful activity, by which signals from the goal can alter the behavior, by negative feedback, after it has been initiated and alter it in such a way that it may succeed in reaching the goal.

It is clear, as Judson Herrick has pointed out, that simple reflexes are not the elementary units of behavior and that the "actual conduct of animal and human bodies is not fabricated by monumentally piling up of simple reflexes."

A glance at the concepts referred to on the last few pages reveals how profound a change has taken place in neurophysiology, not only in the 200 years since La Mettrie, but in the last 25 years. This change in concepts of the nervous system is so great that it is almost impossible to overestimate it. In brief, it is a change from the concept of a passive, static nervous system to an active dynamic one. In the old concept the nervous system was bound in space by the paths of neurones, in direction by the Bell-Magendie law, and bounded in time by the conduction rate of nerve fibers and the delay time at synapses. No persistence in time was possible, and the dimensions of its activity were rigorously imposed by the all-or-nothing law. It was temporally and spatially fettered.

The new neurophysiology has broken the fetters of this concept. Temporal summation, spatial summation, inhibition, all release the synapse from rigidity of response. After-potentials, after-discharge, and reverberating circuits release the nervous system from the fetters of time. No longer is the nervous system seen as responding only when it is stimulated. It can seize and retain stimuli and respond to them at a later time. One no longer seeks merely an individual response to the individual stimulus; it can respond to the category. And now it has been emancipated in space by the discovery of moving fields of direct current potentials, making possible the use of other parts of the brain than those directly served by the specific incoming nerve pathway. An object seen with one eye is recognized with the other. A system learned through one sensory system is recognized by another. The tune that is read from the score can be recognized by the ear.

All this is consistent with the central nervous system being not a mere relay station, which, when unstimulated, is at rest, but a system which is in itself a hive of activity, clues to which can be found in the incessant electrical activity of all neurone aggregates both in the cord and in the brain. The literature of the latter (electroencephalography) is vast.

These new concepts, these new hypotheses of neural mechanisms serving choice, the recognition of universals and purposive behavior, call for an architectonic design involving scanning circuits, reverberating networks, and pathways for feedback, and the neurophysiologist who wants to test these hypotheses is now faced with a search for the anatomical and histological existence of such circuits and for physiological evidence of their functioning in this way.

It is not very widely realized that in fact the existence of examples of this kind of circuit in the central nervous system were discovered histologically before man's reasoning had demanded such structures to account for his observations. On April 28, 1903, the greatest of all microanatomists of the nervous system, Ramón y Cajal, professor of histology at Madrid, addressed the conference of the Faculty of Medicine on the structure of the optic thalamus. He described to his audience some remarkable findings in the lateral geniculate bodies of the cat, the mouse, and the human infant. There he had found two kinds of cells—some small with short axons and many dendrites, others large and star-shaped with long axons traveling to the optic cortex in the calcarine fissure, where he could demonstrate their arborizations around cells of the granular layer. Moreover, the axons of these same star-shaped cells gave off collaterals before they left the geniculate body, these collaterals remaining entirely intrathalamic. But he also found corticothalamic axons running down from the cells of the optic cortex to terminate freely in discrete islands in the lateral geniculate body with arborizations surrounding and enclosing the cells with short axons. These, in turn, arborized with the ascending thalamocortical neurones, thus forming a loop.

Since there is field-to-field representation from the retina to the lateral geniculate body, why, asked Cajal, should some islands of cells in this way station be so exclusively served by returning axons from the optic cortex? And what was the function of the cells with short axons? He suggested three possible functions for the structural arrangement he found. One (hipótesis de la acción espectante) was that impulses from the whole visual field would initially reach the geniculate body and beyond it to the cortex, where the returning corticothalamic neurones would convey impulses back only to these specific islands of the geniculate body and there facilitate transmission at those cells with which they arborized. Such a mechanism would enhance the sensation from a particular section of the visual field, which would then receive the observer's especial attention.

Cajal's second hypothesis (hipótesis de la inhibición) was similar but reversed, namely, that these corticothalamic impulses exert an inhibitory action on the cells around which they terminated, allowing attention to be given to that part of the visual field whose connections in the lateral geniculate body did not receive them. Both these suggestions anticipated the introduction into neurophysiology of the engineer's concept of feedback.

It is in his third hypothesis (hipótesis del refuerzo nervioso) that one hears even more clearly the ring of future postulates. He suggested that there may be some "stored" activity persisting in neurones of the thalamic centers which enables weak impulses in the primary sensory pathways to be reinforced and so reach the cortex and evoke the phenomenon of perception. It is to the many neurones with short axons which he found in the thalamic centers that he allotted this function of accu-

mulated activity, which, had the hypothesis been formulated today, would probably have been named "reverberation." Here is the concept of impulses in a net persisting through time to influence a response at a later date.

The neurophysiologist has still a long way to travel in his search for more of these structures in the central nervous system, and, having found them, has an even harder task in demonstrating that impulses do indeed circulate within them. It is perhaps well to bear in mind Cajal's final warning that his explanations of these mechanisms are _conjetura._

ADDITIONAL REFERENCES


Alpha Content of the Electroencephalogram in Relation to Movements Made in Sleep, and Effect of a Sedative on This Type of Motility

MARY A. B. BRAZIER AND HENRY K. BEECHER. From the Anesthesia Laboratory, Harvard Medical School at the Massachusetts General Hospital, and the Electroencephalographic Laboratory, Massachusetts General Hospital, Boston, Massachusetts

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Alpha Content of the Electroencephalogram in Relation to Movements Made in Sleep, and Effect of a Sedative on This Type of Motility

MARY A. B. BRAZIER AND HENRY K. BEECHER. From the Anesthesia Laboratory, Harvard Medical School at the Massachusetts General Hospital, and the Electroencephalographic Laboratory, Massachusetts General Hospital, Boston, Massachusetts

Of all the many correlations that have been made between electroencephalographic changes and various conditions of the brain, one of the most consistent and striking is their correlation with the state of awareness of the patient (1). There is a change in the electroencephalogram when the subject becomes more alert and another when he becomes less alert. When there is actual loss of consciousness as normally occurs in sleep, or abnormally as, for example, in coma, in anesthesia, in a faint or in the stupor following an epileptic convulsion, the change in brain potentials is extremely gross (2).

There have been many studies concerned with the arrival of sensory impulses at the cortex during these states of impaired consciousness, but little attention has been paid to the motor functions of the cortex. This is possibly partly because no one has yet succeeded in recording a burst of cortical potentials which could with any confidence be regarded as the electrical discharge of Betz cells initiating the movement of a muscle or a limb.

The most pertinent data on this subject have been on another facet of the role of the cortex in the initiation of movements. In 1938 Jasper and Andrews (3) studied the electroencephalogram and tremor movements in man; in the classic experiments of Adrian and Moruzzi (4) the electrical activity in the axons of the cortical motor cells was recorded (in the pyramidal tract of animals) and the discharges were found to correspond in time with the rhythm of the cortical potentials of the motor region. More recently Bates, (5) working with normal, awake, unanesthetized subjects, has demonstrated that the onset of a voluntary movement coincides with a certain phase of the alpha rhythm. By superimposing photographs of several records he was able to show that for a period of approximately half a second before each voluntary movement of the hand was made, the alpha waves from the contralateral motor cortex were locked in similar phase. Kibbler, Boreham and Richter (6) independently studying eye-opening movements found that the probability of the oc-
Incurrence of a motor discharge depended on the phase of the alpha rhythm, but in their experiment a sensory stimulus had preceded the eye movement, thus making the situation more complex.

In the light of this work it seemed of interest to us to investigate the electroencephalogram during normal sleep with special reference to the occurrence of movements. The incidence of movements made when a normal subject is apparently asleep is usually high and yet the presence of alpha activity in the brain potentials is very much reduced from that in the waking state.

We were interested to see whether this paucity of alpha frequencies during sleep persisted when the subject made a movement, and whether a movement could in fact be initiated in the absence of an appreciable amount of alpha. We were also interested in another aspect of this question, namely whether movements are in fact made during deep sleep or whether there is always some rise in level towards the waking state before such a thing is possible. An extension of this line of thinking was a search to find whether any justification existed for using the number of movements made during sleep as an index of depth of sleep, for some objective index was required in a further study we were making on the comparative hypnotic powers of various sedative drugs.

It is now generally accepted that decrease in the amount of alpha activity (and, within limits, an increase in the amount of delta) is an index of depth of sleep. We have therefore made quantitative measurements of the amount of alpha, and of delta, of nine subjects when awake, when asleep, in a period just before movement made in sleep, and again just after the movement has been made. Six scalp electrodes were used in each case but the results to be reported are all measurements of the recording from a parietal-occipital linkage.

**METHOD**

The subjects slept for 3 hours under controlled conditions after a long fatiguing day of controlled occupations, and while they slept their electroencephalograms were recorded continuously. In addition, their movements were recorded in three ways: by a motility recorder under their hips, another under their shoulders and by the appearance of muscle potentials in the electroencephalographic record. The last of these proved to be the most sensitive indicator. All three motility devices registered graphically on synchronized recorders. Each subject was tested twice at an interval a week apart; on each occasion he would take an identical-appearing pill; in one case this would be lactose and in the other 90 mg. sodium pentobarbital. In no case did the subject know which he was taking.

For analysis of the EEG records the following procedure was followed: A sample of record 10 seconds in duration was measured by hand for every wave present whose duration was from 125 to 77 msec. (i.e. waves of a frequency of from 8-13 cycles/second). The amount of delta activity (i.e. of frequencies slower than 4 cycles/second) was also measured. In the section of the hospital where these recordings were made at night no automatic analyzer was available, so that all these measurements were made by hand by a method which has been published previously (7).

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For establishing the amount of alpha during an individual’s waking state, six to eight such 10-second periods were measured. For the samples of the sleeping state, six to eight more 10-second periods were taken, each being picked midway between two movements when the subject was asleep. The results from these samples were examined statistically and the standard error established.

For the samples preceding and following a movement the synchronized recorders
were matched and the electroencephalographic tracing measured off to give three 10-second samples for each movement: namely 20 to 10 seconds before the movement, 10 to 0 seconds before it and 0 to 10 seconds after the movement. In all, analyses of over a thousand 10-second samples are represented in the following data.

**Results**

**Quantitative Data on Reduction of Alpha During Sleep and on Incidence of Delta Activity.** In table 1 the measurements of the amount of alpha activity (8–13 cycles/second) and of delta (frequencies below 4 cycles/second) are expressed as percentages of the 10-second sample occupied by waves of those frequencies. Each figure is the mean of six to eight samples.

<table>
<thead>
<tr>
<th>SUBJECT</th>
<th>ALPHA (AWAKE)</th>
<th>ALPHA (ASLEEP)</th>
<th>DELTA (AWAKE)</th>
<th>DELTA (ASLEEP)</th>
<th>SUBJECT</th>
<th>ALPHA (AWAKE)</th>
<th>ALPHA (ASLEEP)</th>
<th>DELTA (AWAKE)</th>
<th>DELTA (ASLEEP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(87.0)</td>
<td>(l) 28.0</td>
<td>0</td>
<td>21.8</td>
<td>6</td>
<td>(l) 76.2</td>
<td>(d) 25.6</td>
<td>0</td>
<td>36.4</td>
</tr>
<tr>
<td>2</td>
<td>87.0</td>
<td>(d) 44.6</td>
<td>0.8</td>
<td>7.0</td>
<td>7</td>
<td>87.2</td>
<td>(l) 18.4</td>
<td>0</td>
<td>73.0</td>
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<tr>
<td>3</td>
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<td>(l) 26.6</td>
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<td>26.4</td>
<td>(l) 7.2</td>
<td>3.6</td>
<td>56.0</td>
</tr>
<tr>
<td>4</td>
<td>84.4</td>
<td>(d) 37.4</td>
<td>0</td>
<td>4.6</td>
<td>9</td>
<td>66.6</td>
<td>(d) 16.2</td>
<td>1.2</td>
<td>18.0</td>
</tr>
<tr>
<td>5</td>
<td>45.2</td>
<td>(l) 32.8</td>
<td>0</td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>74.2</td>
<td>(d) 40.2</td>
<td>0</td>
<td>22.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>69.6</td>
<td>(l) 26.6</td>
<td>0</td>
<td>35.4</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

1 = Placebo. 2 = Drug.

The reduction in alpha activity and the increase in delta are both statistically significant. It was rare for the alpha content of the sleeping record to reach even 50 per cent of that of the waking record. The differences between these values for each individual in natural and in sedated sleep are not significant. (The samples for the waking records were always taken before ingestion of the pill and hence are not subject to an effect from the drug.) We have found no subject in whom alpha was entirely absent during sleep, contrary to the general impression on this question; if the definition of alpha as rhythmic activity in the frequency band between 8 and 13 cycles/second is used, then it can be stated that measurement reveals such frequencies to be present in the occiput even in deep sleep, although they are usually riding on slow waves of much greater amplitude. Cutting the gain of the recording system in order not to block the amplifiers often causes these smaller waves to be lost from the recording.

**Change in Alpha Content Preceding a Movement Made in Sleep.** Examination of table 2 indicates that in the 10-second sample before a movement (center column) there is a marked increase in alpha content from that in the sleep period in all except

All statements made in this paper as to statistical significance are based on the critical evaluation of these results by statistical methods kindly done for us by Prof. F. Mosteller of the Department of Social Relations, Harvard University.
# Table 2. Alpha and Delta Content

<table>
<thead>
<tr>
<th>SUBJECT</th>
<th>ASLEEP</th>
<th>20-10 SEC. BEFORE MOVEMENT</th>
<th>10-0 SEC. BEFORE MOVEMENT</th>
<th>0-10 SEC. AFTER MOVEMENT</th>
<th>AWAKE</th>
<th>NO. OF MOVEMENTS MEASURED</th>
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<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<td>86.2</td>
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<td>(d) 44.6</td>
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<td>57.6</td>
<td>63.6</td>
<td>86.4</td>
<td>18</td>
</tr>
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<td>11</td>
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<td>41.2</td>
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</tr>
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<tr>
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<td>(d) 22.6</td>
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<td>(d)</td>
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<td></td>
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<td></td>
</tr>
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\[ ^1 \text{l} = \text{placebo, } ^2 \text{d} = \text{Drug.} \]
one subject on one occasion (case 5, after a hypnotic). Even this single exception does, however, show an increase in alpha in the 10 seconds just before the movements over the period 20 to 10 seconds before the movement. In fact, the whole table shows this augmentation of alpha as the sample is taken closer to the movement.

The figures listed in table 2 are the means of the measurements of the electroencephalograms at every movement made, the number of these being indicated in the right-hand column. Hence the number of samples was from 7 to 25, according to the individual.

The alpha content before a movement and immediately after one shows an increase over that of the sleep sample which is statistically significant; it will be noticed

that it is still considerably less than the amount present in the waking state; the inference is therefore that there is a change in level of sleep in the direction of wakefulness before a movement is made but that full wakefulness as defined in electroencephalographic terms is not a prerequisite.

Typical examples of an EEG of an individual in sleep (midway between two movements) and also just before and during a movement are shown in figure 1. In the upper section a record typical of sleep is seen with a focus of slow transient waves just forward of the vertex. This phase-reversal has been enlarged in the sample shown on the right. Slow activity located in this area has been demonstrated as characteristic of the electroencephalogram during sleep. In the lower section the EEG of the same subject preceding and during a movement is shown. Some runs of alpha appear in the record before the gross movement. As a matter of fact, some muscle potentials appear in the frontal leads ahead of the gross movement but after the appearance of alpha activity.
Change in Delta Activity Preceding a Movement Made in Sleep. The measurements for activity of a frequency slower than 4 cycles/second are included to demonstrate that the alpha frequencies that increase in amount just before a movement do so very largely at the expense of the delta. Delta activity can be used only as a partial index of depth of sleep for there is great variation in the amount present throughout a period of sleep. As a general rule it is present in greater amounts during the first hour of sleep than in later periods, and although it indubitably decreases as the subject emerges towards wakefulness and disappears when he does so, the relationship with degree of wakefulness appears to be less direct than that of the alpha content.

In spite of these reservations, the change in delta content preceding a movement made in sleep was found to be a statistically significant one. In no subject in our series was a movement made while the EEG was exhibiting the phase-reversal of slow waves just forward of the vertex, which is typical of sleep (8). This statement includes case 5, who, in one test, showed no increase in alpha.

Effect of a Hypnotic Drug on Number of Movements Made During Sleep. A glance at the column on the extreme right of table 2 shows that only in one subject were there more movements during the sleep period following ingestion of 90 mg. sodium pentobarbital than in natural sleep. These results would certainly support the suggestion that restlessness is reduced by a hypnotic (in the usual clinical dosage).

Discussion

Some results have been presented which would give support to a hypothesis that movements are rarely made at a level of deep sleep, and that the degree of cortical arousal necessary for a movement to be made is one at which alpha activity is present in the EEG in an amount exceeding that present in deep sleep.

Exceptions to a general finding are usually of interest. Our one case in whom, after a hypnotic, the mean alpha content before a movement was not higher than the mean of the readings midway between two movements, raises several questions, the two principal ones being: Did the movements (four in number) which lowered his mean take place without cortical mediation? Or, could an increase in alpha content have taken place but be missed by our rather small number of recording electrodes? Speculation on this point is not really fruitful without more data.

The effect of the hypnotic seems to be to reduce the incidence of movements made during the observation period and hence also the number of times sleep becomes more shallow. There is no significant difference in the degree of change in alpha content necessary for a movement to be made between natural and sedated sleep. These results can be interpreted as giving some support to the hypotheses (9) that allot a mediating role to the alpha rhythm not only in respect to the fate of incoming impulses but also to efferent cortical discharges, but no critical proof is contained here that the alpha rhythm actually participates in the cortical conditions necessary for a movement. That the return of alpha is the sign of an arousal mechanism seems indubitable.

Summary

Electroencephalograms have been recorded throughout 3 hours of the night on nine normal subjects on each of two occasions. Quantitative measurements of the amount of alpha have been made. In all the tests (with one exception) the mean of the alpha content in the period 10 to 0 seconds before a movement increased over
that present in sleep. This trend towards wakefulness was found to have started in
the period 20 to 10 seconds before the movement and to persist into the period 0 to
10 seconds after it. Using decrease in delta content as an additional index of in-
creasing wakefulness this was found to support the evidence for a decrease in depth
of sleep preceding a movement. The quantified data show that this change in level
of sleep in the direction of wakefulness occurs irrespective of whether the sleep is
natural or sedated (90 mg. sodium pentobarbital). A clinical dosage of sodium pento-
barbital (90 mg.) reduced the incidence of movements made during the 3-hour sleep
period (from a mean of 21 in normal sleep to a mean of 15 in sedated sleep). It would
seem that the number of movements made during sleep can therefore be used as an
index of depth of sleep when testing drugs for their comparative hypnotic power.

The authors wish to express their thanks to Prof. Frederick Mosteller for examining the results
presented for statistical significance; to Mr. Robert Goodnow for organizing the experimental setting;
to Mr. Chandler Cushman for running the recordings throughout the night; and to Mrs. G. Lothrop
for her patience and skill in measuring many hundreds of EEG samples.

REFERENCES

CHAPTER 13

Electroencephalography

By MARY A. B. BRAZIER, B.Sc., Ph.D.

If one may hazard a prediction, last year may prove to have been a most productive one for electroencephalography. There have been no large Congresses to draw people from their clinics and laboratories and fewer papers have been published. Therefore, why not infer that more work has been done?

Last year's publications have been helpfully summarized, and a general discussion has been published. Two symposia are now in print, both of which deal with the organization of cerebral mechanisms. No electroencephalographer who is concerned with the implications of the information derived by his technics can afford to miss these discussions.

A thoughtful essay on the various theories advanced to explain the nature of the EEG has been written by Wyss. He rejects the hypotheses that the waves are envelopes of spikes; that they are the direct result of centripetal impulses; that they are caused by reverberation in closed circuits; that synaptic transmission is responsible for the timing of the rhythm. He gives his allegiance to the concept of an autorhythmicity of the somatodendritic potentials of cortical cells maintained by metabolic processes and synchronized by the electrical fields of the active neurones themselves. He emphasizes that these are local processes and not propagated potentials. The question of motility of cell parts is not discussed.

Eccles, on the other hand, makes a different interpretation, basing his argument on the premise that the responses of neurones have essentially the same characteristics anywhere in the central nervous system. Paying due regard to the orientation of cell structures in the cortex, he supports Burns in the thesis that 'spontaneous' cortical rhythms derive from activity in neuronal chains and not from any inherent rhythmicity of individual neurones. The schema he suggests would encompass not only Burns' finding of electrical silence in the unanesthetized cortex when completely isolated from the rest of the nervous system, but also the superficial negative response obtained by Adrian on stimulation of the cortical surface, a phenomenon investigated further this year by Burns and by Chang. Eccles regards this as the synaptic potential of apical
pyramidal dendrites excited by spread of discharge in the axons of the superficial layer of horizontal cells. With stronger stimulation a surface positive response follows the initial negative one as the excitation spreads to deeper layers.

Lilly's technic of 25 electrodes implanted within a space of 0.64 sq. cm. of cortex is giving a type of information about the character of 'spontaneous' activity and evoked responses in the auditory area that has not been available before. Measurements have been made of the speed of the travelling waves. This is one of the most promising of the new approaches to this problem.

Another method which brings us finer resolution in our search for signals of low voltage (evoked responses) hidden among noise of higher amplitude (the background EEG) is the use of an electronic correlator. A description of the application of this technic to electroencephalography was given by Brazier and Casby at a meeting of the Eastern Association of EEG.

Yet another method for detection of time-locked evoked responses is available to users of automatic frequency analyzers of the Walter type (Casby). By very narrow tuning of the resonating circuits which correspond to the frequency of the stimulus and to its harmonics (so that the die-away time for each is very long), responses of the cortex at these frequencies will stand out from the background EEG. The resonating circuits (without integration) assigned this task write their information independently on the record through the standard pens of the inkwriting electroencephalograph. If phase is rigidly controlled, a reasonable replica of the response can be reconstructed from addition of the harmonics. This modification of the technic in some degree anticipates suggestions made in the critique presented by Vogel at the Marseilles Symposium.

A technic for detecting the presence of a recurrent response in the EEG has been published by G. Dawson. This, although it does not give information on the phase of each component frequency as does the electronic correlator, is an improvement over the method of superimposed sweeps in that a summation technic is used, i.e., the records are added automatically to obtain the mean. A regularly recurring response will in this way give a mean standing clearly above that of the random background activity.

The study of evoked responses in the animal and in man, both with and without metrazol, has this year engrossed more workers than any other single facet of EEG. The wide use of photic stimulation in clinical work has directed attention to the detailed character of the responses to light not only at the cortex, but along the optic pathway. Some clue as to the neurones immediately responsible for the several components of the cortical
response to light may come from the work in progress on their relation to maturation of these neurones in infant animals (Hunt and Goldring). More evidence has been gathered that the response to flicker is not a driving of the alpha rhythm. All workers do not differentiate clearly between evoked responses and “driving.” Fundamental for the understanding of the evoked response at the visual cortex is the paper by Bishop and Clare whose analysis shows that there is only one spike in the optic radiation on single shock stimulation of the optic nerve although there are three (or more) in the cortex, these others being contributed by wholly intracortical neurones, cells in other cortical layers being responsible for the subsequent slow waves. This interpretation (supported by the observation of Marshall that all components except the first spike are affected by spreading depression) differs from that of Chang who has postulated that the three spikes evoked at the cortex by a single volley to the nerve may indicate three fiber sizes, and consequently three conduction rates, in the optic radiation. This is a field where orientation of electrodes within the three dimensions of the brain is indeed critical. The detection of phase reversals as the exploring electrode penetrates succeeding layers of the cortex is invaluable in locating electrical events due to intracortical discharges, and is now used by many workers. Caution should, however, be used when the exploring electrode may be in a sulcus.

Bremer has been able to analyze evoked responses at the cerebellar cortex and finds, after the initial positive wave, a negative spike associated with discharge of the Purkinje cells. A slower negative wave follows, and would appear to represent temporally dispersed efferent discharges. He has also demonstrated a remarkable convergence of afferent systems in the cerebellar cortex so that response to one type of sensory stimulation can inhibit response to another.

One of the most striking reports on cortical concomitants is Bates demonstration that the onset of a voluntary movement coincides with a certain phase of the alpha rhythm. If photographs of several records are superimposed it is found that for a period of approximately half a second before each voluntary movement of the hand is made, the alpha waves are locked in similar phase. This does not occur when the same movement is involuntarily induced (by stimulation). Shunning the question of the neurophysiology lying behind the word “voluntary,” other than that it implies the inclusion of the brain in the circuit, one may observe that here are data that need to be considered in any hypothesis framed to explain the alpha rhythm.

Dell has traced the thalamic, cortical and cerebellar representation of the vagus; a primary response at the insular cortex follows 8 to 10 seconds
after a stimulus to the end of the vagus cut at the neck. To obtain secondary responses he found frequency of stimulation to be critical and traced them in mesencephalic nuclei, thalamus, hypothalamus and in the amygdaloid complex.

There is a growing interest in the responses (electrocortical, autonomic and behavioral) to electrical stimulation of various parts of the rhinencephalon, and the effects also of its fractional ablation. For a comprehensive review of previous work on animals, together with considerable new material, the reader is recommended to consult the monograph by Kaada. In man, studies have been made of autonomic responses during stimulation of the cingulate gyrus and uncus as well as the anterior temporal and orbital cortices by several workers; the uncal effects are the more striking. M. Lennox, from her results on anterior cingulate stimulation in animals, suggests a possible relation with the mechanism operating in petit mal epilepsy. Stoll has published electrophysiologic studies of the subcortical connections of the anterior temporal region in the cat.

A most interesting discussion of the possible mechanisms acting in an epileptic seizure was given by Jung at the Geneva Symposium. In fits induced in animals by electrical stimulation the spike at the site of excitation is followed by a slow wave of long duration and later by trains of normal waves which Jung suggests are the expression of an equilibrating mechanism for restoring the cortex to its normal level. Just before a seizure, these later potentials are depressed (as though the restraining mechanism had failed). The same author has also made a study of the pathways of propagation of discharges in the various phases of a convulsion.

EEG responses to sound during sleep have been recorded by Passouant in epileptics. An apparent recruitment of response follows slowly repeated stimuli (10 to 15 per minute); in non-focal epilepsy, the resultant discharges are generalized but in focal epilepsy they are asymmetrical (with the exception of cases with unilateral temporal lobe foci which on auditory stimulation discharge bilaterally).

Gibbs has described a type of spike discharge which he found in eight out of 300 control subjects and 312 out of 5000 epileptics. He describes these as 14 per second and 6 per second positive spikes but makes his use of this terminology admirably clear by his statement that “when recordings are made from a distant, relatively inactive reference electrode to the center of the discharging area, the spike discharges are negative to the reference electrode.” Stephenson has also found this type of activity in 32 out of 2500 adult patients (but he omits the clarifying statement). Both authors suspect a correlation with epileptic disorder located in the thalamus or hypothalamus, for a reference electrode consisting of the two
ears linked is negative to the scalp electrodes during the spiking, from which
they conclude that the superficial layers of the cortex are not involved
in the discharge.

The clinical application of activation methods has now been tested in
many centers and assessments of the various technics have been made by
several independent workers. Taking first the criterion that the chosen
method of activation is required to evoke EEG abnormalities in epileptics
whose resting records are normal, the various reports are as follows: With
photic stimulation alone, Hill finds less than 5 per cent showing this change,
Hutchinson, 0 per cent (in 100 cases), Walter, 0 per cent (in 2000 cases).
However, Rémy reports three cases and Lloyd-Smith 13. Compared with these figures, secoral sleep was found successful by this
criterion in 0 per cent of 60 cases by Hutchinson and in 13 per cent of 76
cases by Merlis. Metrazol alone, by slow injection of divided doses,
was found specific in 12 per cent of 100 cases by Hutchinson and in 47 per
cent of 58 cases by Merlis. Both workers consequently recommend this as
the preferred technic.

A more important criterion, perhaps, is that the method of activation
should evoke abnormalities of a nature specific to epilepsy where the rest-
ing record, although abnormal, is non-specific. By this criterion, Walter finds photic stimulation alone successful in 32 per cent (37 cases); this
figure may be raised by using flashes from multiple sources (Hodge).

A report is now available (Badier) on the postmortem findings on five
patients in whom myoclonic responses could be evoked by recruitment
(without metrazol). The findings were: a cerebellar hemangioma, an ependo-
myoma of the fourth ventricle, an epidermoid cyst of the brainstem and two
acoustic neuromas. The authors postulate the common factor to be pressure
on, and consequent irritation of, the reticular substance of the brainstem
resulting in an irradiated response to the thalamus and cortex.

Reports that activation technics bring out abnormalities similar to epi-
leptic discharges in patients whose clinical diagnosis has been hysteria
continue to come in.

A report from the Laboratoire de Neuroélectrologie at Lyon gives a
useful analysis of the results of activation by photic stimulation combined
with metrazol in 400 patients classified in six clinical categories. These
workers, Bonnet, Bonnet and Courjon, confirm the original observations
made by Rémond and Gastaut in 1949. They agree that although a “positive” activation test is not specific to a clinical category, a “negative” one
effectively rules out generalized epilepsy of subcortical origin. The value
of the positive result lies, not in the fact that it is positive, but in the
information it gives as to the location of the trouble.

There would appear to be a continuum of sensitivity to photic stimulation
ranging from those who require no metrazol for the eliciting of a myoclonic response to those at the other extreme who are very resistant and require a great deal. Where the so-called normal lies in this continuum has been the subject of some debate and was the subject of Kershman's current researches at the time of his tragic death. It was beginning to emerge that certain differences in technic were the basis for conflicting reports. Schwab has drawn attention to such variables as intensity of the light source, rate of injection, and anxiety on the part of the patient (resulting in over-breathing). All of this has been discussed in detail by Gastaut, who considers the first two the most influential and advocates an exact standardization of technics before comparison of thresholds is made. From direct observations of responses (to flash) in the optic nerve, lateral geniculate and visual cortex of the cat, the reviewer has been led to wonder whether another variable may be responsible for reported differences between laboratories, namely, the effect of ambient light in the eye. All responses to a flash of given intensity are increased in amplitude when the room is darkened. (This effect is probably more marked in a predominantly scotopic eye.) Most of the clinical electroencephalographers reporting on this subject have not stated whether their patients were tested with the room light on or off (and if on, whether constant in intensity). The energy distribution in time (e.g., sine wave, square wave, sectored light, gas tube, etc.) as delivered to the retinal elements would also have an effect on the impulse dispersion in the visual pathways. Some results of Daly's might suggest this. The wave-length content of the light stimulus is also not the same in all laboratories, a red light being favored in some centers.

That wave-and-spike discharges resembling those encountered in epileptics can be evoked in non-epileptic subjects by a careful timing of paired flashes of light (during metrazol injection) has now been demonstrated by Gastaut. Although he has found some impairment of consciousness in these artificially induced attacks he has not as yet found true “absences.” Cornil has published an ingenious modification of Schwab’s reaction-time method for testing impairment of consciousness in petit mal. It consists of a circuit by which the wave-spike from the brain triggers the stimulus to which the patient has been instructed to respond. The critical timing, according to Gastaut, is not the rate at which the pairs are repeated, but the interval between the members of the pair, i.e., the second flash of each pair should fall in the supernormal period following the neuronal discharge set up by the first. Curves of cortical excitability cycles for man have been published and also for the anesthetized and non-anesthetized cat. In a system containing so many elements (including those of the retina), one might expect these curves to represent some form of integrated effect, and that different components would be respon-
sible for various of the factors influencing them in different degrees (e.g., retinal elements reacting primarily to intensity, synapses to barbiturates, etc.). Excitability curves for the auditory cortex have been worked out by Chang in animals under barbiturate anesthesia.

An interesting study of wave-spike foci, suggestive of a subcortical origin, yet appearing first and more markedly in one hemisphere has been made by Dell. Of the nine cases reported, seven had giratory fits. A direct attempt to get evidence on the origin of spike-and-wave activity in human subjects has been made by Spiegel and Wycis. Recordings from the diencephalon have demonstrated the presence of spikes and of spike-and-dome discharges in cases with petit mal attacks but no circumscribed focus was found common to all cases. This work led to the placing of small lesions in the diencephalon in an attempt to relieve seizures in six cases in whom all other therapy had failed. The authors show wisdom in the caution with which they discuss their somewhat equivocal results.

Electroencephalographers concerned with the interpretation of recordings from depth of electrodes are recommended to read Jung's paper on the use of such electrodes inserted through burr holes. His recordings are exceptionally clear. A design for implanted electrodes for recording and stimulating in the thalamus of cats has been described by Koella and Hess. Further material from studies with basal leads has been published and another type of nasal lead has been described. EEG's recorded with basal leads have also been published from Russia, arguing the advantage of linkages between these leads and scalp electrodes when searching for deeply-lying tumors.

Among the studies of psychomotor epilepsy, Cossa brings evidence that psychomotor automatism are not a disease entity but a sequel to many types of epileptic fits. He finds the psychomotor symptoms developing not during the period of the seizure discharge but during the phase of slow waves and lowered amplitude which follows it, i.e., the impairment of conscious behavior occurs during the period of depressed neuronal activity. He gives excellent illustrations of the EEG in cases of automatism following temporal lobe seizure, petit mal attack and grand mal convulsion. A discussion of this problem has also been published by Dongier. Gibbs in a series of 163 cases with EEG foci in the anterior temporal lobe found 95 per cent had clinical psychomotor seizures. Iobst and Forster have also published details on a series of 50 patients with temporal lobe dysrhythmia.

The early confidence in the value of focal EEG spiking as an indicator of cortical epileptogenic tissue in other parts of the brain has been questioned in the light of new experience and the knowledge that the focal spike may
have been propagated from a distance. The influence of this on the surgeon’s evaluation of EEG spiking in making the decision for or against cortical excision has been discussed by Walker. Bailey and Gibbs, however, think that in the cases of psychomotor epilepsy the seizure discharge is primarily temporal in origin and not conducted from deeper areas. Their description of temporal lobe surgery for psychomotor epilepsy reveals great reliance on the EEG findings especially in sleep and during pentothal anesthesia, both of which states were found to activate anterior temporal foci.

Green, who attaches considerable importance to the electrocorticogram, has reported on the effects of anterior temporal lobectomies in patients with psychomotor epilepsy who failed to respond to medical therapy. In all of his 23 cases focal EEG abnormalities were present in the anterior temporal lobe, and gross or microscopic pathology was found in association with them in 14 of the 23 patients. This paper contains an interesting analysis of the seizure patterns and of the results of surgical treatment, and promises a follow-up report on these patients after some years have passed.

Hoefler and his colleagues have added to their series (published ten years ago) of cases with paroxysmal abdominal pain as an apparent epileptic equivalent. They now have 31 of these interesting cases, and in 30 per cent of these, the interseizure EEG was abnormal (in four of them it was actually spike-and-wave). However, only 11 were helped by anticonvulsant therapy.

A review of the experience gained in a general hospital from 500 records has been summarized by Arieff but, as in so many previous reports, the seizure patterns of petit mal have been included with the interseizure patterns of other types of fits to reach a figure of 80 per cent abnormal EEG records in epilepsy. It would be interesting to have data from more centers on the percentage of abnormal interseizure records in all types of epilepsy including petit mal. Presumably the seizure record not only for petit mal but for all types is abnormal. (The purpose of activation is to approximate this record.) Kershman’s large series of 2648 epileptic patients has demonstrated that focal disturbances are by far the commonest single type of EEG abnormality in epilepsy.

A monograph of work on EEG has been dedicated this year to Professor Bremer. This includes a review of the diagnostic scope of the EEG in epilepsy by Noel. He finds the Gibbs classification more useful than the Montreal classification. Titeca discusses the use of the EEG in assessing medication in epilepsy. A review of clinical electroencephalography that is concisely and explicitly written is, however, disappointing in that, with few exceptions, its statements reflect the state of our knowledge in 1941
rather than in 1951. The illustrations are a challenge to our detective abilities since the derivations are not indicated.

In the search for early electrical signs of tumor growth some progress has been made. In gliomas, where early diagnosis is of prime importance, Chavany finds EEG signs occurring before x-ray signs or changes in the eyegrounds.

Disturbed by some of the reports of untoward effects resulting from the use of contrast media for cerebral angiography, Bloor has used simultaneous EEG recordings as a measure for subtle changes in cerebral physiology occurring during injection of the dye and has correlated these changes with postmortem histologic findings in rabbits and monkeys. Dio-

drast was found to be the least noxious of several media examined.

In thrombosis of the major cerebral arteries Jones and Bagehi find that the EEG more frequently lateralizes than locates the site of damage. Serial EEGs, however, usually bring out a differentiation between thrombosis and neoplasm. From a large series of aneurysms, Roseman concludes that the EEG definitely aids in lateralizing and may indicate location of the lesion. In experimental occlusion of the middle cerebral artery in animals, however, Harvey finds that the resultant abnormalities are not necessarily restricted to the side of the lesion.

Some of the EEG clues to the presence of a subdural hematoma have now been formulated empirically from surgically verified cases. The experiences of Sullivan (32 cases), Friedlander (39 cases) and Marinacci (7 infants) will all prove useful guides to the clinical electroencephalographer. Martin describes some interesting observations made during sleep on a case of one-sided hematoma. The EEG both during wakefulness and sleep was profoundly asymmetrical but the evoked response to a noise during sleep appeared in both hemispheres. The clinical significance of hemispheric asymmetry in EEG tracings has been examined in some detail by Aird who finds it of considerable value in locating lesions.

In an analysis of 50 cases of closed head injury, Courjon finds the EEG of great prognostic help. In those cases where the EEG was normal (even with photic stimulation) all recovered from their neurologic defects without surgical intervention. Serial EEG’s ameliorating progressively with the clinical signs are also contraindicative of surgery. Local abnormalities persisting in spite of clearing clinical symptoms are thought to presage trouble, usually the eventual development of epilepsy. In eight operated cases with previously localized EEG signs, three had hematomas and one cerebral softening. Where diffuse EEG abnormalities are found the author advises against surgical intervention. Another series has been published by Clark and Harper who contrast the EEG findings with those in “open” head injuries.
In patients with a history of head injury, but with no clinical signs, Weil found 41 per cent to have EEG irregularities indicative of cerebral pathology. Much has been claimed for the value of serial EEG's in such cases and now some data have become available on 45 cases. R. Dawson finds the EEG changes to lag behind the clinical changes (in either direction, i.e., recovery or deterioration). General suppression of activity when it occurred early (i.e., within 30 hours of the injury) was invariably fatal. The authors interpret their findings of focal and general suppressions as in agreement with those of Leão in rabbits. Mechanical stimulation of the cortex in these animals produces depression and even extinction of activity in the area stimulated. With strong stimulation the suppression may spread and become complete over the entire brain. Leão has published some new work from which he concludes that the early stages of voltage variation of spreading depression are identical with those produced by circulatory arrest, and in which he traces the potential changes in succeeding layers of the cortex. Marshall has discussed the criticisms of Van Harreveld who has presented some data on the reversible effects of exposure of the cat’s cortex to high concentrations of potassium, a condition conducive to spreading depression, as is also cooling of the cortex and exposure to air.

More information is now available about the “diffuse” thalamic projection system on the one hand and the reticular activating system on the other. In the case of the first, the thalamic stations are found by Starzl and Magoun to be, in the cat, the center median and intralaminar nuclei (confirming Dempsey and Morison), the ventralis anterior and anterior nuclei, and the cephalic pole only of the thalamic reticular nucleus (not the whole nucleus as proposed by Jasper and by Rose and Woolsey). They find these nuclei so closely interconnected at the thalamic level that stimulation (of the strength used in these experiments) of any one of them excites the others, thus producing a mass discharge with resultant effect at the association areas of the cortex; the receiving areas for this diffuse thalamic discharge are not themselves diffuse but are as clearly delimited in cortical zones as are the specific primary receiving areas, into which, according to these workers they do not trespass. Marsan and Jasper have, however, reported some projection of these systems into the primary visual cortex. Nor can Starzl and Magoun find any electrophysiologic evidence (using the recruiting response as their criterion) that the intralaminar nuclei project to relays in the cortex of the rhinencephalon, or that the reticular nucleus in its entirety plays the main role as relay station for a diffuse projection system.

Some workers will be worried that ablation of the neocortex is not followed by degenerative changes in the cells of these thalamic nuclei.
Starzl and Magoun, however, are satisfied that collaterals of these thalamocortical afferents could be sufficient to keep the cell bodies viable.

From their studies of the reticular activating system in the brainstem, Starzl, Taylor and Magoun\(^{148}\) conclude that the diffuse thalamic projection system plays only a minor role in the ascending pathways. They located the main thalamic relay in the ventromedial part of the thalamus but an extrathalamic path from the sub- and hypothalamus into the internal capsule was also found. This was the route originally suggested by Forbes for the “secondary” cortical response. The secondary cortical response of Forbes, and of Dempsey and Morison is invoked by Dell\(^{48}\) to explain the evolution of the slow wave component of the cortical epileptic discharges produced in the cat by sensory stimulation during injection of metrazol.

That the brainstem reticular system receives collaterals from the ascending specific somatic and auditory afferents seems indubitable,\(^{149}\) the evidence from earlier degeneration studies now being supported by electrophysiologic data. The experimental fact that arousal follows stimulation of the brainstem reticular system is now clearly reconciled with the everyday observation that afferent stimuli can wake the sleeper. Strong alerting stimuli can even break through the “sleep” of animals whose hypothalamus has been destroyed as has been shown by a detailed study by Ingram\(^{48}\) of the role of the hypothalamus in the cortical activity of chronically prepared animals.

Arduini and Terzuolo\(^{7}\) have studied the polarity of the recruiting response by investigating the effects of asphyxia, local cocainization, and removal of cortical gray matter. The positive recruited potentials survive cortical ablation and hence seem identical with what Adrian called “afferent cortical waves;” hence, recruitment would appear to have taken place not on the cortex but in the thalamus. The surface negative responses of the cortical neurones can also be differentially extinguished by asphyxia or cocaine. The waxing and waning of the recruiting response, judged by the same criteria, also appears to be thalamic.

Thus, evidence is collecting that diffuse activation of the cortex may not require the concept of non-specific thalamo-cortical fibers but may be rendered diffuse by intrathalamic connection and carried to the cortex by the known specific projection pathways. Systematic serial ablation of thalamic nuclei may be one way of gaining evidence on this controversial issue although it is difficult to design the critical experiment. Work along these lines is now in progress in the Montreal laboratories (Jasper\(^{48}\)).

In attempting to interpret all the recent work from the various laboratories on the diffuse activation of the cortex, McLardy’s\(^{115}\) clarifying critique is most valuable. In this paper, he assembles the evidence for the observed diffusion being intrathalamic in location, the pathways to the cortex being
the recognized specific afferents from the thalamic specific projection nuclei. Degeneration studies militate against the existence of direct projections to the neocortex from the intralaminar nuclei (nuclei centralis lateralis, paracentralis, centralis medialis and centromedian) but there is evidence of projection from the intralaminar nuclei to the caudate nucleus and from the centromedian to the putamen (Fortuyn). Nor do degeneration studies give any stronger support to a cortical projection from the reticular nucleus. McLardy suggests that Jasper’s finding that cortical recruitment can be evoked by electrical stimulation of the medial intralaminar nuclei may be interpreted as an activation of fibers passing close to the centromedian nucleus and coming from cell bodies in or near the anterior or cingulate region. Fortuyn makes a somewhat similar suggestion. One wonders whether possibly the differential effect of drugs (perhaps acetylcholine) might be used to examine this point or the differential destructive action of ultrasound on cells rather than fibers (Wall). Such an interpretation would explain the failure to elicit recruitment by introduction of strychnine into the massa intermedia as demonstrated by Cohn in 1949.

In the search for new anticonvulsants, several drugs have been tested for their effects on the abnormal EEG’s of epileptics. Water-soluble desoxy-corticosterone gluconide (I.V.) produces a small but consistent decrease in the frequency of abnormal waves in patients unresponsive to other forms of therapy (Aird). Glutamic acid (Pond) also seems to decrease the amount of spike-and-wave activity in patients with petit mal, but the effect is slight and only transitory. The use of this drug and of many other anticonvulsants has been reviewed this year by Aird. The effects on the EEG of prolonged treatment by ACTH and of cortisone are only slight. 

In a study of the effect of different anesthetics on the electrocorticograms of patients at operation, Woringer concludes that nitrous oxide is the least likely to mask epileptic activity (ether masks it almost completely). Concurrent studies in animals suggest different mechanisms for the actions of various anesthetics and not a simple effect produced by inhibition of the cerebral metabolism.

EEG correlates for levels of anesthesia have been published for nitrous oxide and ether (Courtin) and for pentothal (Kiersey). The EEG patterns of the latter are in close agreement with those published by Brazier. The results vary in many respects from those published last year by Schneider for nitrous oxide. Bickford’s development of his servomechanism for automatic control of anesthesia employs selection and integration of certain frequencies by the circuits of an automatic frequency analyzer so that artifacts and interference outside this range have no part in the feed-back system. Verzeano has published a modification eliminat-
ing the use of tubes and relays. Swank\textsuperscript{144} has found that barbiturates produce the same effect on the fast cerebellar potentials (1000–2000 c/s) as they do on the cerebral activity.

Faure\textsuperscript{82} has continued his search for changes in the EEG evoked by emotional stress and intellectual effort. The present report is restricted to the behavior of the alpha rhythm, whereas possibly a study of the rhythms from the anterior temporal lobes (not linked to the occiput) might have proved more fruitful. He concludes that alpha instead of being a rhythm of repose, is, in fact, a release phenomenon appearing on relief from pain, on achievement of a solution and on release from tension. He has incorporated the EEG in a battery of recordings made during psychiatric interviews\textsuperscript{82} under narcoanalysis and has used a Walter analyzer in correlating his results with simultaneous changes in skin resistance, respiration, electromyograms, and microphone recordings of the interview.

Hill’s\textsuperscript{77} investigations of the disturbance of homeostatic mechanisms in schizophrenic patients exposed to stress (insulin hypoglycemia) also employ simultaneous recordings of the EEG, palmar skin resistance and heart rate. Use has been made of the several types of information made available by automatic frequency analysis—especially in the detection and quantification of 6 c/s activity appearing as a new rhythm at a stage in the hypoglycemic response. This theta activity appears sooner (i.e., at a higher level of blood sugar) in normal subjects than in schizophrenics. Some normal standards for the occurrence of theta (and beta) activity have been published by Mundy-Castle\textsuperscript{120} for healthy adults in two widely disparate age groups. We still have more hypotheses about the theta rhythms than we have data.

A line of investigation which is new (although it owes its basic suggestion to Cushing) is the study of the effects on the activity of the brainstem reticular area in cats of intraventricular injection of acetylcholine on the one hand, and of cholinesterases on the other. The outcome of these experiments led to the interruption of long-persisting stupor in four catatonic schizophrenics by intraventricular cholinesterase. There was a concomitant change in the insulin tolerance curve and in alpha production in the direction of the norm (Sherwood\textsuperscript{144}).

Two studies have appeared on the effect on the EEG of lowering the body temperature in animals that hibernate. Kayser\textsuperscript{99} finds activity still present at 10° C in gophers, but absent at 5° C, at which temperature the heart rate is reduced to 10 beats per minute. In hamsters, although the body temperature may drop to 2.5° C during hibernation, no EEG reappears until the temperature rises to 19° C (Chatfield\textsuperscript{21}). In these conditions electrical silence of the brain, although immensely prolonged, is clearly a reversible process.
In the field of apparatus development, the toposcope of Walter and Shipton has now been published in considerable detail and with a block diagram of the circuit. This ingenious method will probably prove to be more readily applicable to study of EEG responses to rhythmic sensory stimulation than to some other types of activity, for there is some frequency selection imposed by the rotational speed chosen for the radius vector (although this can be controlled). Knott has published construction notes on the automatic frequency analyzer he has built after the Walter design using readily available American components, and Krakau has described an optical method of analysis based on density modulation of a photographic film. Drohocki has discussed some of the limitations of the various types of analyzers now in use and presents a schema for a spectrograph designed to overcome some of the errors introduced by the use of resonating circuits. It employs a system of modulation, the EEG potentials causing amplitude modulation of the output of a variable oscillator. This oscillator periodically covers a range from 800 to 860 c/s so that superimposed EEG frequencies of from 1 to 60 are consecutively selected by a single filter and recorded as vertical deflections of a cathode ray trace. Here they are identifiable as to frequency by their position along the abscissa formed by the horizontal sweep (this being triggered by the regulator of the oscillator's frequency). The use of a single, widely selective filter, overcoming the difficulty introduced by the long time-constants of more highly selective circuits, is the major advantage claimed by the designer.

The pros and cons, design and maintenance, application and fruitfulness of automatic analysis were the subjects for discussion at a meeting convened for this purpose in June of this year. This was attended by representatives from ten laboratories in the United States where such methods are now in use. All who are using this technic should read the criticism offered by a mathematician (Vogel) in a discussion with Walter.

It now seems generally agreed that an indifferent electrode does not exist anywhere on the volume conductor we call the human body. It remains for us to choose the least misleading of the available reference leads. In a careful comparative study, Corriol analyzes the advantages and disadvantages of four common reference leads: the lobe of the ear, the two ears linked, the non-cephalic reference electrode proposed by Stephenson and Gibbs and the average electrode recommended last year by Offner. His conclusions are that the first of these is only adequate for a strictly contralateral focus; the second is virtually useless; the third, being off the head, is indicated when the dysrhythmia is bilateral; the fourth proves to be more satisfactory in practice than in theory, especially if the electrodes nearest to the focus are disconnected from the average. Corriol recommends
finding the focus by bipolar methods and deciding from these findings which reference lead to use for further investigation. This paper is important in that it emphasizes that the choice of reference lead will influence the recording obtained, something a truly indifferent lead would never do. Nietzsche is invoked to warn us that our choice will load the dice. This reviewer has previously proposed, and Coriol concurs, that the plotting of electrical fields in EEG work will serve to sort out activity brought in by the reference lead. Rémond has plotted the field for eye-blinks, a study which will be valuable to clinical electroencephalographers searching for signs of frontal lobe tumor. Monnier has also made a detailed study of eye movements (including nystagmus) and has used nasal leads as well as surface electrodes in his exploration.

Thiry recommends recording push-pull with the average electrode leading not only to the reference grid through a high resistance but also to the grid which receives the input from the active lead. In this way, instabilities in the average lead itself being in phase and of the same magnitude on both grids will not be amplified by push-pull circuits and hence will not be recorded. This short report does not contain enough details (as for example, ratio of resistance used to the resistance to ground) for the reader to be able to judge for himself what effect this would have on the value above ground of the exploring electrode. One gains the impression that only an approximation of the desired result could be given by this method and that interference pick-up would be a real hazard.

One might wonder, when such difficulties lie in the way of finding a satisfactory reference lead, why electroencephalographers should still want to record by “unipolar” leads. Apart from the information it brings to the plotting of fields, many workers find a reference lead of practical help in tumor location provided they can be alert to any false clues it may introduce. A study of this question has been made this year by Fischgold in a series of intracranial tumors. He finds the earlobe almost useless, for in deep lesions it is nearly always active. He finds the nose, the chin and non-cephalic reference of Stephenson and Gibbs all useful, though the manipulation of the potentiometer in the last method is too time-consuming with very sick patients and not always satisfactory. In his experience, the average electrode gives the best results, although again it is contraindicated when the EEG abnormalities are generalized.

Among the recently developed electrodes are a 7 cm. long needle inserted under local anesthesia until the tip rests against the sphenoid wing, and a curved orbital lead inserted until it rests against the roof of the orbit. The latter requires no anesthetic for its introduction and records primarily from the orbital surface of the brain whereas the former (which appears to resemble those described previously by Jones and Kristiansen)
records mainly from the under surface of the temporal lobe. These would appear to be tools for the neurosurgeon rather than for the electroencephalographer. Examples of application of their use will be found in the discussion on the surgical treatment of epilepsy published by the neurosurgical clinic at la Pitié. This article gives a careful assessment of the authors’ experience with cortical excision in the absence of tumors.

The EEG has been used in attempts to find the locus of effect of electric shock treatments and as a method for controlling the shock technic and for assessing this form of treatment. In newborn animals (rats) the EEG is not affected by electroshock until the 4th or 5th day, and no convulsion can be induced until the 7th day. Fortunately, there are no data on the effects in newborn humans.

Of interest to all concerned with medico-legal problems is Hill’s and Pond’s report on the EEGs of 105 murderers (an extension of the series published previously by Stafford-Clark and Taylor). Eighteen of these cases were epileptics, but over half had abnormal EEGs. In a smaller series, Delay also found a high incidence of abnormal EEGs. He also examined prisoners accused of lesser crimes.

An assessment of the use of the EEG in psychiatry has been given by Rémy. In child psychiatry, the leading contribution has been the paper by Hill with its wise presentation of the present state of our knowledge. Emphasis is put on delayed maturation as being a likely etiologic factor behind both the behavior disorders and their accompanying EEG abnormalities; the trend towards the study of EEG responses to stress is welcomed as this promises to be more fruitful than study of the resting record.

In other branches of pediatrics the EEG has been found useful in such problems as the detection of brain damage causing hearing loss in very young children (Marcus), and in the evaluation of neuro-ocular pathology (Levinson). In acute purulent meningitis the EEG may detect damage to the brain which is not obvious on clinical evaluation alone (Hughes) although the opposite may also occasionally happen, viz., a normal EEG in spite of persisting clinical signs. Some results are now available on the EEG signs of tubercular meningitis. Passouant, from a study of 500 tracings from 150 cases, has been able to establish prognostic criteria based primarily on a differentiation between diencephalic and cortical involvement. In epileptic convulsions in children, Berlin makes a plea for more recognition of an emotional factor influencing the severity of the symptoms.

In a series of 70 cases of infantile hemiplegia, Bezos and Lérique-Koechlin found the EEG only rarely to be normal and believe it to be useful in weighing the pros and cons of surgical intervention. EEG tracings in single cases of sporadic subacute encephalitis have been described by each of two authors with characteristics in essential agreement with those de-
scribed a few years ago by Cobb and Hill. The abnormalities they described (marked periodic bursts) differ from those of the commoner encephalitides.

Results from studies of the correlation between steady cortical potentials and the EEG are impinging more and more on the interpretation of the latter, and users of standard resistance-coupled amplifiers are realizing the restrictions imposed by their apparatus on the information they derive.

A survey of this year’s work in electroencephalography shows that it is being used to attack the basic problems of the nervous system from two angles: on the one hand, to observe the total pattern and break it down into its components; on the other, to study the component parts and build them into a whole. A welding of the two approaches promises the most.

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CHAPTER 13

Electroencephalography

By MARY A. B. BRAZIER, Ph.D.

This year there are many books for electroencephalographers to read. First there is the second volume of the Gibbs’ Atlas, giving in a clear, didactic way a description of the electrical signs and their incidence in epilepsy based on the very great experience of these authors with the particular techniques they use. Strauss, Ostow, and Greenstein also base classification of EEG’s mainly on frequency characteristics. They admit more fast records into the “normal” fold than do the Gibbs, and take their main lead for diagnosis from the slow activity present in the record, paying relatively less attention to spikes, sharp waves, or fast activity. Walter’s book, is written for a much wider audience and will most certainly get it. In it Walter makes clear his allegiance to Pavlovian physiology and the importance he believes this to have in the meaning of electroencephalographic potentials. Ashby describes his search for a mechanism capable of self-organizing and adaptive behavior comparable to that of the brain, and gives construction details for building such a mechanism on the principle of ultrastability. At long last, McCulloch’s essay has been published as a monograph. It would have been good to have this explanatory text before the (chronologically) later papers were published some years ago.

There have been many symposia this year, the proceedings of which have been, or will shortly be, published and will be of interest to those concerned with the neurophysiology behind the EEG potentials (Macy, Cold Spring Harbor), and there are two large volumes dealing with the C.N.S. at the organizational level of behavior. This year, the centenary of Ramón y Cajal, has seen several symposia in his honor. Our interpretation of EEG’s rests on neurophysiology; Wyke has summarized the classic work in this field. Liberson’s comprehensive article on the contribution of experimental electroencephalography to the problem of epilepsy is extremely valuable. Both these reviews carry excellent bibliographies. Reference sources will also be found in the annual reviews, and two rather contrasting points of view on the present status of EEG have been published.

In EEG, specifically, there have been the usual national meetings in the various countries, some of whose proceedings have been published more
fully than others. The papers given at the Heidelberg meeting last year are now in print in the form of abstracts. At the Physiological meeting in Strasbourg this year four papers were given that cover very completely the present knowledge of the autonomic nervous system and point up the interrelationship of the somatic and visceral systems in a way that allows one more form of dualism to be dropped from physiological thinking. Colle discussed the mutual interaction between somatic and visceral stimuli with specific reference to the brainstem and medulla. Gastaut presented new experimental data about the influence of stimulation (in animals) of the amygdala on respiration, blood pressure, pupillary dilation, pilo-erection, gastric motility, and defecation, as well as on movements such as mastication and swallowing. Both acute and chronic experiments were described. For recordings from the amygdala in man see Paillas. The importance of this work for the epileptologist is very great. Dell's paper, the third on this subject, is the most complete account yet published of cerebral integration of somatic and visceral afferent systems; it deserves to become a classic. The references given with these three papers form a complete bibliography of the subject. The effects of vagal stimulation on the EEG of cats can be shown to be a neurogenic one and not secondary to circulatory changes (Zanchetti).

At the joint meeting of the English and French EEG societies held at Brussels in June, Bremer gave a detailed analysis of the cerebral and cerebellar responses to sensory stimulation, demonstrating among other things the usefulness of strychnine for differentiating the components of the classic sensory response. Current knowledge of the EEG in cerebrovascular disease was brought together at the Brussels meeting when the problem in cerebral ischemia was discussed by Rohmer, intracranial hemorrhages by Y. Gastaut, and vascular malformations by M. Dell. Thus the clinical electroencephalographer now has a valuable source of information about the EEG signs in these conditions and some clues as to the disturbance of physiology responsible for them. Faure also reported his experience in such cases.

In some long-standing cases of hemiplegia resulting from cerebro-vascular accidents, Passouant and his colleagues have found more EEG asymmetries in these patients when asleep than when awake (80 per cent instead of 50 per cent).

The EEG record during carotid artery compression in patients with aneurysms or arteriovenous fistulas of the head and neck has been found by Laufer to be an unreliable index of the adequacy of collateral circulation. A useful bibliography will be found in the paper by Subirana on thrombosis of the internal carotid. Giraud has compared carotid artery pressure, ocular pressure, and carotid sinus pressure as methods for pro-
voking EEG changes in cardiovascular disease and in vagal dystonias. In cats and dogs, ten Cate⁷⁰ finds collateral circulation to be adequate to maintain EEG potentials even when major arteries are ligated.

The case for regarding combined electroencephalography and angiography as the best method of localizing cerebral tumors is given by Grèzes-Rueff in a monograph for a thesis.⁷⁸ Successful localization was made in 46 out of 51 cases later verified by operation (90 per cent accuracy). Another thesis on this combination of diagnostic techniques has been published by Rougerie,¹⁴⁴ who achieved 87 per cent accuracy of localization in 97 cases of verified neoplasm. This work brings further support to the opinions of Fischgold, whose experience some time ago led him to the conclusion that this combination was a more useful diagnostic method than ventriculography. With David⁴⁶ he has examined its use in gliomata and has described signs that can be used to indicate or contraindicate ventriculography. Gastaut⁶⁸ has published an interesting case of psychomotor epilepsy in which a temporal angioma was detected by these methods.

A volume has been devoted by Malec¹¹⁷ to the subject of the EEG in cerebral tumors. Since this begins with a fairly detailed description of technique and discusses the experience, not only of the author but also of other workers, it will prove useful as a teaching text. Guillaume⁸⁰ and his co-workers have found Metrazol injection useful in the localization of tumors. A series of verified cases of brain abscess has been published by Hoefer¹⁷⁸ with a 50 per cent accuracy of localization, although only one of the 28 cases had a normal EEG. Pine,¹⁸⁷ who uses focal flattening as well as focal slow activity as localizing signs, could localize abscesses in 13 out of 18 verified cases. The only normal EEG in this series was in a case of cerebellar abscess. The localizing value of minor asymmetries has been further stressed by Aird,¹ who emphasizes the value of series EEG's. Minor asymmetries in response to photic “driving” have been found by Weil¹⁷⁴ to correlate with homonymous hemianopsia. Some new conceptions of handedness and hemisphere dominance have been published¹⁵⁵ with some reference to EEG asymmetries.

Parsons Smith¹⁳⁴ has stated lucidly and conservatively the degree of help that the EEG can give to the neurologist who suspects a cerebral tumor. He believes it impossible to localize or even to lateralize posterior fossa tumors by the EEG. Loeb¹¹¹ also reports lack of success below the tentorium, but he was able to localize 75 per cent of hemispheric supratentorial tumors. Bagchi,⁷ however, as the result of careful study of 37 verified cases of posterior fossa tumor is more hopeful and has drawn up some criteria on which to base suspicions of a subtentorial tumor. It is important to note that these criteria consist of specific combinations of
neurological and EEG signs. Bagchi's work confirms Parsons Smith's statement of the folly of attempting "blind" EEG interpretations.

In a study of post-ictal coma from Montpellier, evidence for four types of EEG activity has been described. In those cases in which there was hemispheric asymmetry in the post-ictal EEG this was found to have verified lateralizing significance. In coma induced by insulin in schizophrenics, Chamberlain has found some relationship between insulin sensitivity and the presence of theta activity in the resting record.

The EEG changes in adult cases of tubercular meningitis have been found to parallel the clinical course of the disease more closely than the C.S.F. or eyeground changes, according to the Montpellier group, but they are of less prognostic value at the beginning of the disease in adults than in children. A study of the EEG in neurosyphilis has come from Denmark. The most common abnormality found was diffuse slow activity, which was more marked in the younger patients and was not a function of the duration of the disease. A characteristic transient (usually a rather sharp triphasic wave) has been found by Cobb in a sufficient number of children with cerebral lipidosis for him to feel it to be a sign with diagnostic value.

Among other clinical papers is a study by Ulett of the EEG in cases of headache, without other neurological signs, that will guide the clinical electroencephalographer in what to expect in these puzzling cases. EEG abnormalities in certain types of migraine headache have been described by Weil. There have been rather few studies this year on children's EEG's.

The problem of alcoholism has engaged the interest of several EEG workers. Little finds no more abnormality in the records of confirmed alcoholics who have no evidence of structural brain damage than in those of normals, but finds the former group to have more alpha with less amplitude variation. Courjon finds metrazol (and photometrazol) helpful in differentiating subgroups among alcoholics; this technique has revealed temporal foci in some of his patients with psychopathic behavior. Antabuse, now so widely used in the therapy of alcoholism, has itself been found to increase any tendency to dysrhythmia that may be present in the pretreatment record, although therapeutic doses rarely affect a fully normal record.

An experimental approach to the problem of the spread of convulsive discharges has been made by Shimizu, Refsum, and Gibbs, who have injected metrazol into one common carotid artery in cats, and have compared the degree of spread in nembutalized and nonanesthetized animals. Spread of discharge to the contralateral side can be suppressed by nembutal injected into the carotid of that side or applied locally to that cortex.
The authors suggest that the use of nembutal to restrict the discharging areas to the primary focus may prove of value for clinical work. Since they used the carotid artery they held that the thalamus was not necessarily involved in the spread, and they applied Curtis's classic paper of 1940 on transcallosally evoked responses in interpreting their data. (However, one may note here that all Curtis's animals in whom he demonstrated transcallosal spread were under barbiturate anesthesia and only locally applied nembutal blocked the contralateral response.) As Shimizu and his colleagues point out, the depth of the anesthesia is an important factor. This same paper of Curtis has been invoked by Houdart to explain the EEG findings in a case of traumatic epilepsy in whom focal surface positive spikes appeared during subclinical attacks. In this case Curtis' paper is used to support the hypothesis that the epileptogenic zone lay very deep. The antagonistic actions of metrazol and the barbiturates have been demonstrated by Kirstein in man. The arguments underlying the interpretation of drug effects on transcallosally conducted responses have been presented by Marrazzi. Himwich concludes from his experimental work that all the anticonvulsant drugs now in use prevent the neural spread of the convulsions and that none affects the focal activity. That there is interaction between transcallosally and directly conducted impulses in the auditory area of the cat has been demonstrated by Bremer.

That cortically induced seizures in monkeys remain lateralized if the corpus callosum is cut was shown by Kennard and her colleagues in 1950. Yet Jasper's group in 1947 had found that contralateral spikes resulting from unilateral alumina cream implants persisted for several hours after section of both the corpus callosum and the anterior commissure. The problem of mechanism of spread in epileptic seizures remains a stimulating field for research. Some aspects of it have been discussed this year by Ward.

The question of diffuse projection to specific cortical areas has been examined further. Last year Starzl and Magoun gave evidence to support their view that close interconnection at the thalamic level played the important role in the phenomenon of recruitment restricted to the association areas, whereas Jasper's results suggested a diffuse projection system, having however a certain degree of systematization and invading the specific receiving areas.

Starzl and Whitlock have explored the diffuse thalamic projection system in the monkey for comparison with their earlier work on the cat. They find that recruiting responses can be evoked by stimulation of the center median, intralaminar, inferior part of the medial, ventralis anterior and anterior reticular nuclei of the thalamus; these travel via relays in the association nuclei of the thalamus (medial, anterior, lateralis complex, and
pulvinar) to the association areas only of the cortex. It is interesting that the frontal association cortex is so plentifully served by this diffuse system. Terzian and his colleagues\textsuperscript{187} have investigated recruiting responses in the auditory cortex of the cat and find that these can indeed be evoked in the specific receiving area by stimulation in the lateral and caudal part of the reticular nucleus of the thalamus. However they believe the diffuse projection system to be more rigidly systematized than Jasper has suggested, for from no point in the diffuse projection system could they evoke a recruiting response generalized over the whole cortex. Jasper and his colleagues,\textsuperscript{95} stimulating in the thalamic reticular system in the monkey, have repeatedly found recruiting responses in the sensory receiving areas as well as in the association areas. In the mesencephalic reticular system stimulation (which does not evoke recruiting responses but "arousal") was shown to awake a monkey from fairly deep Pentothal anesthesia. The connections between the cortex and these nuclei were traced by recording the after-discharge to applied stimuli and the results support the authors' view that there is a network in the upper brain stem with two-way connections to widespread areas of the cortex. Jasper's hypothesis regarding the possible functions of this system has been published in some detail.\textsuperscript{92} A succinct review by Jasper and Feindel\textsuperscript{84} gives a useful summary of current knowledge in this field; in this same paper Jasper gives a spirited reply to Walsh's attack on Penfield's classic studies on localization in the precentral gyrus of man.

In metrazol-induced fits in cats Starzl\textsuperscript{149} found the seizure discharges to begin in the cortex and then spread to the sensory nuclei of the thalamus. Only later were the diffusely projecting thalamic nuclei affected, and even then they showed no spike discharges but a waveform more suggestive of those seen in coma.

For combined metrazol and auditory stimulation Starzl and his colleagues\textsuperscript{149} found that seizure induction was abolished by removal of the auditory cortex but persisted after destruction of all thalamic nuclei except the medial geniculate. Direct stimulation of the nuclei of the diffuse projection system did not provoke seizures in their animals (only recruiting responses), and hence these authors feel that the diffuse projection system does not play an essential role in metrazol-induced seizures. Johnson and Walker\textsuperscript{96} found that they could lower the convulsive threshold in monkeys by making focal cortical lesions with alumina cream, and that focal abnormalities were then augmented in the EEG. Such focal abnormalities were also extremely sensitive to topically applied drugs, even when these were applied to homologous areas of the opposite hemisphere.

A beautifully illustrated article on the current state of knowledge of the brain stem reticular system has been published by Magoun.\textsuperscript{114} A click in
the ear and a stimulus to the sciatic both reach the reticular system by collaterals from their specific afferent systems, but once there they share the same relays.\textsuperscript{61} Hence on passing through this system they cease to be differentiated as to sensory modality and their effect on the cortex is solely an alerting one (similar in effect to direct experimental stimulation of the reticular neurones).\textsuperscript{115, 116} This is the area the destruction of which results in chronic somnolence\textsuperscript{60, 62} and disappearance of the alerting response. For the understanding of the activity of this system two papers on its anatomy by Rose\textsuperscript{142} and by Yakovlev\textsuperscript{176} will be found useful. Akert\textsuperscript{3} has published with great clarity the conditions necessary for obtaining Hess’ sleep response.

The implications of these results, together with the original observations of the group of workers at Pisa, have been discussed by Moruzzi.\textsuperscript{127} This work has centered around the mechanism of the arousal reaction and the behavior of cortical neurones during activation of the ascending reticular system. Bremer\textsuperscript{24} has presented his arguments for the role of the cortex in arousal and in maintenance of the waking states. To study descending systems the Italian workers use, instead of an encéphale isolé, a “pyramidal preparation.” Their techniques include micro-electrode recordings, and the preliminary results are promising.\textsuperscript{123}

The current hypotheses about arousal mechanisms have been applied to phenomena seen in the human EEG (Li\textsuperscript{104}). In general, cases with abnormalities primarily of subcortical origin were found to be affected by sensory stimuli or mental activity, whereas slow waves due to a local cortical lesion remained unaffected (this did not include reflex epilepsy). These results might be expected by extrapolation from Moruzzi and Magoun’s early observations that strychnine spikes (of cortical cells) are not affected by stimulation of the reticular system. However, this has recently been called into question by the work of Arduini and Lairy-Bounes,\textsuperscript{4, 101} who have shown in three unanesthetized rabbits that with concentrations of strychnine that just produce threshold spikes, sensory stimuli will block the spikes (but not a full convulsive discharge). It will be remembered that Bremer some years ago found that a continuous sound would block strychnine spikes on the acoustic cortex. That the problem is not simple is shown by the fact that stimulation of the bulbo-reticular system may either inhibit or facilitate threshold strychnine spikes in the cat (encéphale isolé), apparently depending on the level of cortical excitability.

At the Cold Spring Harbor symposium on the neuron,\textsuperscript{41} someone lightly remarked that the status of a neurophysiologist was rapidly becoming inversely proportional to the size of the electrode he used. Several studies of microelectrode recordings of cortical potentials have been published
this year. Li finds that electrodes of one to three \( \mu \) diameter record, on the somato-sensory cortical surface, the alpha-type rhythm in its familiar pattern, but that in a layer 0.5 to 1.5 mm. below the surface (in the cat) negative spikes appear superimposed usually on the negative phase of the waves but are apparently independent of them. Another layer at which spikes appear lies between 2 and 2.7 mm. below the surface. (In the second of these papers rather different figures are given for these depths.) Unlike the alpha waves the spikes disappear in light nembutal anesthesia and hypoxia. (In the present stage of our microelectrode techniques absence of activity is less impressive than its presence.) These authors point out that their results do not support the concept that alpha waves result from envelopes of spike discharge (a notion that has teased electroencephalographers from the earliest days). They suggest that they represent synchronized oscillations in membrane potentials, possibly involving small interneurones and dendrites in the cortical matrix, oscillations which would have a definite effect upon neuronal excitability, but not dependent upon neuronal discharge. One is reminded of the classic findings of Renshaw, Forbes, and Morrison. The apparently differential effect of nembutal anesthesia on the spikes and on the waves is of interest in the light of the observations of the behavior of evoke responses and "spontaneous" waves under different levels of dial anesthesia as studied by Lilly's technique. Von Baumgarten and Jung find, in cats with encéphales isolés, spikes independent of the slower waves as well as some that seem related (again these appear more often on the negative phase of the wave). These workers have extended their study to the investigation of responses to visual stimuli. They find one type of neurone in the visual cortex that reacts to light with a rapid discharge of spikes after a latency of 18–22 msec., and others that, although spontaneously active, are not responsive. Thomas has also published a preliminary note on microelectrode studies of evoked responses. It would appear that some aspects of cortical cell functioning missed by the classic EEG techniques may be revealed by these methods. Amassian has also published microelectrode studies of significance.

Some further experiments have been made by Burns on areas of cerebral cortex disconnected from the rest of the C.N.S. but with intact blood supply. Such preparations show no spontaneous activity in unanesthetized cats, but are electrically excitable. Different neuronal units appear to be responsible for the surface negative and surface positive components of this response. Evidence is given for allotting the first of these to radial axons reaching up to pia and there branching parallel to the surface, and the second to a network of self-re-excitng neurones at a depth approximately 1.2 to 1.7 mm. below the pia (as determined by micro-electrodes)
with some processes stretching up to the surface and presumably capable of surface excitation. This hypothesis thus differs from that suggested last year by Eccles.

A fine study of suppression burst activity recorded from the undercut frontal cortex in man has been published by Henry. This distinctive type of activity is now familiar to us from the work of Bremer and many others on animals. The operation in this case is a cortical undercutting; the results are strikingly similar to those seen in barbiturate anesthesia, especially when there is some disturbance of blood flow due to edema at the operative site, but these authors feel they have adequately ruled out any influence of barbiturates persisting from the premedication in pre-recording periods. By analogy with Magoun's work it is suggested that these bursts represent cortical activity freed from the influence of the reticular activating system, and it is possible that this may also be the mechanism in deep pentothal anesthesia. This paper includes an interesting discussion of the evidence for autogenous activity in cortical neurones. Arguments about the mechanism of the alpha rhythm based on the behavior of suppression bursts are of doubtful validity in the present state of our knowledge. Echlin has also examined this type of activity in the neuronally isolated cortex of both man and animals; his work very largely confirms not only Henry's findings but also his conclusions about the degree of independence of this phenomenon from the barbiturate effect. He comments, however, that Pentothal (and curare) will enhance both the bursts and the suppression, and his published records demonstrate this very clearly. This "potentiating" effect would perhaps be evidence for a similar mechanism underlying the action of the knife and the drug.

In prolonged pentothal anesthesia combined with 25–30 per cent CO₂ inhalation in man (used as a therapeutic procedure in schizophrenia) Busse and co-workers found periodic electrical silence in the EEG. Prolonged (reversible) electrical silence, similar to that previously found in animals, was also seen by these workers in man during diffusion respiration. These authors hold that CO₂ is the main factor in producing the electrical silence.

Lysergic acid, which even in tiny quantities has a very powerful effect on human behavior, flattens the EEG (in rabbits) until there is electrical silence, although the animal is in a hyperactive state. Delay finds that responses to photic stimulation can be evoked on this flattened EEG record, as can bursts of fast waves of barbiturate injection.

The hypothesis that the alpha rhythm might act as scanner of the visual projection areas, and hence play a role in the perception of form, was independently suggested some years ago by McCulloch and by Craik and by Walter. Some experiments by Walsh on the relationship of alpha to
reaction times and visual thresholds have not supported this hypothesis. Other more adequate experiments in his own laboratory, specifically designed to test the hypothesis, have led McCulloch\textsuperscript{122} to the opinion that this is not the mechanism for perception of form. These experiments made use of a square on the face of a cathode ray oscilloscope (MacKay\textsuperscript{112}) expanding and contracting at set frequencies in a way rather similar to that used by Marshall\textsuperscript{119} for a different purpose.

Alpha blocking has always received more attention\textsuperscript{125, 146} than the blocking of beta on voluntary movement or tactile stimulation, but this phenomenon (described by Jasper in 1938 and in 1949) comes to mind in relation to the “rythme en arceau” recorded from the rolandic regions by Gastaut.\textsuperscript{45} This rhythm appears to have a frequency half that of the accompanying beta and has been demonstrated maximally in the motor areas; on voluntary or passive movement (and even to a certain extent on reflex movement) of the corresponding contralateral muscles this rhythm is blocked, and on cessation of the movement there is a return—in a “rebound.” The author presents these data as evidence for a prerolandic projection area for proprioceptive afferents.

Some further studies of sleep have been published. In sedated sleep an apparently “conditioned” response to slowly repeated sensory stimuli at constant intervals has been demonstrated both by Passouant\textsuperscript{125} and by Pampiglione.\textsuperscript{133} A study\textsuperscript{20} of movements made in sleep indicates that alpha activity returns to the record (i.e., there is some degree of waking) before a movement is made. The influence of sleep on focal slow wave activity has been examined by Grossman\textsuperscript{79} and an interference with normal sleep spindles in patients after frontal lobotomy has been noted by Krueger.\textsuperscript{109}

Seconal is the most commonly used drug for inducing sleep for EEG tests. Some other hypnotics have now been tried especially for children.\textsuperscript{52, 162} In the reviewer’s opinion, the choice of drug would appear to depend very largely on whether the goal were sedation (in order to get a clear recording) or “sleep activation.” Seconal favors the latter.

In the symposium on the EEG in relation to psychiatry held at the annual meeting of the American EEG Society, the problem of wakefulness was discussed by Ingram\textsuperscript{90} with reference to impulses reaching the cortex from the brain stem reticular formation and the posterior hypothalamus. The same paper gave the author’s experience with the savage behavior of cats following destruction of the ventromedial hypothalamic nucleus. At the same symposium the role of the limbic system in affective behavior was described by MacLean\textsuperscript{113} in a particularly fine presentation. Lindsley’s\textsuperscript{169} summary of the correlation of the EEG with psychological events laid stress on an excitability cycle which he related to alpha activity and pro-
posed as the means by which sensory impulses are pulsed and coded. The psychological correlates of the EEG have been discussed by Gemelli.\textsuperscript{74} (See also Walter\textsuperscript{179, 181}.)

In the field of clinical psychiatry, Hill\textsuperscript{84} has examined EEG data in reference, not to classic diagnostic categories, but to the occurrence of episodes of grossly psychopathic or psychotic behavior in adults. Several distinct types of EEG anomaly occur more frequently in these patients than in the normal population; of these some are thought to be due to maturational defect (since they are seen in the records of normal children). These are excess theta rhythm in central and temporal areas; alpha locked in phase with its subharmonic; posttemporal slow wave foci that usually block on visual attention; and dominant postcentral theta activity. The other types of abnormality having a high incidence in these patients (although not likely to be due to defective maturation) are paroxysmal in character and similar to those seen in epileptics. One subgroup of Hill’s patients (the murderers) has been reported on in more detail.\textsuperscript{85}

Another study\textsuperscript{38} attempting to use the EEG to differentiate between psychoses divided into categories termed “organic” and “functional” was, not unexpectedly, somewhat barren. Verdeaux,\textsuperscript{165} in assessing the relative usefulness of activating techniques in psychiatric cases, rates overbreathing first, photic stimulation next, and scopochloralose as the preferred chemical activator.

An interesting application of photic stimulation to psychiatric problems has been made by Faure,\textsuperscript{84} who has paralleled his observations with recordings of skin resistance.\textsuperscript{56} He has also studied the eosinophil reaction\textsuperscript{58} to photic stimulation in normal adults and has found the drop in circulating eosinophils to be maximal two hours after the test.

Photic stimulation has also been used by Burian\textsuperscript{28} in amblyopia ex anopsia to differentiate between retinal and central factors with the results implicating the latter. Stillerman,\textsuperscript{161} examining resting records only, noticed a higher incidence of EEG abnormality in strabismus cases with amblyopia than in those without. An application of ERG recordings to other ophthalmological problems has been made by Faure.\textsuperscript{57}

With visual stimuli by single flashes Monnier\textsuperscript{124, 125} has recorded responses through the skull and scalp in man. He found a latency for the first surface positive component of 35 to 40 msec. reaching a peak at 50 msec.; the typical surface negative wave of longer duration (maximal at about 105 msec.) followed (as well as a later repetitive wave similar to that seen in barbiturized animals). These results may be compared with those of Cobb,\textsuperscript{37} (who used a brighter light) in a study essentially devoted to the electroretinogram; this author, however, raises the question of the possible direct
spread of retinal potentials across the base of the brain in his records since he found the major EEG deflexion to be synchronous with the "b" wave of the ERG. (In Monnier's records this question does not arise as the cortical response follows the ERG's "b" wave by a delay of about 5 msec.)

The detection of evoked responses against the background of the EEG potentials in unanesthetized animals may be described as a problem in signal-to-noise ratio; some work is in progress for developing cross-correlation techniques to sort the evoke responses from this background (Brazier and Casby).\(^{(21)}\)

The doubling and tripling responses to rhythmic photic stimulation have received some further study from Cohn.\(^{(39)}\) That harmonics of the EEG frequencies during sensory stimulation have a real and independent existence in their own right has been demonstrated by Walter\(^{(169)}\) with his toposcope (and by Brazier and Barlow by auto-correlation techniques).\(^{(19)}\) Walter's article contains clear and instructive reproductions of the toposcopic appearance of resting alpha and responses to flicker. The persistence of responses, especially in the temporal regions, after the stimulation has ended is of interest.

The subject of cortical excitability cycles has been investigated by Bishop and Clare\(^{(15,16,35)}\) with special reference to the visual system. Factors that will influence the response to optic nerve stimuli include: phase of the alpha wave in which the evoked impulses arrive, state of excitability of the geniculate neurones, and impinging impulses from other sources (and, of course, the after-effect of a previous stimulus). In photic stimulation further complications are introduced at the retina. The question of a cycle of excitability of the motor system subject to the influence of visual stimulation has been examined by Wall.\(^{(167)}\) The results are intriguing and have immediate bearing on the mechanism of photosensitive epilepsy. Several workers have been interested in relating skin resistance changes with the EEG both in normals during sensory stimulation\(^{(17,155)}\) and in patients.

Photo-Metrazol activation was the subject of a symposium held in Canada in the spring. At this meeting Rémond\(^{(189)}\) outlined the standard procedure used in France, and Gastaut\(^{(67)}\) (in absentia) summarized his current classification of the components of the myoclonic response\(^{(72)}\) into fronto-polar (of palpebral origin) and fronto-central (of cortical origin). The former response has received detailed study by Bickford and his associates,\(^{(13)}\) who have suggested that a stretch-reflex mechanism may be responsible for its appearance. They found that they could abolish it with curare. In their opinion the fronto-polar spikes evoked by photo-Metrazol should not be regarded as an abnormal response when a light of high intensity is used. Some experiments\(^{(29)}\) on the wavelength of the light used have suggested
that this may be a factor in the activation of certain photosensitive epileptics. Gastaut\(^6\) in a paper devoted to these muscular responses produced by intermittent light *alone* emphasizes their progressive build-up in amplitude ("recruitment") and the fact that they never occur when the eyes are open. If photic stimulation is continued, they may lead into a generalized convulsion. He considers them an abnormal response when there is no metrazol used and has found them in neurotic and psychopathic cases but not in epileptics. His colleague, Gallavardin\(^4\) has suggested a tentative psychological hypothesis for them. Those who are eager for more data on the response of normal subjects to photo-Metrazol activation and of epileptics with normal EEG's persisting through overbreathing and photic stimulation should read Bartschi-Rochaix.\(^5\)\(^9\)

Some interesting figures on the response to Metrazol injection have been published by Fuglsang-Frederiksen.\(^4\) In only one of his 63 normal subjects did 350 mg. evoke a paroxysmal response, in contrast to 79 out of 96 epileptics (who had previous normal or borderline EEG's), and 51 out of 92 patients with syncopal attacks. Idiopathic epileptics were found to have a lower threshold than symptomatic cases.

The differential diagnosis between epilepsy and hysteria, a problem facing every clinic, has been explored by Tucker and Greenblatt\(^1\) who suggest that in those hysterics who have abnormal EEG's, the cerebral dysrhythmia may have conditioned the neurotic manifestation to take a convulsive form.

The effect of rapidly injected Metrazol on the EEG's of several types of psychosis and psychoneurosis has been examined.\(^1\) Thirty-nine per cent of these patients gave a repetitive spike and wave type of discharge although none had epilepsy. This response was not significantly altered by bilateral pre-frontal lobotomy or by subsequent electroshock. The rather scanty literature on the effect of electroshock on the EEG has been reviewed by Chusid\(^4\) who finds the resultant slow waves to be more marked anteriorly. This was also the experience of Roth.\(^4\) Neither writer finds any relationship of these to clinical improvement. The latter author presents an interesting hypothesis as to the action of E.C.T. on the diencephalon. Hurst\(^8\) invokes EEG evidence in favor of a genetic factor in schizophrenia and Rowntree\(^4\) has published some detailed biochemical studies of some cases of recurrent schizophrenia.

The EEG changes following topical application of acetylcholine to the exposed cortex of man have recently been described by Chusid.\(^3\) The reaction, consisting of negative waves or spikes, takes several minutes to develop. An interesting synthesis of some of the data from clinical and from experimental epilepsy has been made by Moruzzi\(^9\) in a paper in which he discusses the differences between normal and convulsive activity, the
mode of spread from the epileptogenic focus and the role of diencephalic centers in generalized seizures.

Some previously rather rigidly held views on the interpretation of bilaterally synchronous spike-and-wave forms have to be modified in the light of Tükel and Jasper's finding of this pattern in 26 out of 31 cases of verified parasagittal lesions. A finer definition both of form and location has to be used to differentiate between this and the pattern of petit mal epilepsy (the fields reveal the differences when a coronal line of electrodes is used). Cohn, in a comparative study of provocative agents, concludes that spike-dome activity evoked by them is not pathognomonic of epilepsy.

The vexed subject of "suppression" has been examined by Druckman, who has reviewed the literature and added some experiments on cats. He concludes that long-latency suppression is identical with the spreading depression of Leão and that the short latency effects from stimulation of the anterior cingulate cortex, basal ganglia, cerebellum and reticular formation, are a true inhibition. The mechanism of spreading depression of cortical activity has received more study by van Harreveld and Stamm, who conclude from their data that this may be an asphyxial phenomenon caused by a wave of vasoconstriction which slightly precedes it, and that in this respect it is unrelated to the slow potential change which accompanies it. A clarifying critique by Marshall of an earlier paper by these authors is important for the understanding of this phenomenon.

Among technical contributions are a stimulator, a critical examination of EEG amplifier characteristics, a signal pen, an automatic method for instantaneous recording of the contours of the potential fields on the head, and a synthesizer for studying the wave patterns of mixed frequencies. Thiry has reported in more detail on his "monopolar" method for recording push-pull that was criticized in these pages last year. It has received a much fuller criticism from Gordon.

A comparison of two methods of manual frequency analysis (one of which took account of amplitude) with automatic analysis of the same records has been published by Faure. The correspondence was considerable.

The clinical papers that have been published this year bring further support to the growing idea among electroencephalographers that too many years have been wasted since 1929 in the examination of the resting rhythms of the brain, recorded when the patient was in a quiet, darkened room sheltered from stimuli. That it is not the alpha rhythm that reveals the most about the physiology of the brain, or the resting record that gives the clue to malfunctioning becomes clearer with each new investigation and the reasons for this emerge from the work of the neurophysiologists. We should have taken the hint from Adrian, when in 1934 he remarked that "the Berger rhythm is disappointingly constant."
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A REVIEW OF PHYSIOLOGICAL MECHANISMS OF THE VISUAL SYSTEM IN RELATION TO ACTIVATING TECHNIQUES IN ELECTROENCEPHALOGRAPHY

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INTRODUCTION

At the second International EEG Congress in Paris in 1949 the symposia included three papers on activating techniques. In the four intervening years these methods have had wide application in many laboratories and the other speakers in this symposium will present the clinical evaluation based upon this experience.

I have been asked to review some of the basic physiological mechanisms brought into action by these techniques, but to do this at all adequately would impose a review of the whole of brain physiology. Limitations of time impose some selection, and in making this selection it has seemed wise to restrict myself to the one method whose use has spread most widely in the last three years. This is photic stimulation. I have been influenced in this choice by the fact that the other participants will not be covering the subject of activation by light without drugs, and such a choice may perhaps make our symposium on activating techniques more complete.

RESPONSE TO PHOTIC STIMULATION

The cortical response to a flash in the eye has been fairly thoroughly studied, though not quite so thoroughly as the cortical response to electrical stimulation of the optic nerve. For our purposes it is rather important to make this distinction, since our techniques in activating patients by light alone do not include the bombardment of the lateral geniculate body by a synchronous volley of impulses. In all our clinical work the distributing effect of the retina is playing its part in the delivery of impulses to central structures.

Considering first the results of a single brief flash of light, there are four distinct classes of phenomena recordable with macroelectrodes at the cortex that are causally related to the flash. Three of these are also detectable in the lateral geniculate body.

The four cortical events are:

1) The primary evoked response.
2) The secondary response (of Forbes).
3) The fast after-discharge (of Bremer).
4) The slow after-discharge.

We are concerned to know which, if any, of these phenomena is responsible for triggering the photo-sensitive patient into an epileptic fit, or whether, on the other hand, they are to be regarded as concomitant signs of a common process having its critical site of action at a subcortical level.

In reviewing briefly the characteristics of these electrical events at the cortex, reference may be made first to Figure 29a. Here in a lightly anesthetized cat is the response from the visual cortex to a flash 35 microseconds in duration. The first surface positive deflection (recorded downwards) begins approximately 12 msec. after the flash. This is within the range of latency found by Fischer in his work on dogs in 1934 and by many workers since then. This is the primary response, the sign at the pial surface of impulses that have travelled through two relays of synapses in the retina and through one relay in the lateral geniculate body. This earliest positive deflection is usually interpreted as being primarily due to potential...
gradients in the geniculo-striate fibers caused by the approaching impulses. Bremer (1943) and Eccles (1951, 1953) would recognize some participation of cortical neurones with short axons. This deflection is almost certainly the algebraic sum of several components, for some of these can be identified by using the synchronized stimulus of an electrical shock to the nerve instead of retinal illumination.

Fig. 29

a). Primary evoked response recorded at the visual cortex under oil in a cat lightly anesthetized with nembutal. The stimulus was a flash of white light 35 micro-seconds in duration. Surface negativity recorded upwards. The time-line is 200 eps.

b). Primary and secondary responses recorded at the cortex after a single flash 35 micro-seconds in duration. The time-line is 100 eps. Flash signalled by artifact in the baseline.

Even with retinal illumination, as in this illustration, one can see many spikes on the descending limb of the positive deflection. This is a response to white light, but it may be added that similarly appearing spikes can be recorded as responses to monochromatic light. In the case of an electrical stimulus to the optic nerve, Bishop’s work would identify the first positive spike of the resultant deflection as being due to activity in the radiations. In making any interpretation one is faced with the classic problem of how presynaptic and postsynaptic current flows are to be differentiated in a volume conductor, and by the fact that the changing sign of a potential as recorded by a single pair of electrodes represents not absolute polarity but direction of change and the net gain in the change of that polarity over its opposite. This should be remembered in all the discussions of latency that follow in this paper.

The slower negative wave that follows the marked positive deflection is regarded as the electrical concomitant of discharging cortical neurones and that its sign reverses polarity as an electrode penetrates the cortex has been demonstrated by Albe-Fessard (1951) among others. There is little if any difference in the characteristics of this initial response as recorded in a lightly anesthetized animal like this, and that of a non-anesthetized cat as used by Claes (1939) and others. The influence of barbiturate on this response begins to be seen at a level of anesthesia lower than that used here.

The classical experiments of members of this Congress have been the principal contributions to interpretation of these potentials. In our understanding of the electrophysiology of the visual system the work of Professor Adrian (1941) and of Dr. Bishop, Dr. O’Leary (1940), Dr. Marshall (1941, 1949) and many others has given us our ideas as to the neuronal structures responsible for these various components.

If one uses a slower time sweep in order to record over a longer period the second of the four cortical events that were listed can also be seen, viz. the secondary response of Forbes (1936, 1939). This secondary response was described by Forbes for sciatic stimulation, but is known to follow other types of sensory stimulation (c.f. the ‘main cortical response’ of Bishop and O’Leary (1936), also King, Schricker and O’Leary (1953) ). This is illustrated in Figure 29b.
In this animal in a very light stage of narcosis the positive deflection of this secondary response begins at about 70 msec after the flash. In the case of sciatic stimulation Forbes' secondary response has been shown to travel in part by an extrathalamic path and is not abolished by destruction of the specific sensory nuclei of the thalamus. (Dempsey, Morison and Morison, 1941).

The third event following a sensory stimulus is the fast after-discharge demonstrated (for the auditory system) by Bremer (1950) in unanesthetized cats and interpreted by him as a transitory intensification of spontaneous cortical activity. This after-discharge, which may be as rapid as 60 waves per second follows immediately on the primary evoked response and is most marked in the primary receiving area. It is depressed by barbiturate narcosis. The relationship of this activity to the repetitive unitary phenomenon recorded with micro-electrodes in the lateral geniculate body by the group in Sydney still remains to be elucidated. These workers, Bishop, Jeremy and MacLeod (1953) found as many as 10 repetitive post-synaptic waves following a single brief stimulus to a single optic nerve fiber. The intervals between them were less than 3 msec in duration. This type of after-discharge was also found to be depressed by barbiturates. It does not seem to be the same phenomenon as the repetitive response to a single click as recorded from micro-electrodes in the medial geniculate by Galambos (1952) for these responses had different time characteristics from those recorded by the Australian workers, but we have ourselves seen in our records a phenomenon at the visual cortex having about the same time characteristics as the one they report for the lateral geniculate.

According to Bremer, the slow after-discharge is by contrast seen only when the brain is under the influence of barbiturates or of anoxia or in natural sleep (Bremer and Bonnet, 1950). It is usually a surface-positive wave repeating every 100 to 140 msec. This response seems to be restricted to the primary receiving area and has been identified by Adrian (1941) with repetitive activity in thalamic neurones (for it can be recorded in the radiations (Adrian, 1941, 1951) after removal of the cortex). Bremer (1950) is in only partial agreement with Adrian's interpretation, in that he invokes participation of cortical interneurones. Neither Bremer nor Adrian agree with Chang's hypothesis (1950) of a thalamo-cortical reverberating circuit.

In the visual system (which is our particular concern in this symposium) a fast type of after-discharge has been demonstrated by Fields, King and O'Leary, (1949) and by Gastaut (1951) and the slow type by Chang (1950) and by Gastaut (1950).

The question for this symposium is: are any of these cortical events primarily involved in triggering the fit in the photo-sensitive patient?

**FREQUENCY**

From recordings from the exposed cortex of animals Forbes showed in his original paper the secondary response to be obliterated if the repetition rate was above 4 per second. Records on man published by Cohn (1952) show an occiput-positive deflection with a latency of about 110 msec. present at a flash rate of 4 c/s but absent at 7 c/s.

As regards the surface negative component of the primary response, Adrian's work (1941) on the response to touch showed that this is obliterated when the stimulus rate exceeds 10 per second. This is the component identified with discharge of cortical neurones. Remaining for consideration is the initial surface positive wave which has been principally identified with the approaching impulse in the thalamo-cortical radiation. These radiations in the somatic sensory system have been shown to become unresponsive when the stimuli are spaced at intervals of 60 msec. or less (corresponding to a rate of about 17 per second). Yet at the cortex a common finding is that of repetitive responses or so-called ‘driving’ at frequencies higher than this.

Several investigators have been interested in working out excitability cycles for the response of the cortex to sensory stimuli. In the case of the visual system with which we are concerned in relation to photic stimul-
tion, Bishop in 1933 demonstrated a fluctuation in size of cortical responses to successive electrical stimuli of the optic nerve. To obtain any response to the second of a pair of such stimuli Bartley (1936) found an interval of at least 80 msec to be necessary in the rabbit, whereas at an interval of twice that length the size of the second response was maximal. A decaying cycle of waxing and waning excitability followed. Early work on flicker led Bartley (1936) (using both electrical stimuli and flash) to suggest that with higher frequencies of stimulation no single element of the cortex had impressed on it the high stimulation rate but that successive responses occupied alternate elements. A syncopated response of this kind originating serially in different populations of neurones could result in a surface-recorded response, not only at the stimulation rate, but at multiples of it. The phenomenon of doubling and tripling is familiar to all who use photic stimulation. A mechanism such as Bartley suggested would also result in a surface recording of responses at far higher rates than those at which any individual neuronal component of the pathway could respond. In any case, as Bishop and O'Leary (1940) showed, the threshold for cortical responses to optic nerve stimuli is not consistent with a one-to-one connection through the geniculate to the cortex.

At each synaptic step on the way to the optic cortex (i.e. at the stage of cortical neuronal activity as well as at the geniculate) the facilitating effect of a well-timed preceding stimulus can be demonstrated for paired shocks. An attractive hypothesis to explain this facilitation at the synapse was proposed by Bishop and O'Leary in 1940 that the long lasting potential that one can record at the cell stations represents serial recovery of polarization over the surfaces of all sections of the neurones (surfaces that may have different time-constants of recovery), a process outlasting the brief axon-spike and that this has an influential effect on any new impulses arriving at the cell-body during this period. It will determine the polarization level found by the newly arriving impulses.

Since then several studies of cortical excitability cycles have been made not only for the visual system (Gastaut, Gastaut, et al., 1951; Marshall, W., 1949) but also for the auditory (Tunturi, 1946; Chang, 1950) and the somato-sensory (Marshall, W., 1941; Forbes, Battista, et al., 1949; Heinbecker and Bartley, 1940; Jarcho, 1949) and for the response to direct electrical stimulation of the cortical surface (Chang, 1951). In 1951 Gastaut drew attention to the role of the cortical excitability cycle in activation by intermittent photic stimulation. The excitability cycle he established reflected the well-known effect that barbiturates lengthen neuronal recovery time (Marshall, W. et al., 1941) and also revealed the augmentation of the evoked responses by metrazol. With metrazol he found an augmentation of amplitude of every response including the first, so concluded that the effect of this drug was to produce an increased synchronization of the component neuronal discharges rather than an effect on the recovery cycle of the neurones.

In connection with the use of photic activation it is of interest to attempt to identify in man the responses equivalent to those just described for animals. The primary response evoked by flash is recordable through the human skull, as Monnier (1952) and Cobb (1950, 1952) have demonstrated. The shortest latency from the flash to first cortical response reported by both the workers quoted was approximately 35 msec. A response evoked by flash has been recorded in the optic radiations in man by Gastaut (1949) and by Bickford (1953) and from the exposed occipital cortex of man by Gastaut (1951) who found a latency of 90 msec. Some of the many factors affecting latency will be discussed later but here it may be remarked that both in the animal (Chang and Kaada, 1950; Monnier, 1952; Rosenzweig, 1951) and in man (Cobb and Morton, 1952) electrical fields of activity in non-cortical structures earlier in the pathway to the cortex may spread to one’s recording electrodes before the cortex responds.

As Monnier has stressed, the most easily recordable response to flash in man with an
intact skull is a response later than the primary evoked response, namely one beginning about 100 msec. after the flash. This response is familiar to most electroencephalographers for by careful searching for the optimal position of one's electrodes it is fairly easily recorded by an ink-writing oscillograph. The fact that the usual scalp electrode is fairly large and that its separation from the cor-

Fig. 30
Responses to flash recorded through the skull and scalp of man.
Flashrate 2.5 cps.

was probably the response found in 1936 by Jasper in his own EEG and by Cruikshank in her recordings from man in 1937. This
activation of the cortex by scalp, skull and meninges makes it at the cortex an even larger effective electrode leads one to attribute the easy recordability of this late response to its having a wider distribution than the primary evoked response. This observation together with the time of its latency from the flash supplies some reason secondary response, and if one may extrapolate from cat to man, one would not expect it to follow flash-rates much faster than 4 c/s. (In this illustration the flash-rate is 2.5 c/s).

Figure 31 shows in this same subject the effect of increasing the flash-rate to 5 per second and then to 16 per second. At a 5 per second flash-rate the wave-form of each of the first four flashes is similar to that for single flashes (again with a latency of about 100 msec.), but after this some other activity appears to vie with it. At 16 per second only the first of the responses is true to form and, after a momentary hesitation, the phenomenon commonly called ‘driving’ develops. Those who remember the early descriptions of Bartley’s (1936) work with rabbits will recognize how closely this record from a
human subject resembles the effect he found in rabbits. He called this "a reorganization of activity to accommodate for response to high frequency stimulation".

It will be noticed also that at 16 c/s although the maximal response at the flash-rate is in the mid-occiput, there is clear evidence of 'doubling' in the right occiput.

BEFORE INJECTION:

DURING INTRAVENOUS SECONAL INJECTION (200 mgm)

Of course full localizing data are not present in these 7 channels but there is a suggestion of other neuronal areas joining in either at double the rate or in syncopation.

The question of whether the familiar doubling and tripling effect is the recording from different neuronal aggregates each discharging in rhythm with the stimulus but to changing states of the subject. The usual scalp electrodes, forming as we have seen, such large effective electrodes, sample all these rhythms.

How does this doubling and tripling of the cortical response affect our problem of activation in epileptics? If the cortex is not a way-station in the path of photic activa-
tion one could expect that a photo-sensitive epileptic who had a very critical frequency for activation by flash might be impervious to rhythmic activity at that same frequency in his cortex provided it were the second harmonic of the flash-rate and not the flash-rate itself. That such patients can be found is certain. An example is a patient who was particularly sensitive to a flash-rate of 12 c/s which would always make her jerk but if she were flickered at 6 c/s she would give a rhythmic doubling response at 12 c/s but not be activated by it.

Gastaut has drawn attention to the great potency of a flash-rate of 15 c/s in most cases and has explained this on the basis of the excitability cycle (Gastaut, Gastaut, et al., 1951). All who work with photic stimulation will agree with him that flash-rates of about 15 c/s are potent activators in most cases. But we have also to explain on the one hand those cases who are activated by a single flash and on the other, those who are activated by almost any flash-rate. We have probably all had cases of patients who can be activated by a single flash, and Dr. Gastaut has published a striking example of such a response. At the other extreme is the patient who reacts to all flash-rates.

Figure 32 shows an example of a patient who gave an abnormal response to every flash-rate used, although she did not react to the first flash of any series. Samples of only five of the flash rates used are given here. They are seen in the top row. There was a jerk in every case. In the lower row the same flash-rates were being used but secondal was being run into a vein. If the action of barbiturates is to lengthen the recovery period in the excitability cycle, one might question why the drug renders every flash-rate ineffective. Some other aspect of depressant action would appear to be acting in addition, for although the EEG was disturbed in every instance, there was no true activation and there was no jerk. As Gastaut (1951) has suggested, the amplitude of responses to serial flashes probably never exceeds that of the first of the series when barbiturate has been given, and hence no effective facilitation occurs.

**INTENSITY**

Passing from the question of frequency to that of intensity of the flash, we find several workers who regard this as one of the most important parameters in activation by light (Schwab and Abbott, 1951; Van Buskirk, et al., 1952). If we go back for a moment to the evoked responses we can record in animals, Adrian and Matthews (1927) demonstrated in the eel that both increase in intensity of illumination and increase in area of retina illuminated had the effect of shortening the latency of response in the optic nerve, and Bernhard (1940) showed this for the frog. The areal effect on the latency is due to interaction at retinal synapses (Adrian and Matthews, 1928).

That the latency of response at the visual cortex to a flash in the eye lengthens with decreasing intensity of uniform illumination of the retina can readily be demonstrated, as in Figure 33. In this experiment neutral density filters of known characteristics were used to cut down the light. An arbitrary value of 100 per cent has been given to the unfiltered white light source and the per­centages on the left represent the various de­grees of cut in illumination used. On the right are the latencies in milliseconds to the begin­ning of the first positive deflection. It is apparent that the change in latency has taken place very largely, if not entirely, by the time this positive deflection begins. This would be in keeping with such delay being a retinal phenomenon. And in fact, in the cat, as in other animals in whom it has been previ­ously demonstrated, the effect of intensity of illumination on the latency of the electro­retinogram can be shown (Granit, 1933).

Very briefly, our technic is as follows. A stroboscope with a diffusion screen is placed so that the whole of both eyes of the cat are uniformly illuminated by every flash. This white light source has been analyzed for us by Prof. Edgerton at the Massachusetts Institute of Technology and has been shown
to have the same spectral content as sunlight. Neutral density filters or monochromatic color filters can be inserted between the light source and the diffuser. The cat’s

FIG. 33
Primary and secondary responses of a cat’s visual cortex under oil to a flash 35 microseconds in duration but of decreasing intensity.
Time-line 100 cps. Flash signalled by artifact in the baseline.

nictitating membrane is cut and the pupils dilated. A dam of cement is made round the craniotomy hole so that warm oil can cover the brain before the dura is cut and the electrodes placed in the pia. We have in this technique tried to follow Dr. Wade Marshall’s

the spectral curve for the white light source used.

In Figure 34 are shown electroretinograms from one of our cats, and as may be seen, these differ in many respects from most of those that have been previously
published for the cat, (e.g. Granit, 1933) for these are responses to an extremely short flash, far shorter than that used in most of the work published by others. The flash duration has a time-constant of 32 microseconds.

In this illustration two sweep speeds are shown, a slow one on the left of each pair, so that the whole of the 'b' wave with its differences become apparent. In man, Gastaut (1951) has also found that the 'a' wave remains prominent provided the stimulus is sufficiently brief in duration. The rise-time of the 'b' potential, which may reasonably be expected to be the critical determinant of the optic nerve discharge is also seen to be little affected until the intensity is quite low. The ERG in man shows discrete responses to notches may be seen, and a fast one on the right, so that the latency can be estimated (an upward deflection indicates that the retina is becoming relatively negative to the cornea; the time-constant of the amplifier was approximately 1 second). It will be noticed that in this range of intensities there is little falling off in the amplitude of the 'b' wave until the intensity is below 10 per cent of our maximum illumination, and that even at the lowest intensity used an 'a' wave is still present. At weaker intensities still more repetitive flash up to a rate of about 55 c/s (Dodt, 1951). Subjectively this is about the limit that the intermittent nature of the stimulus can be differentiated. Data from micro-electrode studies in cats (whose ERG's give discrete responses up to 72 c/s) would appear to justify the inference that the fusion frequency of ganglion cells in the retina is directly proportional to their spike frequency (Enroth, 1952).

That in photo-sensitive epileptics there is no simple relationship between intensity of
light and activation is, however, clear from the fact that so many of these patients are not activated by intermittent light provided they keep their eyes open. We are all familiar with the patient who, on closing his lids, is triggered to an attack, and I expect all electroencephalographers have encountered patients who discover independently that they can protect themselves against activation by flicker by opening their eyes. An example is shown in Figure 35.

It has been suggested by Bickford (1952) that this effect of eye-closure may be caused by a feed-back mechanism from frontal muscles facilitating the impulses from the eye at hypnosis is needed that covers also the case of the cortical myoclonic response. In this record the reversal of the spike at the electrodes marked LC and RC is very clear. These electrodes in our placement, lie just anterior to the rolandic fissure.

We have to go further in our search for a mechanism of facilitation by eyelid closure because we can demonstrate its effect on the occipital response in the absence of a spike or a jerk, as may be seen in Figure 36. With a flash delivered once per second there was in this case a response to each flash in the mid-occipital region (in the 5th channel) and in the right occiput. On the instruction

Fig. 35
EEG recording from a photo-sensitive patient who could cut short the activating effect of the light by opening his eyes. Duration of whole strip = 20 seconds.

Eyelid closure involves not only a contraction of the orbicularis oculi muscles, for if the lids are shut tightly with a sudden voluntary closure the eyeballs roll upward (Bender, 1943) and, in spite of the consequent decrease in light intensity, there is an associated pupillary constriction. In contrast, as Bender has shown, with gentle eyelid closure the upward roll of the eyeballs does not take place and the pupil dilates as one would expect. Bender’s investigations of the innervation of eyelid closure mechanisms im-
plicate interconnection in the brain stem including of course the nuclei of the facial and trigeminal nerves. The exact pathways for interaction with the oculomotor fibers responsible for eyeball rolling and pupillary constriction are now under investigation by Bender who has demonstrated that both phenomena can be evoked by electrical stimulation in the central tegmental fasciculus in the ventral and caudal region of the pons.

**WAVELENGTH**

Another effect of eye closure is of course to redden the source of light. That red light may in a few patients be a more potent activator than light of other wave-lengths has been suggested by some workers (Van Buskirk et al., 1952) and Gastaut (1951). But when the effective transmission has been equalized as nearly as possible by the use of neutral density filters, the differences in latency found by us have disappeared.

As for the amplitude parameters of the responses to different wave-lengths any discussion is probably meaningless for this type of recording in the light of evidence for a topographical distribution of maxima of response according to wavelength. Some more subtle method and finer resolution than that used here is clearly needed. Undoubtedly the micro-electrode techniques being used by Granit (1939) and by Rushton (1953) and others will bring valuable new knowledge.

**DISCUSSION**

A discussion of this length cannot cover the whole of our knowledge of the mechanisms involved in photic stimulation, but perhaps enough has been reviewed to point up the
difficulties encountered in trying to gather evidence for variants in the occipital cortical response acting as triggers to an epileptic explosion from some other locus in the brain. A hypothesis that would better satisfy the supportive evidence related here, but that would present grave difficulties for critical proof in the epileptic, is that the abnormal events we record at the cortex of the photosensitive patient are secondary and not causal events we record at the cortex of the photosensitive mechanism. For whether there is a correlation between them and photosensitivity in epilepsy appears to be a matter of some controversy.

In making this postulation I have been much influenced by the work of Dr. Merlis and his collaborators and by that of Dr. Gastaut on the dissimilar but related problem of photo-metrazol activation. It will be remembered that Gastaut and Hunter (1950) first showed that the motor cortex was not essential for a myoclonic response to light in a metrazolized cat but held at that time that the visual cortex of one hemisphere was an essential relay in the path. Later Merlis and his colleagues (1953) demonstrated that even this could be dispensed with and that the myoclonic response could be obtained in a totally decorticate animal. The use of the drug and the possibility that it alone may have a maximal locus of action makes a strict parallel with photo-stimulation alone unjustifiable. The difficulty of gathering critical evidence, as I have said, is very great for we can easily mimic in animals the photo-metrazol response that we see in man, but we do not find spontaneously photo-sensitive animals, and any information we gain about the activity of the human brainstem is necessarily inferential rather than direct.

In closing, I would suggest for your consideration that the visual cortex is not a necessary way-station on the path of activation by light in photo-sensitive epilepsies.

I would like to thank my many colleagues in the Electroencephalographic Laboratory of the Massachusetts General Hospital for their help in making these recordings possible. I would especially like to thank Dr. John Loesch, now of the University of Illinois Medical School, for his skilled technical help in some of the experiments reported here.

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THE ACTION OF ANAESTHETICS ON THE NERVOUS SYSTEM

WITH SPECIAL REFERENCE TO THE BRAIN STEM RETICULAR SYSTEM

By

M A R Y  A. B. B R A Z I E R

M.D. 1 9 6 0

Many excellent reviews dealing with this subject have been published, but no comprehensive appraisal has been made since the revolutionary discovery that the specific afferent systems in the brain are not the only sensory route for inflow to the cortex. Within the last decade the existence of an ascending system from the reticular formation of the brain stem has been established beyond doubt. That this new knowledge needs to be incorporated in any modern theories of general anaesthesia is obvious, and hence no apology is offered for giving so much space in this paper to a review of its development during the last few years.

Before proceeding to an examination of these neurophysiological data there are some other facets of the action of anaesthetics that it might be well to review quite briefly.

Among the aspects of anaesthetics which should have some attention are, besides their pharmacology, their effect on cellular metabolism; on the propagation of the nerve impulse in axons; on isolated neuronal systems; and on the behaviour of the organism as a whole. It is clearly impossible to cover all the known anaesthetics and therefore most attention will be given to the barbiturates, bringing the others in as they illustrate contrasting or comparative effects.

Barbiturates have been chosen because so much of the animal work in neurophysiology has been done on animals under dial or nembutal and because so much electrocorticographic work has been done on patients under pentothal. Another reason is that

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1 Butler, 1950; Gerard, 1947; Henderson, 1930; Mécanisme de la Narcose, Paris, 1951; Toman and Davis, 1949; Winterstein, 1926.
sleep induced by such drugs as seconal and nembutal have been made. If another reason for giving star billing to the barbiturates is needed, one may add that they are frequently used on the one hand as anti-convulsants in epilepsy, and on the other as activators of EEG abnormalities in temporal lobe epilepsy.

THE CHEMICAL STRUCTURE OF BARBITURATE DERIVATIVES

The barbiturate linkage is derived from urea by combination with malonic acid. The formula is:

```
R
\|\nN—CO—R
O = C
\|\nN—CO—R
\|\nR
```

with the structure of each radical, R, varying with the specific derivative. It may be remarked in passing that a part of this structure is common to several anti-convulsants and hence by inference is suspected by some of being the structure responsible for this specific action on the nervous system. The part of the structure referred to is:

```
R
\|\nC
\|\nN—CO—R
\|\nR
```

This linkage is found to be common to the barbiturates, dilantin, tridione and phenurone. It does not necessarily follow that the mechanism of action by these drugs on nervous tissue is the same, and of course there are many substances with a depressant action on the nervous system from which this linkage is absent. There is no specific molecular group common to all anaesthetics. For this
reason no further description of chemical structure will be given here, although some chemical reactions will be discussed later in this paper. Nor will space be given to a survey of the physical properties of anaesthetics (e.g. lipid solubility, water solubility (Collander, 1947), molecular weight (Beecher, 1940), thermodynamic properties (Brink and Posternak, 1948), etc.) since conflicting reports as to the relationship between physical properties and anaesthetic potency can be found in the literature. References to the classic papers on these hypotheses can be found in the bibliography listed here. To this author the old controversy as to whether the action of anaesthetics is a 'chemical' one or a 'physical' one has very largely lost its meaning in the light of modern science where physics and chemistry merge.

ACTION OF ANALGESICS ON CELL METABOLISM

In 1912 Verworn suggested that anaesthesia was in fact a form of asphyxia and that narcotics exerted their influence by interfering with cell oxidations. A very great deal of work along these lines has since been carried out in vitro, references to which will be found in the bibliography.

This concept began to be more meaningful when it was realized that the action of the narcotic was probably on an enzyme step in the oxidation cycle, for this would explain the conflicting reports on brain metabolism. The major part of modern work along these lines stems from the studies of Quastel on the oxygen consumption of brain slices and chopped brain tissue in vitro.

Restricting this discussion, for reasons of space, to the action of the barbiturates, it may be stated in summary that Quastel and his associates have been able to demonstrate that these narcotics inhibit the oxidation by brain tissue in vitro when the available substrate is glucose, lactate or pyruvate, but not when it is succinate. (This differential effect is, in fact, not restricted to the

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1 Behnke and Yarbrough, 1939; Lawrence et al., 1946; Meyer, 1899; Meyer and Gottlieb-Billroth, 1920; Meyer and Hemmi, 1935; Meyer and Hopff, 1923.
2 Field, 1947; Fisher, 1942; Fisher and Stern, 1942; Fuhrman and Field, 1943; Fuhrman and Field, 1948; Fuhrman et al., 1941; Keilin, 1925; McElroy, 1947; Warburg, 1912; Warburg and Negelein, 1921; Zorn et al., 1939.
3 Johnson and Quastel, 1933; Jowett and Quastel, 1937; Michaelis and Quastel, 1941; Quastel, 1952; Quastel, 1939; Quastel and Wheatley, 1932a, b; Quastel and Wheatley, 1934.
By process of exclusion the enzyme step in the oxidation chain most commonly suspected of being the vulnerable link is flavoprotein (Grieg, 1946a, b; Michaelis and Quastel, 1941) and it is thought that inactivation of this substance by a narcotic inhibits the interaction between dehydrogenase and cytochrome b. Succinate oxidation does not involve this step and hence such an hypothesis would explain the immunity of succinate to narcotic action (Quastel and Wheatley, 1932a).

Whether information of this kind about brain tissue respiration in vitro can be carried over directly into studies of general anaesthesia can be questioned. Several attempts have been made to do so, and conflicting reports have been published. Soskin and Taubenhaus suggested in 1943 that, by argument from Quastel's work succinate might be a useful antidote for barbiturate poisoning since it would supply the brain with a substrate whose oxidation would be impervious to the drug. They tested this hypothesis by studying in rats and dogs the length of recovery time from amytal and nembutal, and reported that they could shorten this recovery time in rats, but not dogs, by giving succinate. They also found it effective in a case of barbiturate poisoning in man. Attempts by others to confirm these findings have mostly failed (Corson et al., 1945; Lardy et al., 1944; Shack and Goldbaum, 1949), but some give partial support (Beyer and Latven, 1944; De Boer, 1946; Pinschmidt et al., 1945). Paradoxical results with glucose were also found by some workers (Lamson et al., 1950).

Enthusiastic reports on the ability of succinate to cut short recovery time from barbiturate anaesthesia in man have come from Barrett (1947, 1948), but as he used mostly clinical surgical cases no man in the series could be used as his own control. Conflicting reports have come from others (Zuckerbrod and Graef, 1950). In our experience variation in response to barbiturates from one individual to another is too great to permit the use of one person as the control for another.

In our laboratory we tested Soskin's hypothesis in man using

1 Fuhrman and Field, 1943; Michaelis and Quastel, 1941; Quastel and Wheatley, 1932a; Quastel and Wheatley, 1934.
pentothal anaesthesia (Tucci et al., 1949), and at first we thought we too had found a similar result, but were troubled by variations. In the course of making several control tests on the same subject with pentothal alone (before adding succinate) we found the probable explanation of the conflicting results. The mere repetition of the same dose of pentothal given to an individual in the same amounts and at the same rates of injection at intervals of a few days revealed a developing tolerance to the drug, evidenced in a reduction of the length of time before recovery. Recovery was assessed both clinically and electroencephalographically. Our conclusion is that some acclimatization to pentothal can occur, a finding which has clinical meaning in surgical procedures by stages requiring repeated anaesthesia. Some years ago Fulton (Fulton et al., 1930) demonstrated a developing tolerance to dial in cats and some recent experiments have indicated that a similar tolerance to pentothal can be acquired by living mice (Hubbard and Goldbaum, 1949) but not by mouse brain in vitro as measured by oxygen consumption (Hubbard and Goldbaum, 1950).

The most recent work of Johnson and Quastel (1933) on the inhibition by narcotics of the oxidative synthesis of adenosine-triphosphate must await evaluation for the over-all problem of general anaesthesia until the controversy about the role of acetylcholine has been satisfactorily resolved. That the inhibition of respiration caused in vitro by narcotics has different characteristics from that observed in vivo has been stressed by Buchel and McIlwain (1950) in their studies of phosphate metabolism of the brain.

It would seem unjustifiable in the present state of our knowledge to make direct application of data from studies of tissue respiration of minced brain to the brain in living man.

THE EFFECT OF ANAESTHETICS ON THE RESPIRATION OF THE BRAIN IN LIVING MAN

Until recent years attempts to measure the respiration of the brain in situ had been centred around determinations of arteriovenous oxygen differences and calculations of cerebral blood flow. A great many first-rate studies (Himwich et al., 1947) have
employed this method yet none could surmount the inherent physiological reasons for doubt as to the validity of such measurements (such as, for example, the assumption of a constant oxygen consumption (Kety, 1952)).

Outstanding in this context has been the work of Himwich (1952) and his associates who established that a decreased cerebral oxygen consumption followed surgical anaesthesia with pentothal. On the assumption that the venous drainage of the cortex and that of the subcortical areas was not evenly distributed between the two internal jugular veins (an assumption based on anatomical studies by Batson (1944) and by Gibbs (1934)) Himwich expressed the view that the activity of the cortex was depressed more and sooner than that of subcortical areas (Etsten and Himwich, 1946). Techniques developed since then (Kety and Schmidt, 1945, 1948) have shown this assumption of asymmetry of blood content to be unjustified (Wechsler et al., 1951), although the differentiation between cortical and subcortical effects may receive support from other arguments. Himwich's finding of the decreased oxygen consumption at surgical levels of pentothal anaesthesia has been confirmed by Kety but has since been shown to be a secondary and not a primary effect of the anaesthesia (Kety, 1952). That pentothal might directly inhibit nerve function (as distinct from the metabolic effect) was suggested by Himwich (1952).

A great step forward was made when Kety and Schmidt (1945, 1948) developed their nitrous-oxide method for recording cerebral blood flow in man. To summarize their most recent conclusions, their data support the concept that surgical anaesthesia with pentothal suppresses neuronal activity and hence the oxygen demand by the neurones in their inactive state is lowered.

This hypothesis, covering as it does the activity of living neurones, inevitably seems more promising to the neurophysiologist than any hypothesis based on the chemical behaviour of minced tissue.

To the neurophysiologist, and to the electroencephalographer in particular, the postulate that the mechanism of action of anaesthetics on minced brain tissue in vitro can necessarily elucidate the effect anaesthetics have on functioning discharging neurones and on their interplay upon each other in the whole brain in vivo,
is one with little appeal. Information about interaction cannot be obtained from ‘atomized’ material. It should perhaps be remarked that the wheel has turned its full cycle and that Lillie’s opinion (1923), expressed before the period of most intense work on the oxidation theory of narcosis had been done, may well be repeated today: ‘Diminished oxidation is to be regarded rather as a secondary consequence than as a cause of narcosis.’

Kety’s work has a further interest for electroencephalographers for we are all familiar with the difference between the electrical characteristics of sedated brains and of anaesthetized brains. The former evince considerable electrical activity, whereas the latter in deep anaesthesia show long periods of electrical silence.

It is interesting that Kety (Kety et al., 1948) finds no measurable alteration in the rate of oxygen consumption by the brain during sedation.

This is perhaps the place to note that neurophysiology has now emerged from the era when the principal frame of reference was based on an energy system. Interest is now focused on the nervous system as a communication system and on the ability of nerve impulses to travel their normal routes. To draw a parallel from the vacuum tube, it is not the energy of the filament current that interests us but the ‘message’ on the grid.

The next logical step is to examine the effect of anaesthetics on the propagation of the nerve impulse and on its ability to cross synaptic junctions.

ACTION OF ANAESTHETICS ON THE CONDUCTION OF IMPULSES IN NERVE AXONS

The suggestion that anaesthetics produce nerve block by decreasing the irritability of the neurone was made in 1932 by Bishop, who gave evidence that depressants can cause block long before the sources of energy available to the nerve have been exhausted. Barbiturates were not among the agents used by Bishop, but pentobarbital as well as ether was used by Heinbecker and Bartley (1940) in their demonstration that either of these drugs will raise the excitation threshold of frog nerve, as well as lengthening its refractory period and slowing its conduction. In the main barbiturates have been little used in studies of peri-
pheral nerve. The outstanding work by Lorente de Nó (1947) (mostly on frog nerve) has not been with barbiturates either, and one hesitates to attempt an hypothesis suggesting a similar mode of action for all anaesthetics. Lorente de Nó has emphasized that in addition to rendering nerve fibres inexcitable, ether also profoundly affects the electrotonic potential, whereas cocaine has the first effect but not the second. Lorente de Nó assigns the effect of ether to a depolarization of the resting membrane potential (for excitability can be restored by an applied current). The same is true in asphyxia of the nerve (by anoxia), but is not true for cocaine (Bishop, 1932). These findings (i.e. of a difference in action of cocaine and of anoxia) are another ground for doubting that all anaesthetic action can be due to interference with oxidation processes. In the case of ether, even, the nerve can recover its membrane potential in the absence of oxygen and hence its blocking (depolarizing) effect must be by some mechanism other than that of asphyxia.

Barbiturates have been used by Larrabee and Posternak (1952) as blocking agents in a comparative study of the sensitivity of myelinated and unmyelinated nerves, and have been found to have no differential effect on fibre type. This lack of selectivity is shared by other anaesthetics (ether, chloroform, chlorotone). In fact, Larrabee (Larrabee, 1952; Larrabee and Bronk, 1952) from his extensive work with sympathetic neurones concludes that there is no unassailable evidence that anaesthetics exert their effects by modifying metabolism. From his work with chlorotone and azide, Brink (Brink et al., 1952) postulates that a different oxidative pathway is concerned in maintenance of the resting metabolism of a nerve from that involved in its activity. That there might be a qualitative difference between resting metabolism of nerve and that during activity was suggested by Gerard and Meyerhof (Gerard and Meyerhof, 1927; also Holmes et al., 1930) long ago; the latter process may well be dependent on oxidative phosphorylation (Eiler and McEwen, 1949; Gerard, 1932) and hence the action of the azide may be, not an interference with oxidation of the substrate in the resting axon, but an interference with the uptake of free phosphate.

Recent work along these lines gives us the explanation of the independence of oxygen uptake and energy utilization in the
ACTION OF ANAESTHETICS ON THE NERVOUS SYSTEM

axon (Doty and Gerard, 1950), and further points up the possibility that anaesthetics may impair nerve metabolism without concomitant changes in oxygen consumption. That the enzyme systems of mitochondria (Brink et al., 1952; Davies and Krebs, 1952; Potter and Recknagel, 1951) are involved in these phosphorylation processes in nerve has been stressed by several workers.

ACTION OF ANAESTHETICS ON SYNAPTIC TRANSMISSION

It has become one of the tenets of neurophysiology that anaesthetics (Sherrington, 1906) (and barbiturates in particular) have a selective blocking action on synaptic transmission. Direct evidence for some degree of selectivity comes from the work of Larrabee (Larrabee and Posternak, 1952) on the cat's perfused stellate ganglion, a simple monosynaptic preparation without interneurones. For anaesthetics the highest selective action, a relative one, was found to be that of sodium pentobarbital which blocked synaptic conduction at 1/10th of the strength necessary to block the preganglionic axons. Similar results were found with the rat's superior cervical ganglion. Some degree of selective action at synapses was also established by Larrabee for chlorotone, chloroform, ether, cocaine and n-octyl alcohol but not for urethane or ethyl alcohol. In fact if anything, the latter drug had a more depressing effect on axonal than on synaptic conduction. An important finding was that some substances which have no anaesthetic action (e.g. nicotine) can block synaptic transmission in the ganglion far more selectively than any known narcotic. Larrabee points out that his experiments do not determine whether the depressive action takes place at the fine presynaptic endings, the cell bodies or the dendrites, or whether at all three.

Another important finding for us who work in the brain is that the selective action of pentobarbital on the synapse is potentiated by repetitive activity, although the question must remain open as to how close a parallel we may legitimately draw between sympathetic ganglia and synapses in the central nervous system. Other work implicating the synapse as the weakest link during anaesthesia includes the observations made on ascending impulses in the medulla by Forbes (Forbes and Miller, 1922) and on spinal roots by Bremer, by Lloyd, and by Eccles.
The specific difference in spinal root behaviour that can be seen between the unanaesthetized (decapitated) cat and the cat under pentobarbital anaesthesia is in the long lasting electronic potential found in dorsal roots after one of them has carried an afferent stimulus. This has been called by Lloyd and McIntyre (1949) the D.R.V. deflection for it is the fifth discernible potential change seen in neighbouring dorsal roots after stimulation of one root by an afferent volley. It is this long-lasting negative deflection that shows the effect of pentobarbital – not in its rising phase but in the prolongation of its falling phase (Lloyd, 1952a). Lloyd has found this in the cat, and Eccles in the frog (Eccles and Malcolm, 1936). The negativity of D.R.V. interpreted originally by Barron and Matthews (1938) and later by Brooks and Fuortes (1952) as persisting negativity in the terminal fibres of the active dorsal-root axons, has been ascribed by Bremer (Bremer 1933; Bonnet and Bremer, 1952) to interneurones. Lloyd (1952a) also considers it to be post-synaptic in origin; Rudin and Eisenman (1953) have demonstrated that there is no concomitant change in the after-potential of the parent axons of the dorsal column fibres. These results are of interest in the problem of site of action of barbiturates since these drugs have such a marked effect on this component of the dorsal root potential.

As for the motor outflow from the cord, Bremer some years ago demonstrated that the ventral root fibre spike can be abolished in animals anaesthetized by this drug. Eccles's (1946) experiments led him to conclude that the principal action of pentobarbital was on the soma of the motoneurone since the 'synaptic' (non-propagated) potential survived anaesthesia.

Bremer's (Bremer and Bonnet, 1948) experiments and emphasis on the action of barbiturates on interneurones in the spinal cord are well known. His experiments on frog (Bonnet and Bremer, 1948) led him to disagree with Eccles's interpretation for they implicated a drop in synaptic potential as the cause of block by narcotics (e.g. a synaptic potential depressed by narcosis could be raised to threshold by summation with an appropriately timed second stimulus).
EFFECT OF ANAESTHESIA ON BRAIN POTENTIALS

There are two forms of brain potentials that need to be considered: the 'spontaneous' potentials and those evoked by stimulation of a receptor or afferent system.

The first really systematic study of the effects of anaesthetics on cortical potentials was that of Derbyshire, Rempel, Forbes and Lambert (1936). They recorded from aseptic electrodes placed on the dura of cats and left in place for several days. In this paper

![Figure 1a](image)

Recording from a patient in nembutal anaesthesia. The first channel is a bipolar recording from two naso-pharyngeal leads. These leads are evidently so close that no activity is recordable between them. The second channel records between the right naso-pharyngeal electrode and a tympanic lead in the right auditory canal. The seventh channel is recording between the left naso-pharyngeal and left tympanic electrodes and the remainder are from scalp placements as shown in the schema.

![Figure 1b](image)

Automatic frequency analysis of burst activity in the EEG during deep barbiturate anaesthesia. The horizontal line on the far right just below the EEG tracing represents 1 second. The peaks in the histogram represent the activity at the following frequencies respectively (reading from left to right) 20, 22, 24, 27, 30, 3.5, 2.5, 3.5, 5, 7, 9, 10, 11, 12, 13, 14, 15, 16.
these authors described the burst activity with intermittent periods of 'electrical silence' that are now so familiar to us in the human subject during deep anaesthesia (an example of which can be seen in Fig. 1).

They also described the fast activity seen in etherized cats and this we are now familiar with in human subjects. Some years ago (Brazier and Finesinger, 1945) we described how in the case of barbiturates the fast activity appeared first and was most prominent in the frontal regions. It may be remarked that the fast activity at this stage of ether anaesthesia is also more prominent in the frontal areas. The basal patterns of the EEG in etherized and barbiturized animals were described long ago by Bremer (1936b) and later by Beecher and McDonough (1939).

It was in the classic paper of Derbyshire and his colleagues (already quoted) that the observation was recorded that a rather deep stage of avertin or barbiturate anaesthesia (but not ether) favoured the recording of the cortical response to a peripheral stimulus. A surface positive cortical response to stimulation of the sciatic nerve had been recorded in dogs by Nemminski as long ago as 1913, but it is to Forbes that we owe our understanding of its importance. This is the surface positive response of long latency that was named by Forbes the 'secondary discharge'. Beecher’s work demonstrated that low blood pressure and asphyxia also favoured the recording of this late response at the cortex (Beecher et al., 1938), and extended our knowledge of the number of anaesthetic agents under which it could be recorded. More recently acquired knowledge will probably bring a rather different interpretation to these findings, as will be seen later.

In their detailed examination of the cortical response to sensory stimulation under barbiturate anaesthesia, Forbes and Morison (1939) showed the secondary discharge to be a diffuse response of the whole cortex and not (like the primary response) restricted to the appropriate specific projection area. The effect of giving ether to the barbiturized animal was to lengthen the latency of the secondary response and finally extinguish it (reversibly).

It was in this paper that Forbes and Morison (1939) made the suggestion that the afferent paths deliver the incoming volley not only to the sensory cortex, but also the thalamus or other sub-
cortical centres, and that from there impulses are distributed widely in the cerebral cortex).

This suggestion of Forbes of dual ascending systems was followed up and tested on cats by Dempsey, Morison and Morison (1941) who concluded that on stimulation of a sciatic nerve, the primary response of short latency travelled by the medial lemniscus to the contralateral leg area of the sensori-motor cortex, whereas the secondary response of long latency travelled by both crossed and uncrossed pathways. Crossed pathways were shown to exist below the collicular level as well as in the anterior third of the corpus callosum. It was these investigators who established the independence of these two cortical responses; that their different latencies were not merely due to stimulation of different fibre types in the periphery; that the secondary responses did not travel by either sympathetic or cerebellar circuits; and that their spread was not by cortico-cortical connections. These workers later (Morison, Dempsey and Morison, 1941a, b) demonstrated that the secondary response could be obtained by stimulation of brain stem structures. Their discovery and study of the recruiting response to stimulation of intralaminar nuclei led them to the suggestion (Morison and Dempsey, 1942a) that there might be a non-specific thalamo-cortical system with diffuse connections in addition to the classic specific projection system and that the recruiting response was identical with the 8-12 c/s. activity which occurred spontaneously in the EEG (Dempsey and Morison, 1942a) in the association cortex of a nembutalized animal. It is important to note that the parallel they suggested in this paper was with barbiturate bursts, although the distinction has sometimes been lost. Morison, Finley and Lothrop (1943a) concluded that intralaminar nuclei were indeed concerned with the production of these bursts for they recorded them from the region of the internal medullary lamina of the thalamus (and most markedly from the centre median) but never from any relay nuclei of the specific projection pathways (1943b). They also demonstrated that these bursts survived bilateral decortication (Morison and Bassett, 1945) and transection at the intercollicular level for as long as four days before degeneration of the nuclei finally abolished

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1 These authors included in this term the nucleus centralis lateralis, nucleus centralis medialis, nucleus paracentralis and the centromedian nucleus.
rinley and Loutrop, 1943b; Dempsey and Morison, 1942a) that stimulation of 'medial thalamic' nuclei could inhibit barbiturate bursts. From Moruzzi's observations (Moruzzi et al., 1950) it would appear as though the bursts were a sign of, rather than a mechanism for, waxing and waning of facilitation.

In 1947 Jasper and Droogleever Fortuyn reported control of these bursts in barbiturized cats by stimulation of the massa intermedia and moreover demonstrated that they could evoke a bilaterally synchronous wave-and-spike complex by stimulation at a rate of 3 per second, thereby simulating the electrical signs of petit mal epilepsy. Jasper later (1949) introduced the term 'thalamic reticular system' to describe the subcortical connections of what he envisaged as a diffuse thalamo-cortical projection system (i.e. inclusive of intralaminar nuclei and the true nuclei reticularis of the thalamus).

In this paper, Jasper (1949) described the controlling effect on 'spontaneous' activity of stimulation in the intralaminar region and noted maximal effect in the sensory-motor and frontal cortices of both hemispheres, and stated it to be identical with Morison and Dempsey's 'recruiting response'. He felt at that time that the 8-12 c/s. cortical bursts set up by single stimuli to the thalamic reticular system were analogous to the alpha rhythm of the human EEG. Their early appearance in the frontal areas of the unanaesthetized cat's brain (gyrus proreus and middle supra-sylvian) raises the question as to whether they might better be regarded as analogous to the bursts induced by sleep ('spindles'), which closely resemble those produced by barbiturates. They cannot be elicited in the truly wide-awake animal (Jasper). In other words the possibility of a common mechanism in thalamo-reticular stimulation (especially of the rostral and mesial parts of the system), barbiturate narcosis and sleep suggests itself. That the recruiting response may itself be a complex of afferent fibre discharge and cortical neurone response seems likely from the work of Arduini and Terzuolo (1951).

Primary cortical responses are unaffected by thalamo-recticular stimulation, but Forbes's secondary responses are abolished by it. The consideration of these many observations led Jasper to suggest a schema in which cell bodies in the reticular and intralaminar
regions would have direct projections to the cortex (Jasper, 1949; Jasper and Ajmone-Marsan, 1952). Some anatomists (McLardy, 1951; Rose and Woolsey, 1949) were reluctant to accept the postulate of such direct connections (except for the limbic cortex) since they conflicted with evidence from degeneration studies. However, the failure of nuclei to degenerate after decortication is not felt by Starzl and Magoun (1951) to be critical, for they hold that abundant collateralization could keep the cell bodies viable. The suggestion has however been made (McLardy, 1951; Rose, 1952) that an interconnecting system within the thalamus might be responsible for the diffuseness of the phenomena, and McLardy in 1951 pointed out that Dempsey and Morison's results do not exclude the participation by the non-sensory and association nuclei. However, more recent work by Hanbery and Jasper (1952) in which they demonstrated recruiting responses after destruction of the association nuclei would appear to rule them out. In any case it is clear that it is a multisynaptic pathway that is involved, for the latencies found by Jasper are quite long. In this context the finding of Droogleever-Fortuyn and Stefens (1951) that cells of the intralaminar system project not to the cortex but to the caudate nucleus is of the greatest importance. Connections are known to run from the caudate to the globus pallidus; this nucleus in its turn connects with the anterior ventral nucleus of the thalamus.

Although such a circuitous pathway could result in responses of only very long latency at the cortex, those who study the effect of anaesthetics on brain potentials will immediately recognize the cogency of this argument in relation to the phenomena they observe, for it is in the cortical projection areas of the anterior ventral thalamic nucleus (a non-sensory relay nucleus) that these events appear most prominently (i.e. in premotor Area 6, to use Brodmann's numbering). The slow wave type of response to sensory stimuli as recorded in man, whether under barbiturate anaesthesia or in natural sleep, is maximal in what appears to be Area 6.

The cells of the reticular complex of the thalamus, unlike those of the intralaminar region, were found by Rose (1952) to degenerate after removal of the cortex. The type and location of these degenerate changes suggested a widespread but specifically
topographical projection system to the cortex from the thalamic reticular nuclei; this forms an independent afferent system to the same cortical areas as are also served by specific afferents from the dorsal thalamic nuclei. Starzl and Magoun (1951) are however doubtful that any but the most cephalic parts of the thalamic reticular nuclei project to the cortex.

At a level below the thalamus but connecting rostrally with its mesial portion and with the hypothalamus is the ascending reticular system of the brain stem which has been investigated so extensively by Magoun, Moruzzi, Lindsley and others. They showed that stimulation of this ascending reticular activating system (which lies like a core containing many nuclei in a neuronal mesh in the brain stem stretching from the medulla up through the mesencephalon into the caudal end of the mesial thalamus) produces a generalized ‘desynchronization’ of the EEG potentials as recorded at the cortex, a response very similar in appearance to the familiar ‘alpha blocking’. (It will also block the recruiting response of Dempsey and Morison.) This type of generalized response was found to be elicited most easily by low voltage, high frequency stimulation. The ascending effect is independent of the classical afferent lemnisci and the spino-thalamic tracts and survives their section at the midbrain; it relies for its sensory inflow on their collaterals (French, Verzeano and Magoun, 1952; Gerbetzoff, 1940; Starzl, Taylor and Magoun, 1951b), or possibly on independent fine fibres.

Stimulation of the mesencephalic reticular system has an arousing reaction (Moruzzi and Magoun, 1949) (both behaviourally and electroencephalographically) and in contrast, section of its ascending fibres induces a chronic sleep state. Bremer’s (1935, 1936b) classic observation that his cerveau isolé preparation cannot be aroused from apparent sleep is now explicable on these grounds, rather than as the result of section of the specific sensory afferents. Bremer is however correct in using the term ‘deafferentation’ because afferent impulses are necessary to excite this system if it is to keep the animal awake. In fact the work of Lindsley and associates (1949, 1950) on acute and chronic lesions of the brain stem in the unanaesthetized cat and of French and Magoun (1952) in the monkey has confirmed this explanation beyond reasonable doubt. And in the context of anaesthesia, it may be
noted that repetitive stimulation of this system in the mesencephalon has been shown to wake a monkey from deep barbiturate anaesthesia.

The relationship of this ascending system in the brain stem to the thalamic reticular system has been explored by Starzl, Taylor and Magoun (1951a) who find two ascending routes for the impulses: one thalamic and one extrathalamic, the latter being identical with the pathway of Forbes's secondary response described above.

**Fig. 2**
Bipolar recordings from 7 points of an implanted needle electrode (Delgado technique) in the frontal lobe of a schizophrenic patient prior to therapeutic lobotomy. The traces represent serial bipolar linkages from the most superficial recording points in the first trace down to the deepest pair in the lowest trace. Vertical lines represent 1/2 second. Inset on right is an enlargement of the framed section to illustrate reversal of fast activity at the second recording point from the surface.

**AN EXAMINATION OF BARBITURATE ANAESTHESIA**

From observation of both the EEG and the patient’s behaviour it would appear that barbiturates act in rather clearly defined stages. In the first stage of pentothal anaesthesia, for example, the subject shows definitely disturbed behaviour but is not unconscious; eyeball movements are under voluntary control, corneal
reflexes are normal, pupils are normal and react to light and to pain (there is no analgesia). Electroencephalographers are very familiar with the brain potentials concomitant with this stage—they take the form of fast high voltage activity appearing first in the frontal regions (Brazier and Finesinger, 1945) and later spreading back over the head. The generators of this activity appear to lie in the cortex itself and indeed the fast waves can be shown, by implanted electrodes, to reverse in the cortical layer.

In some work initiated by Delgado, Hamlin and Chapman, I have been given the opportunity to study the EEGs of psychotic

Fig. 3
Bipolar serial recordings from an implanted electrode reaching from the cortex of the convexity to that of the orbital surface of the frontal lobe. The schematic diagram underneath is intended only as an approximate indication of electrode placement.
patients in whom Dr. Hamlin had implanted depth electrodes through burrholes made preparatory to therapeutic leucotomy. These electrodes were designed by Delgado and their description has been published (Delgado et al., 1952). The falling gradient of voltage one records from deeper and deeper points of the needle is a consistent finding and all but the most superficial points of the needle appear to record only the field of the cortical potentials, as one would expect from white matter (see Fig. 2).

If one examines the traces from the bipolar linkages of the most superficial points of the needle (lying in the convexity of the frontal cortex) one sees that there is a reversal of sign between them. The framed section in this record has been enlarged in the inset in order to demonstrate this more clearly.

If the needle is implanted through the convexity of the frontal cortex so that it penetrates the underlying white matter as far as the orbital cortex the deepest point of the needle electrode now shows high voltage fast activity. An example of such a case is seen in Fig. 3.

The point to which attention is directed is that the fast waves of the orbital cortex appear to be independent of those of the cortex at the convexity. From evidence such as this it seems reasonable to deduce that the barbiturate at this stage is acting directly on the cortical cells and that the cortex is not being paced into any kind of synchrony from below, although the drug may well be having this same type of independent effect on neuronal groups subcortically.

A patient passes through this stage on the way to surgical anaesthesia and again when recovering from it. Only one further characteristic will be mentioned and that is that sensory stimuli do not at this level evoke a slow wave response from Area 6. Fig. 4 shows an example with scalp recordings from a patient in this stage. Shortly before this he had been in stage 2 of pentothal anaesthesia and on stimulation had given a clearly defined response, as is shown in Fig. 5.

The deeper stages of anaesthesia are also of interest in relation to the new knowledge of a parallel system of sensory relays to the cortex. Electroencephalographers are now familiar with the deep stages of barbiturate anaesthesia (Brazier, 1951; Kiersey et al., 1951), and an example recorded from nasal and tympanic leads
Subject recovering from pentothal anaesthesia (now in stage 1). No pre-motor response to auditory stimulus.

Record from same subject as in Fig. 4, but taken while he was still in stage 2 of pentothal anaesthesia. Marked electroencephalographic response to an auditory stimulus, but no behavioural response detectable.
as well as from scalp electrodes has been illustrated in Fig. 1. The same stage is sometimes seen in barbiturate intoxication and is not necessarily a sign of a poor prognosis, for the process (as in anaesthesia) can be reversible. These are, of course, the familiar barbiturate bursts, so often referred to as 8-12 c/s. bursts, but they are in fact of mixed frequencies. There is very little periodic activity in these bursts and an automatic frequency analyser reports a mixture of frequencies (as can be seen in Fig. 1).

It is in a stage of barbiturate anaesthesia between that illustrated in Fig. 4 and that in Fig. 1 that the role of the non-specific ascending system is so great and it is here that the parallel between barbiturate effect and sleep becomes apparent. Bremer first drew our attention to this similarity by his classic experiments on the cerveau isolé. That barbiturates may exert their influence by producing a block at the reticular level has been suggested (Moruzzi and Magoun, 1949).

It would appear that even cranial nerve II, entering as it does above the level of the transection, has collaterals (or fine fibres) feeding into the alerting system of the brain stem, for photic stimulation of the optic pathway in a cerveau isolé preparation will not alert the animal.

Turning again to the ascending system for sensory stimuli, we have, besides the classic pathways carrying the primary evoked response through comparatively few synapses to the specific sensory cortical areas, Forbes's secondary response travelling by both thalamic and extrathalamic routes, the latter passing through the reticular formation in the brain stem and the mesial portion of the subthalamus and thalamus.

Since in anaesthesiology we are concerned with a problem centering in transmission through synapses it would seem essential in experimental controls to use a physiological sensory stimulus instead of the artificial volley of synchronous impulses that electrical stimulation evokes, for the simultaneous bombardment of a post-synaptic neurone by such a volley probably has no counterpart in nature. As mentioned above, the anaesthetic level that is of interest in this connection is one lower than that in which apparently the predominant effect is in the cortical cells. Hence comparisons need to be made between 'light' barbiturate anaesthesia and a 'deeper' level, in other words the control should
be, not an unanaesthetized animal, but one in light narcosis.

A study of the effect of deepening barbiturate anaesthesia on the response at a cat’s visual cortex to a flash in its eye has been made. Unipolar recordings were made between a reference electrode and leads placed on the pia which had been covered with mineral oil before opening of the dura (as recommended by Marshall). Since there was a likelihood of the drug’s having a depressant effect, it seemed wise to take precautions against cortical depression due to other factors (such as the spreading depression of Leão).

The cat’s nictitating membranes were cut, the pupils fixed and a diffusing screen put between the light source (a Scophony stroboscope) and the cat’s eyes to equalize illumination at the retinae. The flash duration was 35 microseconds.

Fig. 6 shows the response at the cortex to a single flash in the same cat at two levels of light nembutal anaesthesia. Difficulties of reproduction make it impossible to illustrate the whole of an experiment with the many exposures recorded. One typical experiment will therefore be described verbally.

In the lightest stage, so light that EEG potentials were interfering with the response, accuracy in measurement of latency was rather difficult to achieve. However, with these limitations, and from enlargement of the films the latency to the beginning of the first positive deflection for 9 consecutive exposures was found to be (in milliseconds) 11, 11, 11, 11, 12, 13, 12, 12, 11 (a mean of 12 milliseconds).

The secondary response\(^1\) was seen to be extremely variable in amplitude (on calibration it is found to vary from 190 microvolts to 690), and its latency from the stimulus, with the limitations in accuracy mentioned above, lay between the extremes of 63 and 85 milliseconds with a mean of 74 milliseconds.

When the animal was given additional anaesthesia (in this case 30 mgm. nembutal) several effects could be noted. The most striking changes besides the well-known ‘regularization’ of

\(^1\) Attention should be drawn to the question as to whether this response evoked by retinal stimulation is indeed the parallel to Forbes’s secondary response from sciatic stimulation. Space limits a discussion here of its differentiation from a first wave of a slow after-discharge. Distinguishing characteristics include, of course, the diffuse cortical distribution of Forbes’s secondary response and the discrete localization of slow after-discharge to the primary receiving area for the sensory modality involved.
Effect of deepening barbiturate on cortical response to a single flash of light 35 microseconds in duration. (cat)
Note: lengthening latencies and increase in amplitude of secondary response.
Relative negativity at the exploring electrode is recorded by an upward deflection.
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responses were the great increase in amplitude of the second response (the smallest now was 590 $\mu V$. , the largest 800) and the increase in latency of response.

An examination of the latter in detail showed that in the first of the exposures taken 20 minutes after the intraperitoneal injection of added nembutal, the latency to the primary response had lengthened to 17 milliseconds, but even in the next 10 minutes represented by 20 exposures, taken 30 seconds apart, there was a tendency for the latency to continue lengthening (the serial figures for consecutive exposures in this experiment were: 17, 17, 17, 17, 17, 17, 18, 20, 17, 20, 18, 18, 17, 20, 20, 20, 20 milliseconds). The mean of the first ten exposures is 17; that of the next ten is 19 milliseconds, the latter being a 58 per cent increase over the control figure of 12 milliseconds.

There was a striking increase in latency to the secondary response which was also still increasing; in the first ten post-nembutal exposures it averaged 110 milliseconds, in the next ten, 117 milliseconds, the latter being again a 58 per cent increase.

For easier comparison these figures are tabulated in Table I. Thus we have an increasing latency for both primary and secondary responses, a slight decrease in amplitude of the primary response and a very considerable increase in that of the secondary.

From all we know of the secondary response it can be said with some certainty that it has travelled through more synapses than has the primary. If the action of the barbiturate is to slow transmission through the synapses it appears to have done so by the same percentage for the synapses on the primary pathway as on the secondary. It has slowed the conduction pro rata but can it be said to have depressed the responses? In terms of amplitude there has been some depression of the primary (by 30 per cent) but there has been a very great augmentation of the secondary (by nearly 100 per cent).

The latter phenomenon suggests a 'release' effect as though at this stage of barbiturate anaesthesia some inhibitory system, possibly in the diffuse ascending system, had been put out of action by the drug, thereby releasing from control the responses carried rostrally from this system. Such a concept thus envisages that there would be in normal circumstances a condition of balance within the ascending system, a balance between inhibition
and activation, and that by increasing very gradually the depth of barbiturate anaesthesia the action of the one can be depressed before that of the other.

That a deeper level of anaesthesia can be reached at which this differential depression is lost, is, of course, indubitable. The effect of repetitive stimulation has not yet been studied by us, but others have published interesting results from repeated (non-physiological) volley stimuli (Jarcho, 1949; Marshall, 1941; Marshall et al., 1941). That barbiturates prolong the recovery period has been shown by many workers.

It will be noticed that this would be an alternative explanation to the one usually proposed for the necessity for using barbiturate anaesthesia in order to record secondary responses. It would not be merely the suppression of the background EEG waves enabling the secondary response to be seen more clearly: it would be a true augmentation of this response.

Such an hypothesis would also suggest an explanation of the finding, so familiar to those who work on evoked responses, that these have an apparently more widely spread distribution in the anaesthetized animal than in the unanaesthetized one and that the distribution is variable with depth of anaesthesia. This could be an augmentation of previously invisible responses.

It is now of interest to examine the above postulate in relation to barbiturate anaesthesia in man, and to see whether any parallel demonstration of an apparent 'release' effect can be found.

One of the striking features of the EEG in barbiturate anaesthesia, to which our attention was drawn long ago by Bremer, is the similarity of one of its stages to that of sleep. This stage in each of these states is that at which a sensory stimulus will evoke a slow wave response from the premotor regions. It is suggested that this stage might perhaps be more accurately called 'barbiturate sleep' than barbiturate anaesthesia. The sensory response obtained at this stage has sometimes been called an arousal response, but the term seems unfortunate since its major feature is that it occurs without arousing the subject. Another reason for avoiding this term is that it has been used for the quite different phenomenon of generalized alerting that Magoun and his associates have shown to be due to activation of the ascending reticular system of the brain stem.
As is well known, the response first demonstrated in sleep by Davis and co-workers (1939) and since confirmed by too many to mention, is non-specific for sensory modality, although in man the auditory system gives the most easily elicitable response. The location of these slow responses, and of the spindles which so frequently accompany them, is (as far as we can tell in man with an intact skull) in premotor Area 6, by the Brodmann numbering. They are bilaterally synchronous (Brazier, 1949).

![Diagram of EEG waveforms](image)

Fig. 7

'On' and 'Off' responses to an auditory stimulus in a patient under scopolamine and morphine. No observable behavioural response.

An example has already been shown in Fig. 5 of such a response in pentothal anaesthesia. It is not specific to the barbiturates, being, as is well known, readily obtainable with sedatives such as chloral hydrate, and I have found it in patients under operative pre-medication with combined scopolamine and morphine. In view of the strongly analgesic properties of morphine, it may be of interest to illustrate the arrival of sensory impulses at the cortex from a patient 'asleep' under this drug. Fig. 7 shows a response to a sound stimulus. What is of more interest, perhaps, is that one can sometimes get both an 'on' and an 'off' effect to a stimulus that is allowed to persist for some time. To illustrate for the record that this is not a specific auditory effect Fig. 8 shows the
same type of response evoked by the onset of a rather rapidly flickering light.

But to return to barbiturates, probably anyone who has studied sedation with these drugs would agree that in barbiturate-sedated sleep these responses are greatly facilitated. In some recent work in our laboratory, undertaken by Dr. Chafetz and Dr. Cadilhac, they inserted a needle into a vein of a normal person and then allowed him to fall into natural sleep when he felt like it. When

![Strobooscope Image](image)

**Fig. 8**

EEG response to onset of photic stimulation in a patient under scopolamine and morphine. No observable behavioural response.

an adequate recording of the EEG in normal sleep had been obtained, pentothal was run into the vein through the previously inserted needle. Responses to sound were tested before and after introduction of the drug. An experimental design of this kind brings out very clearly the augmentation of response due to the drug. Again one has the impression that activity had been ‘released’ by the drug. The activity that now appears uninhibited would seem to be the parallel in man of Forbes’s secondary response, as many workers have pointed out.

The hypothesis is offered as a starting point for discussion that, at this level of barbiturate action, a differential effect is taking place which has removed a subcortical inhibitory action, allowing the secondary sensory response to travel up unrestrained through
the mesial part of the thalamic reticular system to premotor Area 6 of the cortex. The long latency suggests that it has taken a circuitous route and, extending the hypothesis further, the cortical site (Area 6) suggests that the impulses may have travelled from the intralaminar system to the caudate nucleus (Droogleever-Fortuyn and Stefens, 1951), from there to the anterior ventral nucleus of the thalamus whose projections are to Area 6.

It would scarcely seem likely to be mere coincidence that the same premotor area of cortex in man should be the site of maximal electrical slow activity in each of the following circumstances: 'spontaneous' slow waves (or more probably, responses to intrareceptor stimulation) during sleep; non-specific sensory responses during sleep and anaesthesia; petit mal wave-and-spike complexes (Kaada, 1952); and the fact that all these conditions involve a state of impaired consciousness.

No account of the action of barbiturates would be complete without some mention of their effect on after-discharge. The work of Bremer and Bonnet (1950) has clearly demonstrated that the phenomenon of fast after-discharge can be seen only in the non-anaesthetized animal. The slow after-discharge (which looks like a repetition of the primary response) may be regarded as peculiar to a moderate degree of barbiturate anaesthesia. The distinction that Bremer makes between these two types of after-discharge has not always been clearly understood by others. The former he attributes to transitory intensification of 'spontaneous' cortical activity, whereas the latter he regards as of subcortical origin manifested only when barbiturate anaesthesia is at a level that depresses the autorhythmicity of the cortex. Slow thalamo-cortical discharges can be recorded in specific thalamic nuclei and survive removal of the cortex (Adrian, 1951; Bremer and Bonnet, 1950; Galambos et al., 1952).

In summary, the following hypothesis is presented for discussion.

1. That the initial action of barbiturates is on neurones in the cortex.

2. That at a slightly deeper level of narcosis barbiturates appear to have a differential depressant action on a subcortical inhibitory system, the result being an augmentation of response in the non-specific sensory system that carries Forbes's secondary response.
3. That at a deeper level still, the differential action on inhibitory and activating systems is lost and the sole remaining activity is the barbiturate 'bursts' apparently carried by the same reticulo-cortical pathways that serve the recruiting system.

4. That a state of anaesthesia does not require that sensory impulses should be prevented from reaching the cortex. A disruption of balance between inhibition and activation at a subcortical level of integration would appear to determine whether incoming sensory impulses receive the elaboration necessary for 'awareness'.

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I would like to thank my many colleagues in the departments of Anaesthesia and of Electroencephalography for their help in making these recordings possible. I would especially like to thank Dr. John Loesch, now of the University of Illinois Medical School, for his skilled technical help in some of the experiments reported here. No one, however, but the author should be held responsible for the speculative opinions presented in this paper.

GROUP DISCUSSION

Morison: The secondary sensory response described by Forbes is a long latency phenomenon best seen in deeply anaesthetized preparations by nembutal. It is recordable all over the accessible cortex. During light anaesthesia this response was seen better in our preparations, in which very little of the thalamus on either side had been left, than in preparations with intact thalamus. This would fit well with Dr. Brazier's suggestion. When the subcortical structures are taken out less activity is seen in the anaesthetized cortex and presumably more cortical cells are available for the response just described, hence, the response is bigger. In other words, the lack of Forbes's secondary response in the waking animal may be due not to inhibition but to the fact that the cortical cells being busy doing something else cannot respond in any other fashion, while during sleep the decrease of the spontaneous activity leaves them free to become recruited in a new response. No experimental data are available to distinguish the latter interpretation from one of inhibition.

In systematic explorations of the diencephalon with respect to Forbes's secondary response, it was found that its latency was still
M. A. B. Brazier,
D.Sc. 1960
CHAPTER 12

Electroencephalography

By MARY A. B. BRAZIER, Ph.D.

This year has been a big year for electroencephalography with the 3rd International Congress at which over 500 registered. Supplement 3 of the journal, EEG and Clinical Neurophysiology contains abstracts of the shorter papers given, and Supplement 4 will give the Symposia in full. The 19th International Physiological Congress was an added attraction to many, and there was also a small symposium organized by the Council for International Organization of Medical Sciences devoted to the subject of electrocortical and brain stem activity in relation to problems of consciousness.

There have been few books since those noted in the last year's annual review. Most valuable is Bremer's small book in which he publishes in English three lectures that he gave at the University of London, their subjects being Synaptic Transmission; the Physiological Basis of Electroencephalography; and The Auditory Area of the Brain. Gastaut's monograph on "The Epilepsies," now in press, will bring his work to English speaking readers. Gellhorn's book brings together an immense amount of data, both physiologic and clinical, that have considerable importance for the electroencephalographer. A book on Clinical Electroencephalography written and published in 1950 in Russia is now available in this country. The emphasis in this book is on the application of EEG to psychiatry. There are many original illustrations as well as reproductions from the published work of American authors. Comprehensive review articles on EEG have been contributed by Liberson and by Kaada.

A lucidly written summary of basic information on the potentials of the nervous system has been published by Lussier and makes a compact résumé of the correlation of electrical potential with ionic shift. The author does not, however, take into account the recent work of Grundfest which imposes some modification of Hodgkin's hypothesis concerning the role of internal potassium in the resting potential of nerve. Four comprehensive articles on bioelectric potentials have been published in Germany (Schaefer on muscle and membrane potentials, Kornmüller on EEG, Lullies on peripheral nerve, and Autrum on retinal potentials). All are
survey articles well-illustrated by figures mostly from the familiar classic publications in their respective fields.

An examination of cybernetic concepts and of the hypotheses of scanning mechanisms in the brain has been made by Ganglberger, who has designed an electronic model which reproduces the responses of one of his patients with photosensitive epilepsy. This patient reacted with spike and wave discharges only to certain critical conditions of flicker and this selective response has been mimicked in the model. A courageous attempt to view some of the older hypotheses referring to rhythmic activity of the nervous system in the light of classical physics has been made by Teitelbaum. His essay however omits any of the newer theories that have grown out of knowledge acquired since these earlier hypotheses were framed.

Schwab has given a review of some of the problems in our field that may interest electronic engineers, and Mundy-Castle has written an assessment of the EEG for clinicians based on an analysis of three years' work. The records for illustration have been well chosen and the technics discussed include activation and automatic frequency analysis.

K rakau has published more fully his optical method for frequency analysis of the EEG. The method, although complex, has the advantage that multiple channel recordings run simultaneously can be analyzed for frequency in retrospect, and phase relationships between the EEGs from various leads can be calculated. The author has applied this method to studies of flicker stimulation and of the effect on EEG frequency of artificial fever in man. He concludes that no constant acceleration of the alpha occurs with temperature rises of 1.3 to 2.9 degrees Centigrade, although in one case illustrated the acceleration is quite striking. The competing influence of overbreathing induced by the fever may be a factor to be considered. A technic such as Darrow's or Fischgold's for registering respiration simultaneously with the EEG would be informative in such cases. Lin and co-workers found fast rhythms in some cases of induced fever but slowing more commonly occurred at the higher temperatures. However, in carefully controlled experiments in animals, Koella found an EEG frequency increase that followed rise in temperature in a manner consistent with the Arrhenius equation.

A frequent problem in clinical electroencephalography is the correct assessment of subjective symptoms in patients with a history of an old head injury, especially where compensation may be an issue. Vercelleto and the group at Nantes made a study of 20 such cases without other objective signs and found an abnormal EEG in 14 (three of whom had focal abnormalities). This group of workers feels that in cases with very slow-growing tumors, especially those of the frontal and temporal lobes, the EEG is the best diagnostic aid. An analysis of a large number of cases of head injury
has been published by Meyer-Mickelcit in which he attempts to differentiate concussion from contusion by the EEG. In the former he found only 5 to 10 per cent abnormal records whereas in the latter, in the first month of the injury, there was 70 per cent.

Some basic work on the mechanics of closed head injury has been carried out by Foltz, Jenknner and Ward. On the basis of the known increase in free acetylcholine in the cerebrospinal fluid following concussion, these workers made a study of the EEG changes caused by a blow to the head. They could find no evidence for a paroxysm of intense neuronal excitation at the moment of the blow and hence felt that the acetylcholine increase cannot be explained on these lines. In those animals in whom no anatomic damage was found postmortem the cortical EEG changes were minimal even immediately after the blow and usually consisted of some temporary flattening. As these animals were "knocked-out" it is interesting to note that the electrical activity recorded from the medial reticular formation was more severely depressed than that of the cortex, a fact which may have a relationship to the coma of concussion.

Renfrew and his colleagues have, with an ingenious method of presenting analysis for their data, concluded that in the case of intracranial tumors the EEG gives information that is confirmatory of, rather than additive to, the clinical diagnosis. They found, as would be expected, that the EEG could give little indication of the type of tumor present, although serial EEGs proved helpful in differentiating between rapidly growing neoplasms, static lesions or regressive ones. Martin and co-workers, comparing the relative merits of EEG, air studies and angiography in cases of brain tumor consider that the EEG is only an adjunct to the other diagnosis methods. However they did not use the modern technics of serial electroencephalography or of the multiple linkages devised by Bagchi that have yielded such encouraging results in the detection even of posterior fossa tumors. Their success in detection and location of tumors by EEG is thus not as good as that of some other workers. Kirstein has made a special study of the incidence of sharp waves, spikes, and fast activity in supratentorial tumors.

The group at the Max-Planck Institute have published their findings in 44 cases of tumors near the sella of which 25 per cent gave lateralizing signs in the EEG. Bilateral theta waves were frequently found and were interpreted as caused by disturbance of the diencephalo-hypophyseal system. Vizzioli has reviewed the EEG localizing signs in 100 cases of tumor (foci in 40 per cent, lateralization in 70 per cent of the supratentorial tumors) and some studies of the characteristics of the rhythms found in these cases have been published. Daly and co-workers report their findings in 87 cases of tumors of the posterior fossa and third ventricle. The inci-
idence of EEG abnormalities was high but not localizing in kind. Zappoli\cite{290} reports favorably on the results of using basal electrodes including sphenoidal electrodes similar to those used at the Maudsley Hospital.

One of the largest series of verified subdural hematomas with EEG studies to be published has come from the Mayo Clinic.\cite{159} The location of focal slow waves was found to be a more reliable sign than alpha asymmetry. Walton\cite{196} has followed the EEGs for several years of some survivors from spontaneous subarachnoid hemorrhages with residual clinical signs. Millar\cite{120} in a series of cases of subarachnoid hemorrhage found the EEG to lateralize correctly in all the cases with verified aneurysms.

Obrador\cite{142} has summarized his considerable experience of operative procedures for epilepsy; he finds that the EEG frequently gives an indication of cortical scarring following head injury long before epileptic attacks develop. He considers temporal lobectomy more successful in patients whose fits are solely psychomotor in type than in those with generalized attacks in addition. Four of the former type, followed for one and one-half to two years, have been free of attacks postoperatively, their EEGs also losing their abnormalities. Obrador recommends limiting anterior temporal lobectomy to those cases with the purer clinical signs of psychomotor epilepsy and with EEG foci in the anterior temporal region. Pond and Hill\cite{185} have also summarized the conditions they recommend as indications for temporal lobectomy, and a discussion on the surgery of temporal lobe epilepsy was the main subject at a meeting of the Royal Society of Medicine.\cite{81} The experience of the group at la Pitié has also been published.\cite{183, 125} Of 20 cases with focal clinical and EEG signs, 16 were found at operation to have lesions. In 11 of these followed for three years postoperatively there was clinical improvement. A compact review of "temporal epilepsy" has been written by Mme. Dell\cite{140} who advocates differentiating this syndrome both clinically and by EEG signs from that of psychomotor epilepsy. She regards narcolepsy as a minimal form of epilepsy related to psychomotor epilepsy and to psychic epilepsy.\cite{107}

An excellent and detailed report on temporal lobe epilepsy with supportive material from animal experiments has been published this year by Gastaut.\cite{62} This is recommended reading. The report includes comparison of electroencephalographic and electrocorticographic recordings in these cases, as does also a report by Chatrian.\cite{62} Other shorter reports with statistics on this subject have come from the group at Turin\cite{71, 125} and from the Salpetrière.\cite{183, 188} The endocrine and psychiatric features of temporal lobe epilepsy have been investigated by Faure\cite{63} and studies of the cerebral circulation in such cases have been made by Passouant.\cite{156} Experimental epilepsy in animals induced by injecting alumina cream into the amygdala has been described by Gastaut.\cite{63} Another case of musicogenic epilepsy has
been published. Those familiar with the opinion that psychomotor epilepsy is rare in the child will be interested in the report of 81 cases by Nekhorosheff who found the EEG most useful in diagnosis. Earle, Baldwin and Penfield consider hippocampal herniation during birth to be an important cause of later developing temporal lobe seizures. EEG studies on 54 children with intracranial birth injuries have been made by Morstad.

In connection with the significance of temporal theta in adults, Jarvie's detailed account of a patient with episodes of uncontrollable rage is of interest. Schwade also reports a case of impulsive matricide with EEG anomalies, though whether thalamic or hypothalamic structures are responsible for the specific EEG changes found (as the author suggests) must surely remain speculative in the lack of more direct evidence. Levy and Kennard in a series of 100 criminals found a higher incidence of abnormal EEGs among the repeated offenders than among those convicted of single crimes (34 per cent as against 17 per cent) but although theta was a commonly found abnormality it was no more prominent in crimes of violence than in other offenses. EEG abnormalities in primary behavior disorder and psychopathic personality are well confirmed but there is now strong evidence from Knott's investigation of the parents of these patients for a genetic determinant. Of 115 children with psychiatric difficulties diagnosed initially as neuroses, Nylander found 25 per cent to have abnormal EEGs but on elimination of all subsequently suspected of lesions, this figure fell to 7 per cent. The development of slow alphalike or theta activity precentrally as a response to sensory stimulation is found by Darrow to be exaggerated in emotionally unstable children.

In an interesting paper Williams has reported on six children in whom he was able to record from depth electrodes in the brain during petit mal attacks. The probe was so placed that the two deepest electrodes were in the thalamus, one in white matter and one in the deeper layers of the cortex. All the attacks illustrated were heralded by a few slow waves from the thalamus followed by a spike with accompanying wave that repeated at 3 per second for the duration of the attack. The spike usually died out before the slow wave. Although the illustrations make it clear that the author was hampered by the deficiencies of his recording instrument (wave distortion by pen arc, blocking of amplifiers, limitation of pen excursion restricting amplification until all detail is lost) he feels he can state that the slow waves presaging an attack start in the thalamus, and are followed by a spike (with its own concomitant slow wave) apparently starting deep in the cortex and repeating as a complex for the duration of the attack. These results differ from those of Bickford who with depth electrodes left in place for several days has found clear sharp foci 2 to 3 cm. below the cortical surface in epi-
leptic patients. Williams suggests that the thalamic slow wave initiates the more superficial spike which then paces the discharge, and that the attack ceases when the spike fails to be any longer propagated to the thalamus. From his records he calculates the whole pace-making cycle to occupy 28 msec. (a priori, one would surely expect a longer cycle if the author's hypothesis is correct). Williams further suggests that the clinical picture of petit mal is due to a disturbance of the organism on the afferent side, in contrast to other forms of epilepsy where disorganization of effector mechanisms predominate. Few electroencephalographers will agree, however, with Williams' premise that spike-and-wave discharges occur all over the cortex. This year more support for the localized nature of such discharges has been published by Marossero\textsuperscript{24} including some interesting cases where the discharge was bilaterally asymmetric. Terzian\textsuperscript{177, 178} recognizes five different forms of spike-and-wave and discusses their clinical correlates.

Bennett\textsuperscript{8} has extended the work of Shimizu to human subjects and has provoked classical petit mal attacks in epileptic patients by unilateral intracarotid injections of metrazol in 76 per cent of his attempts but in only one out of eight by intervertebral injections. A not entirely hole-proof argument is advanced for considering this as evidence against a subcortical origin for petit mal attacks. At the Mayo Clinic, a study\textsuperscript{7} has been made of epileptic disorders coming on after the age of 50 (representing 4 per cent of a group of 2700 seizure cases). Of these 107 tumors were diagnosed in only 10 (4 being metastatic). The EEG was found to be particularly useful in detecting these cases. It is interesting that in no case were the seizures of the petit mal type.

The characteristics of seizure discharges were the subject of a joint symposium of the EEG Congress and the American League Against Epilepsy. Moruzzi\textsuperscript{28} described the basic mechanisms involved, Gibbs\textsuperscript{67} reported on changes in seizure foci with age, and Kaada\textsuperscript{93} discussed temporal lobe seizures. Running fits have been described by Sisler\textsuperscript{188} and an account of some rather unusual EEG findings recorded during seizures have been discussed by Terzian.\textsuperscript{178} Petit-Dutaillais\textsuperscript{181} has made some interesting observations on vasomotor changes during seizures in the exposed cortex at operation. He described two cases where a gyrus became red during a fit, but the electrical signs of the fit preceded the engorgement of the vessels and hence he suggests that the latter was a compensatory mechanism for the local anoxia induced by the neuronal hyperactivity of the fit. Those who work in the operating room will be interested in the discussion on technic and interpretation in electrocorticography.\textsuperscript{42}

The overall effects of hypoxia have received some further investigation from Holmberg\textsuperscript{82} who concludes that hypoxia alone (i.e. with the CO\textsubscript{2} tension maintained) has little effect on the EEG and that for slow waves to
appear on overbreathing in normal subjects or spike-and-wave in patients with petit mal there has to be some simultaneous hypocapnia. He would therefore tend to support the hypothesis that hypocapnia is the essential factor in the mechanism of slow activity induced by overbreathing. In some experimental work on animals, Gellhorn has contrasted the effect of different levels of CO₂ on evoked responses at the cortex and hypothalamic potentials. The changes induced by vascular hypotension as a technic in anesthesia have been reported by Bromage who considers the EEG to be a useful guide. In cats, ten Cate has shown that the EEG disappears within 20 seconds of ligation of the aorta, but that it will return provided the cerebral anoxia so induced does not last for more than 15 minutes.

The realization that the electrical response of various brain structures to external stimuli can do much to elucidate the potentials recorded in the EEG gives added importance to many studies in this field. Among these are the papers from O'Leary's group on the thalamic response evoked by cutaneous stimulation and by sciatic nerve volleys. These papers tackle the problem as to the phase in the thalamic potential at which synaptic transfer takes place (it commences soon after the first positive phase begins in the thalamus and is almost over when the negative phase starts). Other interesting findings include a thalamic response to small fiber excitation, which may have considerable bearing on the subject of pain, and a feature of one of these papers is an extremely clear exposition of the fields about an active nerve unit or group of units. For an understanding of the fields a natural source of potential inside the head can produce on the surface Zao has used the eyeball. In an instructive article he shows how controlled rotation of such a source will be reflected at the scalp electrodes.

The role of the thalamus in the perception of pain has been explored by Monnier by direct stimulation in man. His simultaneous recordings from thalamus and cortex are technically superior to those of Williams already quoted.

A survey of flicker response in a large number of neurologically normal young adults and a rather smaller group of normal senile adults has been made by Mundy-Castle. He found epileptiform abnormalities in the responses of 3.9 per cent of the former group and in 2.5 per cent of the latter. "Following" above 26 c.p.s. was found to be rare though one example at 44 c.p.s. is illustrated. The author interprets his confirmation that optimal following is at or near the subject's own rhythm as support for Walter's hypothesis of a resonance mechanism and suggests that the exceptions may correlate with temperamental differences in excitability. It is unfortunate that no automatic frequency analyzer was available for this study. The added information that can be gained and the quantification made possible by the use of such an instrument is exemplified by Ellis and Last's study.
ELECTROENCEPHALOGRAPHY

of 100 normal subjects and by the report of Ulett on 73 "anxiety-free" normal males compared with 32 "normals" with anxiety proneness and 32 patients with anxiety neuroses; analysis showed the latter two groups to have less alpha and to follow flicker less well at or near the alpha range while having more of the higher harmonics than normal. In this series three of the anxiety-prone normal group had seizures.

A study of the response to flicker of 307 inmates of a prison made in 1946 by Ostow has now been published. These results would have been increased in value had the report been brought up to date in relationship to the immense amount of work by others since then. This study (of an admitted abnormal population) also confirmed that flicker following can be induced more readily within the frequency range of the subject's own rhythm. The author regards persistence and prominence of photic driving as suggestive of impaired cerebral functioning.

Leffman confirms the original finding of Gastaut that the mean photometrazol threshold is lower in schizophrenics than in normals. Lieberman also finds a low threshold in catatonic schizophrenics and in 4 out of 5 cases whose myoclonic threshold was determined several times over the course of many weeks, he found that the threshold fell even lower when the patient emerged from the stuporose phase of his illness. Chamberlain however found no change in threshold in his schizophrenic patients during remissions. A search for epileptiform patterns in the EEGs of sleeping psychotic patients gave a negative result, but Stehle has found sleep records useful in differentiating psychoneurosis from epilepsy in borderline types.

One of the symposia at the Congress was concerned with activating methods, the technic of sleep activation being discussed by Fuster and of photometrazol by Gastaut. For sleep activation Coursin has found intramuscular paraldehyde useful as the drug itself introduces few changes in the EEG that are distinguishable from spontaneous sleep. The same may be said for Dormison but Henry finds this drug to be less reliable in inducing and maintaining sleep than barbiturates. A method for standardizing metrazol activation has been worked out by Jasper and Courtois. Several other drugs have been investigated for their activating properties. Bercel using scopolamine hydrobromide and alpha chloralose produced activation in over two-thirds of epileptics with previously normal records and in none of his controls.

Topical application of activating drugs during electrocorticography has been used by Bergamini (metrazol) and by Chusid and by Purpura (acetylcholine). The mode of action of metrazol in evoking seizures has been the subject of experimental studies by Starzl and by Marsan and Marosseno. The transition from normal cortical activity to convulsive
discharges has been followed at different levels of the cortex of rabbit by King in seizures evoked by repetitive stimulation and by metrazol. The effect on the EEG and on autonomic and psychic phenomena of oral doses of lysergic acid have been studied by Gastaut and by Bradley in man, and on the EEG of cats by Bradley.

A report has been published by Buchthal and Lennox of the response to metrazol and photic stimulation of 682 applicants for the Air Force. In those with no trace of neurologic abnormality in their histories, metrazol alone induced paroxysmal activity in 15 per cent (as contrasted with 53 per cent of those with some neurologic involvement and 80 per cent of a group of known epileptics). These authors feel that Metrazol makes this diagnostic distinction more certain than does photic stimulation (without metrazol) in spite of 15 per cent of their normals having given seizure patterns, for light alone activated only 13 per cent of their known epileptics. Browne-Mayers also feels that metrazol is valuable in differentiating an ‘epileptoid’ group among psychiatric patients.

Three more cases of self-induced photogenic epilepsy have been published. Marshall and his colleagues have now described in some detail the case of photosensitive epilepsy who could be protected from attacks if he wore glasses that filtered out red. Bickford in a study of photic activation of children found a slight tendency for some to be more sensitive to red. A possible explanation that occurs to this reviewer is that red light is transmitted through the ocular media to the retina with far less loss than wavelengths at the blue end of the spectrum. Marshall was also able to demonstrate an inhibiting effect of an auditory stimulus introduced about 1 msec. after each flash. The interaction of visual and auditory stimuli on cortical response has been examined further by the same laboratory and reciprocity of effect has been demonstrated in normal human subjects.

The relationship of randomly occurring sharp waves in some subjects to spontaneous excitation by light has been explored further by Evans. Although apparently similar to the “on” response to single flashes it is difficult to account for their initiation as an abrupt stimulation of the retina when the subject is lying with eyes steadily open in a lighted room. Another puzzle is their appearance in some subjects in centroparietal areas, yet some relation to photic stimulation would appear to exist. Roth finds these “lambda” waves to be augmented by light barbiturate anesthesia, which to this reviewer would suggest them to be related to secondary cortical discharges rather than primary evoked responses.

Possible mechanisms by which photic stimulation could facilitate cortical motor cells have been explored by Wall by recording in the pyramidal tract the activity set up by electrical stimulation of the motor cortex with and without a preceding visual stimulus. A prolonged period of facilitation
was found to follow a single light flash of 2 msec. duration (even in the absence of the visual cortex). The composition of the pyramidal tract is, however, more complex than meets the eye in the textbooks as has been shown by the recent work of Lassek, Brodal and others. Whether a parallel can be drawn between these experiments on motor discharges initiated from the cortex and the bilateral myoclonic response evoked by flash in metrazolized animals and man is questionable, since de Haas and his collaborators have demonstrated that the latter is not abolished by complete decortication and hence is not dependent on discharges from cells of the motor cortex. That in fact two pathways exist in the cat by which responses to light irradiate to various cortical and subcortical regions has been demonstrated by Hunter and Ingvar. One route is transcortical spreading forward from the visual cortex and the other subcortical, probably utilizing the collaterals from the visual pathway to the reticulothalamic system and hence directly to wide areas of cortex (responses following the latter pathway have a long latency). A discussion of the role of the cortex in the induced seizures of photosensitive epileptics was given by Brazier in one of the Congress symposia together with a review of some of the underlying physiologic mechanisms.

Motokawa, whose well-known work on the interaction between photic and electric stimulation of the eye in man has been the subject of a critical review this year by Gebhard, has presented some more of his work on animals. His results illustrate the question raised by Brazier as to the difficulty of reliable differentiation between intensity and wavelength as the operative factor in determining the latency, form and amplitude of the cortical response to different monochromatic lights. Lennox, however, feels some confidence in the latency differences for colored light. Another difficulty is that in the cortex, as in the retina, the area optimal for recording response to blue light may not be optimal for red, although Lennox found no evidence for topical color localization in the cortex (but in the cat's retina all areas do not have equally dense representation in the cortex). It is rather of interest that she found the 4 to 6 spikes on the initial deflection of the cortical response to be identical for different colors. Our knowledge of the structures responsible for the several components of this evoked response has been greatly increased by the work of Bishop and Clare who compared the responses evoked by optic nerve stimulation with those evoked by direct stimulation of the cortex at various depths. Stimulation at the level of the radiation endings produces the full cortical response identical with that from an optic nerve volley. The serial disappearance of various components as the stimulus is brought nearer and nearer to the surface gives strong indications of the structures contributing them (radiation endings, cell bodies, basal and apical dendrites). A long analysis of the
potentials evoked by flicker in frogs and rabbits has come from Russia. Smirnov\textsuperscript{170} has recorded the ERG, the optic nerve discharge and the response from the optic lobe, and finds that "following" responses to the faster frequencies (15 to 18 c.p.s.) are rather discretely localized in the rabbit's cortex whereas at slow frequencies (3 or 4 c.p.s.) they are more widespread.

At the EEG Congress symposium on the physiologic basis of the EEG, Burns\textsuperscript{36} spoke on intracortical integration, Jung\textsuperscript{91} on neuronal discharge and O'Leary\textsuperscript{149} on DC potentials. Fessard\textsuperscript{49} has presented a comprehensive and thoughtful discussion of the basic neuronal mechanisms involved in changing levels of consciousness. The behavior of the DC potentials of the brain and their integration with potentials evoked by peripheral stimuli is considerably elucidated by the work of Goldring and O'Leary.\textsuperscript{69} Briefly, the resultant DC potential that one measures appears to be the algebraic sum of two components of opposite sign tending to balance in a manner consistent with cerebral homeostasis. Certain chemical agents applied to the cortical surface will enhance the component contributing to surface positivity (e.g., veratrine,\textsuperscript{69} malononitrile\textsuperscript{70}) and others augment the one which is responsible for surface negativity (e.g., strychnine). The effect of such disturbances of homeostasis is reflected, not only in distortions of the positive or negative components of primary evoked responses to peripheral or optic nerve stimulation, but in the prolongation of cortical disturbance resulting from a single stimulus. This work adds to the growing interest in the role of dendrites in the electrical activity of the cortex, and in the differences of potential that may exist between the various parts of the same neurone so that current flows external to the cell may influence other neurones without classical transsynaptic transmission of impulses.

The subject of suppressor areas has been re-opened by some work from Georgetown University.\textsuperscript{54} These workers searched for and found a region in the temporal lobe (of macaque) where both electrical and strychnine stimulation produced (after a delay) a suppression of electrical activity and of response to flicker. The critical cortical location was small in size and limited to points (on the first temporal convolution at the base of the Rolandic fissure) rather than to an area or band. The work of Sloan and Kaada\textsuperscript{199} would indicate that even the anterior limbic cortex cannot be correctly described as a "suppressor" area, since both facilitatory and inhibitory motor effects can be produced by stimulation. These motor effects were not always paralleled by the EEG changes. Some more information is available on the effects of stimulation of the hippocampus and medial cortical surfaces from the work of Kaada\textsuperscript{95} who has used implanted electrodes in cats. Such stimulation consistently provoked vigilant behavior and searching movements to the contralateral side.
Interest in the interrelationship between cortical activity and the brain stem reticular system led this year to a small international symposium on this subject as mentioned at the beginning of this review. This topic has also been the subject of a short review by Vizioli in a volume of the Rivista Neurologica devoted entirely to the work of the Italian EEG Society. The role of the hypothalamus in maintaining the waking state and its relation to the arousal response has been explored by Bernhaut, and by Gellhorn.

The regulating influence of the brain stem in a descending direction is well-known, especially for muscle spindle afferents. Hagbarth and Kerr have now demonstrated that transsynaptic responses of the dorsal and ventral spinal columns to stimulation of a lumbar dorsal root can be decreased by concurrent repetitive stimulation in the bulbar reticular system and parts of the cerebellum and cortex. Conversely, the responses can be augmented by spinal transection at any level cranial to the root of entry. (This has also been demonstrated by Lindblom and Ottoson in a study of spinal cord responses to stimulation of low threshold cutaneous nerves).

What is of interest to electroencephalographers is that the resultant evoked cortical response is also depressed by this procedure although the primary response in the spinal axons of the dorsal root ganglia is unaffected. This and other evidence indicates that depression of the cortical response is taking place in the higher centers. These authors find a striking augmentation of afferent response in the spinal cord on giving light nembutal anesthesia, and Brazier, working on the visual system, has reported a marked augmentation of secondary, long-latency (65 to 85 msec.) responses at the cortex at a certain light level of barbiturate anesthesia. Her findings led her to suggest that at this stage of narcosis the barbiturates remove an inhibiting influence of the brain stem on the afferent impulses that use this indirect and polysynaptic route to the cortex. Evidence is not yet sufficient to claim that such a hypothesis uniquely describes the findings, but it seems likely that the inhibitory influences depressed by the drug are not only descending ones to spinal centers, for the effect can also be demonstrated on stimulation of a cranial nerve (e.g., on cortical responses to flash). Adrian in his discussion at the same symposium suggested that in the waking state some inhibitory activity at a lower level may check some signals from reaching the cortex and that in states of impaired consciousness suppression of this inhibition may result in pathways being more freely open for random incoming signals. Bremer considers that one need not postulate a specific affinity of reticular cells for barbiturates, since there are so many synapses present.

French and his colleagues have recorded in monkeys the responses to sciatic and auditory stimulation within the reticular system and also their
arrival at the cortex. These medially conducted responses to sciatic stimulation have a latency longer than that of the primary relay system (18 msec. as against 10 msec.), but not nearly as long as those of Forbes' secondary response (30 to 80 msec.). These authors have been able to demonstrate the interaction of stimuli from these two peripheral sources and have made clear the loss of sensory modality in this ascending system. They have also studied the effect of anesthesia and find that the medially conducted responses are depressed before the laterally conducted ones at a stage when the initial spike of the primary response may even be augmented. This augmentation has also been noted by Bremer. Another differentiation thus emerges between French's "medially conducted response" and Forbes' secondary discharge. The latter not only has a longer latency but reacts in a different manner to barbiturate narcosis.

The role of the ascending reticular system in relation to consciousness has been discussed in some detail by Magoun and that of the diffuse thalamic projection system by Jasper. Some anatomists are still uncomfortable that so much physiologic function is assigned to postulated pathways the existence of which their technics have as yet failed to confirm. Fiber connections from the reticular formation of the thalamus to the neocortex are now known but the existence of diffusely projecting fibers from thalamic association nuclei to the neocortex (with the exception of a few fibers to the orbital and lateral gyri) has been called in question by Nauta. He has used a modification of LeGros Clark's silver stain for axoplasm instead of the Marchi technique, in order to be able to trace finely myelinated fibers. He confirms Droogeleever Fortuyn's demonstration of projections from the intralaminar system to the caudate nucleus as well as to the claustrum and putamen. Brazier has suggested that the location of the long-latency potentials evoked by sensory stimulation in human subjects whose consciousness is impaired by sleep or anesthesia may indicate that these impulses have used this pathway through the caudate via the anterior ventral nucleus to cortical area 6. Such a circuitous route would account for their long latency.

Among the investigations of the mechanisms of anesthetics is the observation of von Rosenkötter that the level of barbiturate narcosis as gauged by the EEG can be lightened by giving the animals ether (but not vice versa). Therefore it would seem that the familiar fast activity of ether narcosis can manifest itself in cortical cells even when the usual interplay of cortex and brain stem has been disturbed by barbiturate.

The electrophysiologic evidence for thalamocortical pathways other than the classical projections of the specific sensory nuclei is very strong. Hanbery and Jasper have demonstrated recruiting responses in primary sensory receiving areas after destruction of their own specific nuclei. Of the
several anatomic structures suggested as the principal cell station for the final pathways of the nonspecific thalamocortical projections, the nucleus reticularis is at present the most generally accepted, and Hanbery and Marsan have postulated that the long-latency recruiting responses evoked by stimulation of such nonspecific nuclei as the center median and ventralis anterior may travel this way on their polysynaptic route to the cortex. Some of the discrepancies in the results of stimulation of this system between the Montreal and Los Angeles groups may be due to the parameters of stimulating electrodes.

Three types of electrical activity in the cortex are recognized by the Moscow school. The classical propagated impulse, excitation by electrical spread and slow electrotonic potentials. The last is held to be the mechanism of the neuronal link set up in conditioned reflexes (i.e., between the cortical representation of the stimulus and the conditioned response of a neuronally remote cortical area). Rusinov has mimicked a conditioned reflex (lifting the paw to an auditory stimulus) in unconditioned rabbits by applying a minimal anodal current to the paw area of the motor cortex (a current too weak to elicit a movement by itself) and then giving the sound. This artificially induced conditioned reflex outlasted the period of electrical stimulation by 20 minutes. Since slow electrotonic potentials are closer to constant current than is the nerve impulse, Rusinov concludes that they possibly form the temporary electrical connection between cortical areas in physiologically established conditioned reflexes. This author, incidentally, considers electrical spread (e.g. extra-cellular current flow) to be the principal synchronizing mechanism for the alpha rhythm.

To this reviewer it would seem that the “temporary connections” sought for by the Pavlovian school are more likely to be formed in the brain stem than the cortex, for in the reticular formation much mingling and interaction of modalities is known to take place. In fact the experiments of Pavlov’s pupil, Doline (quoted in) in which he conditioned a dog to a specific frequency of a metronome and then found that particular frequency (but no other) of flash to be equally effective, would support this view. Bremer discusses this finding in his interesting essay on the physiology of memory. As a matter of fact it is noticeable that the Russian neurophysiologists restrict their thinking to cortical phenomena in their search for the mechanisms of Pavlovian reflexes and have not yet begun to go down the neuraxis. Whether or not one can condition an animal with appropriately placed lesions in the brain stem would be interesting to determine. If this has been attempted the results are not known to this writer. Since decorticate animals can be conditioned, the suggestion of participation by brain stem mechanisms seems not unreasonable.

Participation of olfaction in the ascending activating system has been
demonstrated. Arduini\textsuperscript{9} has shown that the sleep pattern of the cerebral cortex of a "cerveau isolé" preparation which we know from Bremer's classic work cannot be aroused by visual stimuli, can be effectively aroused by olfactory ones. Therefore, it would appear that the olfactory impulses join the ascending system at a level of the brain stem cephalad to the Bremer's midbrain transection. Adrian\textsuperscript{1} in reporting his search for spatial and temporal patterns signaling specific odors has discussed in some detail the possible mechanisms by which signals from sense organs are treated differently when we attend to them and when we do not. He suggests that a process of editing is the factor influenced by sleep and by anesthesia. That the maintenance of the waking state is not solely a function of the reticular system is held by Bremer,\textsuperscript{24, 25} who has demonstrated experimentally that weak electric shocks to any point on the cortex will awaken the "sleeping" cat with encéphale isolé and produce a waking type of EEG even after section of the corpus callosum.

Cortical and subcortical potentials in artificially induced sleep have been recorded by Hess,\textsuperscript{79} who has also given a discussion\textsuperscript{80} of the results of the 28 years of investigations that led his father to postulate a sleep center in the diencephalon. Among the syndromes in case reports for which specific EEG findings have been reported are agenesis of the corpus callosum,\textsuperscript{44} hysteria,\textsuperscript{8} tubercular meningitis,\textsuperscript{183} infectious mononucleosis,\textsuperscript{83} tetanus,\textsuperscript{164} hepatolenticular degeneration,\textsuperscript{174} atabrine psychosis,\textsuperscript{75} hyperostosis of the frontal bone\textsuperscript{183} and a case of ponto-mesencephalic hemorrhage.\textsuperscript{116} The EEG's in many cases of amblyopia associated with strabismus have been shown to be abnormal although flicker response was normal in the majority of cases.\textsuperscript{185, 149} Kluytskens and Titeca\textsuperscript{85} have utilized the blocking reaction of the EEG as an objective test for visual fields.

Some of the difficulties in interpretation of children's records have been discussed by Vizioli.\textsuperscript{189} In a two to nine year follow-up study of 61 child survivors of neonatal asphyxia, the degree of severity of EEG abnormalities has been found by d'Avignon\textsuperscript{5} to indicate the likely prognosis. A careful study of the EEG in asthmatic children without convulsive disorders has been made by Holmgren.\textsuperscript{83} Again the figure of 33 per cent abnormality in such children was found but whether this reflects cerebral changes secondary to asthmatic attacks or a more directly causal relationship remains problematic.

The significance of low voltage EEG's with no or little apparent alpha has been examined by Pine.\textsuperscript{184} Although many of these patients were referred as suspects for brain lesions, the final diagnosis in 65 per cent was psychiatric illness, the majority in this category being women with psychoneurotic tension states. The author rather cautiously agrees with the psy-
chologic correlations made by Saul and the Davises for this type of EEG. More enthusiastic support for this theory from far less well documented work is voiced by Palmer.\(^{146}\)

Further refinements in the radio transmission of EEG and other biologic potentials have been made,\(^ {147}\) but the EEGs illustrated in this paper are difficult to assess because the authors keep us in the dark as to the time scale and voltage calibrations used. If the latter were standardized for all examples shown, using the alpha activity shown as a gauge, our credulity is sometimes strained, for only a source outside the skull (i.e., muscle) could give such high amplitude. Such an instrument has however great potential use in many fields and the authors are to be congratulated on overcoming many of the technical obstacles intrinsic to radio transmission of such weak signals.

At the EEG Congress Symposium on technics comprehensive surveys of frequency analysis were given by Knott,\(^ {39}\) of correlation methods by Dawson\(^ {19}\) and of toposcopic display by Walter.\(^ {195}\) Further elaboration of the type of information that this method of display can yield was presented by Walter\(^ {196}\) at the C.I.O.M.S. Symposium. Other technical papers have described an improved write-out system,\(^ {156}\) and a new resonator integrator unit\(^ {134}\) for automatic frequency analyzers, and a device for recording skin resistance on an EEG instrument. Bradley\(^ {15}\) has described in detail a technic for chronic implantation of electrodes in cats; Delgado\(^ {66}\) and Bickford\(^ {12}\) technics for such procedures in man, and Spiegel\(^ {71}\) has described the apparatus he has developed for stereoecephalotomy in conscious patients. Bradley\(^ {16-18}\) has utilized his technic for a study of the effects of various drugs in unrestrained animals.

Every year the task of summarizing papers of importance to electroencephalographers becomes more formidable and a considerable degree of selection becomes inevitable. Gone are the days when the EEG was looked upon principally as a diagnostic test and when most of the papers were to be found in the neurologic journals. With the realization that electroencephalography is one of the most powerful tools in our exploration of brain mechanisms knowledge of much wider fields has become essential for the electroencephalographer and his reading needs to be correspondingly wider.

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A NOTE ON A CORRELATOR FOR ELECTROENCEPHALOGRAPHIC WORK

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A preliminary report on the analysis of electroencephalograms by correlation methods has previously been described in this Journal (Brazier and Casby 1952). The purpose of the present technical note is to make available a description of a new correlator largely modelled after the analogue correlator of the Imperial College of Science and Technology, London, the plans of which were designed by, and supplied to us through the generosity of Dr. E. C. Cherry, Mr. J. M. C. Dukes and Mr. J. N. Holmes of the Imperial College. These workers, who have kindly given permission for this note, have given valuable help and advice in the developmental program for the correlator, which has been constructed in cooperation with Professor W. A. Rosenblith, Director of the Laboratory of Communications Biophysics, and by the Research Laboratory of Electronics at the Massachusetts Institute of Technology. The full details of the original instrument will be published in the near future by the designers; only the operating principles of this instrument will be described here, with special reference to its applications to electroencephalographic work.

As explained in the previous communication, the purpose of the correlator is to compute the correlation function:

\[
\lim_{T \to \infty} \frac{1}{2T} \left\{ \int_{-T}^{+T} f(t) g(t + \tau) dt \right\}
\]

in which

(a) \( f(t) \) and \( g(t) \) are two stationary time series (i.e. functions whose statistical properties are independent of the particular interval of observation). In our case they are samples of EEG records.
(b) \( 2T \) is the duration of the interval of observation in time, in our case the length of the EEG sample.
(c) \( \tau \) is the shift in time of \( g(t) \) relative to \( f(t) \) during the computation process.
(d) \( \rho(\tau) \) is the correlation function, or the average for the interval of observation \( 2T \) of the product \( f(t) \) and \( g(t + \tau) \) i.e. \( g(t) \) displaced by time \( \tau \) with respect to \( f(t) \).
(e) \( \lim_{T \to \infty} \) indicates that the right side of the equation approaches the correlation function \( \rho(\tau) \) as a limit as the interval of observation \( 2T \) becomes infinite.

For a fixed interval of observation \( 2T \), the value of \( \rho(\tau) \) is computed for a large number of values of \( \tau \), e.g. 100. If \( f(t) \) and \( g(t) \) are identical (e.g. the same EEG) then \( \rho(\tau) \) is the autocorrelation function of \( f(t) \); otherwise, \( \rho(\tau) \) is the crosscorrelation function of \( f(t) \) and \( g(t) \). The autocorrelation functions of certain basic functions are of interest; the autocorrelation of a sine wave is a cosine wave, that of a square wave is a triangular wave.

The instrument previously used by us in correlation studies on EEGs was of the digital type (Singleton 1950), operating in principle in the following manner: the instantaneous value of \( f(t) \) is taken, converted to a number in the binary system (i.e. to the base 2) and stored electronically. At time \( \tau \) later, a similar process occurs for \( g(t) \), the two binary numbers thus obtained are multiplied in the binary system, and the resultant product stored. For each value of the delay \( \tau \) a large number (e.g. 12,000) of such products are obtained, and added together (integrated) giving the value of the correlation function for the particular value of the delay. The term digital arises from the fact that the instantaneous values of the functions are converted to numbers (binary digits) in the binary system, and thus are quantized, or reduced to discrete values, in contrast to the continuum of values of the original functions.

In contrast, the present instrument is of the analogue type; there is no quantization process, and the numerical value of the results of the several processes of multiplication and integration are everywhere analogous to the values of the original functions. The analogue correlator is considerably simpler in circuit design, and is more compact than is the digital instrument.

Figure 1 indicates the principle of operation of the analogue correlator. After temporal displacement of the two signals by the delay mechanism, the two functions \( f(t) \) and \( g(t + \tau) \) are multiplied, the product integrated, and the result indicated on the plotter.

(1) DELAY MECHANISM

The method of obtaining the delay that has been used is that of the magnetic drum delay system at the
Acoustics Laboratory, Massachusetts Institute of Technology, kindly made available for our use by Mr. K. Goff who designed the instrument (1953). This instrument consists essentially of a revolving aluminum drum on the surface of which is a magnetic material similar to that of magnetic recording tape. The drum is constructed so that one signal is recorded and played back at a fixed, short interval of time later, and the other signal is recorded and played back at a variable interval later, depending on the spacing about the periphery of the drum of the second set of record-playback heads, giving a relative delay between channels of from —15 to ±190 msec. The input to the magnetic delay system is thus \( f(t) \) and \( g(t) \); the output is \( f(t) \) and \( g(t + \tau) \).

(2) MULTIPLIER

Utilizing the fact that

\[
\frac{f \times g}{4} = \frac{(f + g)^2 - (f - g)^2}{4}
\]

the multiplier consists of circuits which in turn obtain sums and differences of \( f(t) \) and \( g(t + \tau) \), square the sums and differences, eliminate unwanted components by subtraction, giving finally the product \( f(t) \times g(t + \tau) \).

![Fig. 1](image)

Block diagram of correlator.

(Proportionality constants omitted.)

(a) Adder-Subtractor. Use is made of the fact that if an AC signal be applied at the grid of a triode whose plate and cathode resistors are equal in value, the resultant AC voltages at the plate and cathode are opposite in phase (i.e. one is the negative of the other) but equal in amplitude to each other.

![Fig. 2](image)

Simplified schematics of multiplier components.

(Proportionality constants omitted.)
and to the input signal at the grid. The tube thus acts as a phase inverter (fig. 2A). Further, if the cathode of one such triode be connected to the cathode of a similar triode through a center-tapped high resistance, half of the sums of the two AC grid voltages appears at the center tap. Alternatively, at the center tap of a high resistance, joining the plate of one tube with the cathode of the other tube, appears half of the difference of the AC voltages applied at the two grids (since the AC plate voltage of the first tube is the negative of the impressed grid voltage). Figure 2B indicates how $(f + g)$ and $- (f - g)$ to accompany $(f^2 + 2fg + g^2)$ and $-(f - g)$ to accompany $(f^2 - 2fg + g^2)$. (In practice, $-(f + g)$ and $-(f - g)$ are obtained from additional combinations of plate and cathode voltages of the adder-subtractor.) The schematic for one of the two identical squarers is indicated in figure 2C, from which the phase inverter has been omitted. The manner in which the AC plate voltages of the two pentodes are combined to give the square of the input voltage at the grids is indicated in figure 3 for the case in which $f$ and $g$ are identical sine waves.

$(f + g)$ are thus obtained. (For simplicity, proportionality constants have been omitted in figures 1 and 2, and in the subsequent discussion.)

(b) Squarer. The squarer takes advantage of the fact that, over a limited range of operation, the AC plate voltage of certain vacuum tubes (in this instance 6B8) is very nearly proportional to the square of the AC voltage applied at the control grid. Further, if opposite phased signals of equal amplitude be applied at the control grids of two such tubes operated in push-pull fashion (back to back) at very low no-signal plate currents (i.e. biased almost to cut off) the combined plate voltages will be proportional to the square of the impressed signal for both positive and negative values of the signal. Two such squarers are used in the multiplier. Phase inverters obtain $-(f + g)$ to accompany $(f + g)$ in forming $(f^2 + 2fg + g^2)$ and $-(f - g)$ to accompany $(f^2 - 2fg + g^2)$. (In practice, $-(f + g)$ and $-(f - g)$ are obtained from additional combinations of plate and cathode voltages of the adder-subtractor.) The schematic for one of the two identical squarers is indicated in figure 2C, from which the phase inverter has been omitted. The manner in which the AC plate voltages of the two pentodes are combined to give the square of the input voltage at the grids is indicated in figure 3 for the case in which $f$ and $g$ are identical sine waves. The frequency of the output in this instance

$$(f^2 + 2fg + g^2)$$

is double that of the input, as is expected from the trigometric identity

$$\cos^2 x = \frac{1 - \cos 2x}{2}$$

(c) Subtractor. Operating in the same manner as the subtractor in part (a) above, the outputs of the two squarers are combined to give a result that is proportional to the product of $f$ and $g$:

$$f^2 + 2fg + g^2$$

$$-(f^2 - 2fg + g^2)$$

$$= 4fg$$

(3) INTEGRATOR

For the integrator, a simple RC circuit (fig. 4a), whose output voltage $E_3$ is proportional to the integral of the input voltage $E_1$ (in our case the product voltage $f \times g$) provided $E_1$ remains much larger than $E_3$ during the time of integration, is modified

Fig. 3

Operation of squarer for case in which $f$ and $g$ are identical sine waves.
by adding a stage of amplification (fig. 4b). The time constant (RC product) is thereby increased by a factor equal to the gain of the amplifier, making possible longer periods of integration, yet maintaining the condition that $E_1$ remain large compared to $E_2$ (fig. 4a).

For each value of $\tau$, the integrator is in operation for the time $2T$, and is turned off for a short time subsequently, during which the integrating condenser $C$ (fig. 4b) is discharged. The timer may operate autonomously (for instance in the autocorrelation of a sine wave from an oscillator) or may be synchronized with the source of the signals, as described below.

A standard Esterline-Angus graphic milliammeter with a full scale reading of one milliamper is used to record the output of the integrator. Figure 5A is a typical record, the autocorrelation of a 100 cycle sine wave, the integration time $2T$ being 5 sec. A DC component has been added in the integrator in order to obtain unidirectional excursions of the pen, and the correlogram is the envelope of the successive pen excursions. The value of the delay $\tau$ increases from left to right. The effect of the added DC component, with no input signal, appears in the final portion of figure 5A. Similarly, figure 5B is the autocorrelation of a 150 c/sec. square wave, with the same integration period.

In pilot experiments, two channels of EEG were recorded on a two-channel frequency-modulated magnetic tape recorder (Green 1950). During analysis, a continuous loop of tape was made and played back repeatedly at 5 times the recording speed, a new value of the delay setting on the magnetic drum being used for each new revolution of the tape. Since the playback EEG frequencies (5-500 c/sec.) could not be handled directly by the magnetic drum (frequency range 100-10,000 c/sec.), the FM carrier (5000 c/sec.) was delayed on the drum before demodulation to give
the playback EEG signals. The correlator timer was synchronized with the passage through the playback apparatus of a short length of blank tape in the loop of tape.

In the previous report, the phase relationships between right and left temporal rhythms during problem solving were studied by crosscorrelation (Brazier and Casby 1952). The value of correlation methods in the detection of weak signals in the presence of noise was indicated (Lee, Cheatham and Wiesner 1950). Thus in electroencephalography, the presence of periodic components (alpha, delta waves) may be detected in the presence of background aperiodic EEG potentials by autocorrelation. Similarly, the detection of components common to two EEGs is possible by crosscorrelation. Crosscorrelation of stimulus and the EEG of photically or auditorily stimulated patients enables the detection of resultant evoked responses and rhythmic oscillations. Dawson (1951) has used a somewhat similar principle for detection of responses evoked by peripheral nerve stimulation. Further, information concerning the direction of causality (or direction of flow of information) may be gained from correlation analysis of normal or evoked EEGs, employing principles of prediction theory developed by Prof. Norbert Wiener (1950). Essentially, the increase in mathematical predictability of one EEG when one knows both its own past and that of a second related EEG, as compared with the predictability of the first EEG when only its own past is known, is a measure of the causal influence exerted by the second EEG on the first. Auto- and crosscorrelation functions of the EEGs in question form the data for the mathematical computation involved.

This technical note is intended as a description of instrumentation only. A later report will cover further studies along the several lines of investigation indicated above, including the application of this method to some problems in clinical neurology.

We would like to thank Dr. E. C. Cherry, Mr. J. M. C. Dukes and Mr. J. N. Holmes of the Imperial College of Science, and Dr. W. A. Rosenblith and Mr. K. Goff of the Massachusetts Institute of Technology for their help in the development of this method for application to electroencephalography.

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I was attracted to this work and to a program of animal research in connection with it, by some paradoxes that are found in the EEG. Most of these are familiar to you. Probably everyone knows about this effect.


Figure 9 shows a patient emerging from surgical anesthesia with pentothal. When a patient is in a light state of anesthesia, a sensory stimulus of any kind will produce a response in the EEG, although the observer is unable to detect any behavioral response in the patient. There is no noticeable change, for example, in respiratory rate or depth, and no
movement that is visible. The patient has no memory or recall of this event when he eventually returns to a responsive state. This phenomenon is not peculiar to barbiturate anesthesia.

This is very light pentothal anesthesia, as anyone with experience in electro-encephalography can tell from the baseline activity. One does not obtain the responses in deep anesthesia. You will notice that the response is localized to an area that is prerolandic, and as far as one can guess from the outside of the skull and scalp of the human being, is probably area 6 in Brodmann's numbering.

_Fremont-Smith:_ Would it occur if there were no anesthesia?

_Brazier:_ It can be obtained in sleep without waking the patient, but not in the waking state. We can sometimes get an off-response as well.

![Figure 10. On and off responses to an auditory stimulus in a patient under scopolamine and morphine. No observable behavioral response.](image)

In Figure 10 we see the response to a whistle that was left blowing. It is a fearsome tugboat whistle. In this case it was left on for a period of five seconds, and we obtained an off response as well. These are all responses to auditory stimuli, which are the most effective. However, to show you that this is not sense-specific, Figure 11 shows the response under scopolamine and morphine to the onset of a train of light flashes which were signaled with a photoelectric cell on the bottom line of the record.

Figure 12 shows the response in natural sleep to a clap of the hand.
The tugboat whistle, of course, would wake a sleeper. The individual did not recall having heard the clap.

Aring: Is this invariable?

Brazier: It is, at a given level of sleep. At first sight this appears to be a paradoxical thing. In common parlance people speak about anesthesia preventing afferent impulses reaching the cortex and so forth, yet here is some apparent evidence that they do reach the cortex.

Magoun: Is this what is referred to as a k complex?

Brazier: Yes, the one in sleep was found by Davis and Davis (1) in 1939, and named by them. I am unaware that they worked on it in anesthesia, but they well may have because it seems to me to suggest itself as something to investigate.

The Davises did not localize the k complex exactly. I believe they found it very clearly near the vertex. It has been regarded by many as a generalized response, but as we see, if we use an adequate linkage of electrodes, we obtain some information about its location. We find that it appears, as I say, in what one would guess through the skull and scalp to be something like area 6.

Here, we introduce another oddity. I showed you a response to an auditory stimulus. Yet we were not obtaining the response from the auditory cortex. I showed you a response light, and we were not getting it from the visual cortex. Sense modality seems to have been lost. The
ability to find these responses in anesthesia, as well as in sleep, made it possible to investigate them on a more neurophysiological basis in animals, so this is what led to the particular work that I am doing now.

Meerloo: You said there was no conscious recall. Of course, the whole problem of unconscious recall becomes more and more important.

Brazier: Of course. This is a very important point, and I would guess that all this work has some very direct bearing on the problem of memory traces left by sensory impulses, and evidence for their arrival in the brain even when we are not "conscious" of having received them.

Meerloo: This has several implications. In the first place, when brain washing was introduced as a method of political indoctrination, one of the observations was that people under stress and in sleep were still able to perceive the things they were supposed to know, and to write them down later. We also know, for instance, that special nervous types are
able to remember many more things later on when the stimuli are given in hypnotic sleep. Then they can remember verses or poems which they were not able to recall so easily without hypnosis. We find that this form of recall, after sleep or partial hypnosis, is sometimes better than without it, as though the memory improves.

A related problem is the whole question of how deep a general anesthesia has to be, because we find, in analytical patients sometimes, all kinds of reports about the recall of impressions during narcosis. What comes out is completely distorted; patients change those impressions in relation to their former emotions. But there is recall and sometimes a rather dramatic recall, even to a report of what the surgeons have been saying to each other during the narcosis.

**Brazier:** I think that is an important point. Now, I shall talk about EEG changes due to barbiturates.

Figure 13 gives a brief summary of the changes that occur in the occipital regions. You may wish to give different names to these stages, and not call the term second line “anesthesia” at all. You may not even wish to call it “narcosis.” It is, however, a stage which the subject goes through on the way to becoming what the anesthetist calls “uncon-

![Figure 13. Changes in the EEG of a human subject at deepening levels of pentothal narcosis. Lower right: horizontal line represents duration of one second; vertical line the deflection for 100 µV. Reprinted, by permission, from Brazier, M. A. B.: *The Electrical Activity of the Nervous System*. Revised and reprinted edition. London, Sir Isaac Pitman, and New York, Macmillan Co., 1953.](image-url)
scious." If pentothal is given very slowly, as in this case, we can follow these stages quite carefully and we find that there is a very abrupt change at the point where the subject loses consciousness (in this instance I am using the word in the surgeon's or anesthetist's terms). On the way into anesthesia the onset of slow wave activity coincides rather remarkably with the first moment of unresponsiveness on the part of the patient.

In the usual anesthesia procedures for surgery, the drug is given so quickly that the stage of fast EEG activity is just rushed through. In a subject emerging from anesthesia, the stages are not nearly so clearly marked, the EEG returns to this fast activity stage before the patient becomes responsive, so that the two "sides" do not behave the same way. The last stage, which I have labeled here, "Deep Anesthesia," is the stage at which surgery is done and where, in the experimental situation, we first begin to obtain some respiratory and blood pressure changes. In laboratory work we are careful to keep the subject from going into deep anesthesia where there are long periods of apparent electrical silence, and what are popularly called "barbiturate bursts" in between. This is still a reversible stage and one that may be reached by oral ingestion of barbiturates. In the emergency ward of a hospital, it is a stage in which we find would-be suicides.

Rapoport: Are those bursts correlated with any observable events, or do they seemingly come at random?

Brazier: They are seemingly at random, unless you mean that word in its precise sense.

Rapoport: How frequent are they in deep anesthesia?

Brazier: They occur more often than every minute. That horizontal line to the right and at the bottom in Figure 13 is one second, and we can see that the duration of apparent electrical silence is perhaps four seconds long in this case. The usual average length of the silence period is about five seconds. The bursts usually last about ten seconds, or a little more, perhaps.

Hoagland: The rapid frequency in the second trace is of interest, as well as the slow frequency in the third trace, reflecting increasing depths of anesthesia. It has been demonstrated that brain tissue shows an increased uptake of oxygen with small amounts of barbiturate, followed by a marked decrease as more barbiturate is added to the Warburg vessels. This is interesting to me because of the speeding up of the EEG frequency, and its ultimate slowing with increasing depth of barbiturate anesthesia. One sees something like that also with cyanide effects, in which there is first an increase in the respiration of tissue with small doses, and then a slowing of the respiration with added cyanide.

Brazier: I think we have some evidence that the fast activity in the
second line of Figure 13, to which Dr. Hoagland referred, is the activity of cells in the cortical layers, and there is some evidence from the work of others that the activity in the bottom line is not cortical in origin. I have no direct evidence here to present to you about the last two lines, but I can give you some supportive evidence for my statement about the fast activity. Again, I would caution against speaking of a frequency parameter alone, for these phenomena probably come from different parts of the brain.

Nurnberger: Isn't it reported by some (2) that the picture we see in the last line, with deep anesthesia, is obtainable from completely isolated cortex?

EDITOR'S NOTE: Dr. Nurnberger would like to add the following “afterthought” to his remarks at the conference:

In subsequent conversation with Dr. C. E. Henry concerning this problem, he stated that many of the operations which were referred to were done under local anesthesia without barbiturates. Dr. Henry mentioned, too, that suppression-burst activity was still present in chronic cases reoperated many months later, where repeat recordings were made from cortex isolated at the original operation.

Brazier: Yes, I think so. This was a subject, actually, of a friendly argument between Dr. Charles Henry and myself, because he had recorded very much that type of tracing that you see in the fourth line of Figure 13, from undercut cortex (2) in human beings. At that time I was bothered because in the published cases the head had been opened under pentothal, although the patient had emerged to a responsive stage by the time his recordings were made. Again the work with implanted electrodes in human beings gives a report on how long the pentothal effects last. The electrographical effect of barbiturate lasts for days, even when the patient is up and about seeing visitors, having meals, and so forth. I have records showing persistence of pentothal effect for 48 hours, and Dr. Hannibal Hamlin showed me one case that lasted for three days.

Nurnberger: Isn't it so that in the isolated cortex we observe what might be called a pentothal effect?

Brazier: Yes, if you are prepared to say that because the pen moves in a certain way under two separate conditions, the cause has been the same. This is, of course, a continuing and perplexing difficulty for all electroencephalographers; we are always describing pen movements. Because they look alike, are they necessarily causally related?

Kornetsky: What kind of subjects were these?

Brazier: The responses on Figure 13 were of a normal person.
Kornetsky: Were they implanted electrodes?

Brazier: No; they were scalp electrodes. We have a series of psychoneurotic patients and of normal control volunteers studied in this way. The implanted electrodes are two different series. One is a group of schizophrenic patients in whom the electrodes were implanted at the State Hospital for Mental Diseases, Howard, Rhode Island, in some work done by Drs. J. M. R. Delgado, H. Hamlin and W. P. Chapman. The electrodes were implanted prior to frontal leucotomy. They were inserted through the trephine opening that was to be used one week later for the leucotomy. The other patients that I am currently studying with a group of workers at the Boston Psychopathic Hospital (3) are a series of psychomotor epileptics with aggressive, assaultive behavior of such violence during their seizures that they have had to be institutionalized for most of their lives. These are patients in whom electrodes have been implanted in the amygdaloid region prior to coagulation of the amygdaloid nuclei, planned as a therapeutic attempt to avoid more extensive temporal lobe surgery.

Kornetsky: Do you obtain differential drug effects from these various types of people?

Brazier: I think our series would not be large enough to make a meaningful statement about that yet, but it is something we are looking out for.

Rapoport: Do other drugs, besides the barbiturates, give a somewhat similar picture?

Brazier: From my rather limited experience, I should say that this is fairly specific to the barbiturate drugs. I have had some experience with chloral hydrate, which is a very different story. Of course many other workers have had experience with various drugs, but this particular effect is a barbiturate effect. There is even some slight variation between, let us say, sodium amytal and sodium seconal.

Rapoport: However, this is typical for barbiturate?

Brazier: Yes, very typical indeed. I now have grave doubt whether, during a brain operation, a patient is ever free of the electrical signs of a barbiturate, if one has been used while the skull was being opened.

Ginker: It is like the definition of anxiety. We have been repeating the work of Shagass (4) and our findings do not agree with his. We discovered that he was not talking about anxiety, anyway, but about tension states.

Pfeiffer: With chronic barbiturate effect, can you differentiate between barbiturate effect and convulsive phenomena which are known to occur in those addicted to barbiturates?
Brazier: I have not worked on any withdrawal symptoms, but from reading other people's work I think you certainly could.

Pfeiffer: I should expect, even in acute dosage such as this, that you would have some sort of rebound phenomenon.

Meerloo: We clinicians are very much interested in the rebound phenomena after normal narcosis, when we often see peculiar symptoms at a certain level of detoxication. These may be compared with those after prolonged narcosis with barbiturates or morphine. There is a danger period which sets in at the moment the patient comes out of narcosis, even after a small operation and light narcosis. In 1952, at Columbia University Medical Center, an anesthetist counted six acute deaths in a large number of patients; these incidents occurred not during the narcosis but after the patient was returned to his bed. The usual explanation is death from acute heart failure, but the suspicion was that the patient had gone through something, some physical change or mental upheaval six or eight hours afterward. This has yet to be studied. What can we register of this in the EEG? Of course, consciousness gradually comes back and all kinds of stimuli from outside begin to come through. But we have never been warned to check those stimuli from outside during the period of narcosis.

Seevers: You have evidence that there is drug action detectable in terms of effects on the evoked responses or potentials for 48 hours after a single acute dose of pentothal. Is that correct?

Brazier: Yes, but there is fairly long duration of administration of pentothal throughout this brain operation procedure; in fact, during the procedure of implanting the electrodes.

Seevers: How does the chronic picture get into this?

Brazier: I have no information on chronic barbiturate addiction. I have never worked in that field, but I know others have, of course.

Meerloo: You may find traces of barbiturates a week after one injection of a normal dose. Chemically, sometimes seven or eight days later, traces of barbiturates (i.e., somniphen) (5, 6) are found.

Cantoni: Is this delayed or prolonged effect of barbiturates related to the depth of the anesthesia? Can you distinguish this type of response, or is it similar to that which you see with the small dose of pentothal? Presumably, 48 hours after the barbiturate is given, the patient is up and about, and there can remain only a very small amount, if any, of the drug. Therefore, I am asking whether the change which you see in the EEG is related to the depth of anesthesia, to the operating procedure, or is it directly referable to the pentothal?

Brazier: In order to answer you, I would have to have observations with implanted electrodes after operations done at different levels of
anesthesia, and that I do not have. The procedure for anesthesia, in the case of these implanted electrodes, is what an abdominal surgeon would, I expect, call light anesthesia. As you know, all anesthesia for surgery on the head is usually held at a rather light level. All Dr. Hamlin's patients were done at this one level, which was held steady by an intravenous drip of pentothal, with oxygen and nitrous oxide, and adjusted just to keep the patient adequately anesthetized. I have observations with implanted electrodes after only this one type of anesthetic procedure. I cannot give you experimental material which would answer your question.

Callaway: We did some studies at Worcester Foundation for Experimental Biology on the effect of intensive electric shock (7), and found that these patients go through a slow-wave period and into a flattened-out period. One sees this much more clearly with barbiturates. Roth (8), in England, did some studies using much less intensive electric shock, and observed that small doses of barbiturate could produce the same effects as those which occurred with intensive electric shock.

Fremont-Smith: A sort of a summation.

Callaway: More or less, yes.

Seevers: You mean summation in the sense of a residual drug being present?

Callaway: No; some interaction between the effect of electrical shock and the barbiturate on the cortex.

Brazier: Again I think I should issue a word of warning against saying that because the pen movements look alike they have something in common as a cause.

Seevers: Do you have any information as to the effects of a second subliminal dose of barbiturate at the 48-hour period?

Brazier: No, I have not. But if you like I shall take up the question of repeated anesthetic doses, such as those used in procedures for facial repairs and plastic surgery, where the same patient comes again and again. These are very often done under pentothal.

Gerard: Dr. Brazier, you suggested that the spindles at the bottom were not cortical. The point was made that they appeared in the undercut cortex. You said that barbiturate continues to act after the cortex is undercut. It seems to me this has no bearing on that.

Brazier: In the early stage of this work on the undercut cortex, I believe I am right in saying that the cortex was found to be neuronally isolated but not insulated. It was not certain whether it was completely electrically insulated by the rubber dam so that the electrical field of distant events could be recorded from it. The technique was later perfected, I believe.
Gerard: In other words, you are challenging it on the methodological grounds, and simply saying that the starting point is working below, not because it lasts so long but . . .

Brazier: Oh, no, these are two unrelated things.

Seevers: You have evidence of electrical effects when an individual is for all practical purposes a normal individual?

Brazier: Apparently there is some chemical evidence for it too.

Meerloo: It is found in the urine even six or seven days later.

Fremont-Smith: Is that against your experience, Dr. Seevers?

Seevers: I do not have any evidence for or against it.

Meerloo: I have reported on the action of barbiturates in various journals (5, 9, 10, 11).

Fremont-Smith: Do you have any contrary evidence to your finding that it appears in the urine six or seven days later?

Meerloo: It was not the same in all patients.

Fremont-Smith: Do you know any other investigator who has subsequently tried to repeat your work and failed to find the barbiturates?

Meerloo: It was repeated by other research people (12, 13, 14, 15) with the same kind of chemical methods, and it was later confirmed.

Marrazzi: Which barbiturate was that, Dr. Meerloo?

Meerloo: Phenobarbital.

Seevers: That's a different story. We are talking about pentothal, as I understand it.

Fremont-Smith: We were talking about barbiturates, I think it is fair to say, and then we did talk about pentothal within the broad category, and Dr. Meerloo talked about barbiturates.

Grinker: He is talking about introduction by mouth, not intravenously.

Abramson: But the textbooks all say that seconal is oxidized in about two or three hours.

Seevers: It is not that rapid. You might find some phenobarbital or barbital. Neither one is broken down completely; the latter not all. They probably stay in the body a long time. But I doubt very seriously that you would find pentothal after six days. You might find a very minimal trace of seconal but I doubt if you would find any after six days.

Fremont-Smith: Did you use pentothal, Dr. Meerloo?

Meerloo: No, I was speaking of phenobarbital.

Seevers: When one is talking about barbiturates, one has to specify. There are wide differences between them.

Brazier: I have been speaking only of pentothal.
Fremont-Smith: I do not think there is conflict here, because we have been talking about different things. Dr. Meerloo was speaking of phenobarbital, and Dr. Seevers was talking about pentothal. However, the general topic is barbiturates.

Meerloo: At one time there was a theory that when special chemical side chains were introduced to the original barbiturate compound, the new barbiturate would leave the body sooner. We found at that time that there was a large variation between individuals in the amount of time that the body needed to evacuate the same barbiturates. I could describe withdrawal symptoms in a case of addiction after a change from one barbiturate to another.

Kornetsky: Then, why do withdrawal signs appear two or more days after a person discontinues chronic barbiturate use, if the barbiturates are still active in the body?

Meerloo: That is a different question. There is also narcotic action. At the moment the level of the narcosis is lowered, different kinds of rebound symptoms will be provoked. I think the whole question of withdrawal symptoms depends on the speed of withdrawal and the lowering of the concentration of the narcotic, plus other unknown factors.

Kornetsky: Were chronic patients used in these experiments?

Meerloo: No, the acutely ill.

Trumbull: May I ask two more questions on these variables: first, what were the levels of anesthesia? Second, was the apparent displacement of the afferent responses or the traces to area 6 consistent with the different levels and various drugs?

Brazier: These responses are obtained with various drugs, but what do you mean exactly by "different levels"? You do not obtain the responses at a surgical level of anesthesia.

Trumbull: The response is lost at the lower level.

Brazier: In my experience, if the response is present at all it is in area 6, but it is lost at deep levels. Does that answer your question?

Trumbull: It still does not answer the major question, as to what happens or why it is replaced.

Brazier: We shall perhaps come back to this when we discuss the animal work. Now, I should like to ask the pharmacologists present this question: The earlier techniques for detecting barbiturates in the urine or in the blood did not differentiate between some of the breakdown products and the original drug. But is it not true that the newer techniques, using spectrophotometry after extraction with nonpolar solvent petroleum ether, do make this differentiation?
Seevers: They still do not entirely, because most of them are based on spectrophotometric methods and there is no absolute chemical identity.

Brazier: As electro-encephalographers, we have to keep our minds open to the possibility that the breakdown products give us this same electrical sign.

Seevers: That is correct, and we cannot say that it does not occur. We do not have evidence that it does, either.

Fremont-Smith: In other words, what may be detected in the urine may not be the original molecule at all but only a part of it?

Seevers: We just do not know as yet.

Cantoni: Do I understand correctly that you have observed these only in patients with implanted electrodes? Do you have data on the delayed 48-hour responses in patients who are subjected to anesthesia but who have not had a brain operation at the same time?

Brazier: We have no data as yet. This was an unlooked for finding that turned up.

Marrazzi: They were prelobotomy patients, were they not? Would the kind of patients you had influence the situation at all?

Brazier: The patients at the State Hospital for Mental Diseases in Rhode Island were all preleucotomy patients. None of the patients in the Boston Psychopathic series was a psychotic.

Seevers: I am not raising this question in an attempt to discount your results, but it is a fact that if we give animals or man repeated doses of pentothal, we can, at the time these individuals are in a normal state, still find pentothal in their plasma. So there is a certain possibility of having residual pentothal there. I wonder whether by following electrical events, you have a means of detecting that which cannot be observed by any other methods. I think it is a very interesting observation that you have made. We know that if we give a dog pentothal every eight hours, after a few hours he gets back on his feet, and appears to be a reasonably normal dog. However, when you give him another dose, he still has a plasma level of the drug.

Brazier: This brings us, then, to the subject of repetitive doses. The particular individual whose results I shall show you in Figure 14 was being studied in relation to another line of research, one in which we were considering what the mechanism could be behind this fast activity. Quastel (16) reported on an enzyme step in the glucose cycle being inhibited by the barbiturate. We were interested in his demonstration that this particular enzyme step was not vulnerable if the substrate were succinate instead of glucose. Perhaps you remember how many claims (17, 18, 19) were reported in the literature that people could be revived
from anesthesia or from barbiturate poisoning with succinate, so we set up some experiments (20) on human beings to see whether succinate did in fact protect these people if it were injected into the vein while pentothal was being given.

At first we thought we had confirmed Barrett's claims (18, 19) that the length of time a patient was unconscious through any given dose of barbiturate anesthesia could be shortened by giving him succinate, or that he could be kept at a lighter level of anesthesia from an equivalent dose by giving him succinate. We were careful to try the pentothal
alone first to see whether the normal subjects reacted to it before we
gave them the two drugs combined. However, when we reversed the
experiment, giving the combined drugs the first time and pentothal alone
the second time, we found, as had been observed before in animals, that
there was an increasing acclimatization to repeated doses of pentothal.

Figure 14 shows the findings in one individual. On the right are the
anesthetist's estimations (from signs like corneal reflexes, eyeball roll­
ing, and so forth) of the various stages of anesthesia. The subject was
given identical doses at the same rate of injection, which was a rather
slow one: total dosage 0.7 gm. in three-and-a-half minutes. As we see,
the first time that was given he was in the first plane of the third stage
of anesthesia (marked in black on the slide) for a long time. The second
time he was given it after an interval of three days, the third stage was
shorter, and it became less and less with succeeding doses. Then, on the
17th day, the succinate was administered before, during, and after the
pentothal. The rate of injection of the succinate is sketched in the
figure. If we had done that experiment on the second trial and stopped
there, we would have said that succinate had a tremendous effect in
cutting down the length of time that this particular dosage rendered the
subject unconscious. In the figure are two little arrows at each level.
The thin arrows mark the point at which the fast activity came into this
subject's brain wave, and the thick arrows the point at which the slow
delta rhythm came into the brain wave. We notice that those two arrows
get nearer and nearer toward the lower part of the figure, indicating that
the duration of the first stage is also shortened by repetition. This made
us very skeptical of the kind of experiment we had been doing, in which
we had been comparing a dose of pentothal accompanied by saline, or
in some cases a sodium lactate injection, with one combined with a
sodium succinate injection.

This acclimatization to the drug is therefore of considerable im­
portance in surgical procedures, such as plastic surgery, where the
patient comes back again and again for repair.

Fremont-Smith: How long an interval of rest is needed before the
acclimatization is lost?

Brazier: I do not know that.

Fremont-Smith: It is conceivable that this could be accumulated
material in the body.

Brazier: I think that is possible. In Figure 14 the EEG changes are
closely related to the stage of anesthesia when going into anesthesia,
but all the stages are less well marked during recovery from anesthesia.
For example, on the 15th day, on emerging from anesthesia, the man
got down and up several times between the first and second stages, and
on the 18th day that is also shown. There is far more variability in an individual coming out of anesthesia, in my experience, than going into it, which perhaps is not surprising.

Callaway: From what I know about morphine, addicts require more and more of the drug to obtain the same effect as they become tolerant, whereas your patients require less and less of the anesthetic to lose consciousness, although then they come out faster.

Seevers: On the basis of Brodie's studies (21), which I think have been adequately confirmed, the explanation of the fat depot concept is that we are forced, every time we inject pentothal, to saturate fat depots before a plasma concentration is built up high enough to affect the brain, which is the antithesis of this phenomenon.

Have you attempted to reproduce those interesting experiments that started out with Lamson (22) in which an individual, who has apparently recovered from pentothal, can be thrown back into what appears to be an anesthesia state by glucose? There is considerable evidence on this, but what the mechanism is, we do not know.

Brazier: No, I have not done those experiments, but I know the work.

Meerloo: Patients are much more easily hypnotized after that anesthesia, and the EEG shows the same kind of curve when they are brought into deep hypnosis. It is much easier to repeat this experiment under hypnosis, even though the patient was not easily hypnotizable before.

Brazier: When I was discussing the last line of Figure 13 I drew attention to the electrical silence and the bursts. We do find that kind of tracing from the oral ingestion of phenobarbital. Figure 15 is the case of a patient brought into the emergency ward in deep coma. It was a suicidal attempt from which she recovered, and I think we can see clearly the equivalent of the bottom line of Figure 13, the long periods of electrical silence, and the bursts. She recovered and five days later her alpha rhythm had returned. I think this makes the point that orally administered barbiturate, and a barbiturate other than pentothal, can produce that same electrical pattern.

Reynolds: With respect to the specificity of response to barbiturate, it resembles what I have seen in the case of anoxia. Is it quite like it or not?

Brazier: I have done considerable work on hypoxia but I have never gone to the level at which this would happen.

Reynolds: You mean the burst effect? I think I have seen that in dogs.

Magoun: One sees bursts in EEG synchronization in animals at a stage of anoxia. That looks very like this.

Hoagland: Himwich, Campbell and I (23), killed dogs by giving them overdoses of nembutal, and obtained an EEG pattern that was like what you would expect with increasing anoxia; there was complete
Electrical Activity of the Brain

**Figure 15.** Barbiturate intoxication with later recovery. Upper record shows bursts of electrical potentials with intermittent periods of electrical silence in a patient who had taken an oral overdose of phenobarbital. Lower record taken five days later.

flattening of the record. We were interested in relative changes in electrical activity of hypothalamus and cortex as determined with implanted leads. We found that the hypothalamic response lasted much longer and was much less vulnerable to the advancing anesthesia. We also used large doses of insulin, killed the dogs in hypoglycemia, and found a similar ability of the hypothalamus to keep on producing waves after the cortex had failed entirely.
Figure 16. Bipolar recordings from seven points of an implanted needle electrode (Delgado technique) in the frontal lobe of a schizophrenic patient prior to therapeutic lobotomy. The traces represent serial bipolar linkages from the most superficial recording points in the first trace down to the deepest pair in the lowest trace. Vertical lines represent 1/5 second. Inset on right is an enlargement of the framed section to illustrate reversal of fact activity at the second recording point from the surface. Photograph by courtesy of H. Hamlin, W. Chapman and J. Delgado. Reprinted, by permission, from Brazier, M. A. B.: The action of anesthetics on the nervous system. Brain Mechanisms and Consciousness. Oxford, Blackwell Scientific Publications, Ltd., and Springfield, Ill., Charles C. Thomas, 1954.

Brazier: I might show you the type of thing recorded with the implanted electrodes in the work at the Howard Hospital by Drs. Delgado, Hamlin and Chapman (24). Figure 16 is a schematic representation of the needle electrode, designed by Dr. Delgado, that we see on the left. These electrodes are made new for every patient, and the recording points are each 2 mm. of exposure, with say 2 mm. of insulation between adjacent points. In some cases, there have been 4 mm. between the two, but in any case the whole needle is very much longer than the cortical layer, and especially than the cortical layer in the frontal regions, which is not very thick.
Rapoport: How far apart are the electrodes here?
Brazier: In this particular case they were 4 mm. apart, but I should like to say that we cannot make any meaningful statements about exact depth because we have no way of knowing, in this series, whether our electrode shaft went into the cortical layer at a 90° angle or at a slant. We just have not got this information on the subjects in this series.
Rapoport: The asymmetry of the two pictures seems to indicate that what you are measuring is the potential of the region.
Brazier: My interpretation would be that with the exception of the first channel there is a falling gradient from the surface to the depth when recordings are made bipolar between the serial electrodes. With the exception of the two top channels, I should think that this is probably just the field that is being picked up in the white matter.
This figure is meant to demonstrate a reversal in the two channels, that is, at the second exposure point from the top of the needle. I think this gives supportive evidence for saying that the fast activity was coming from the areas tapped by this electrode, i.e., point six.
Rapoport: What impresses me is the large size of that area. You say they are 4 mm. apart?
Brazier: You would have only electrode number six in that area, would you not? Perhaps I do not understand your point.
Gerard: He is taking the two different electrodes rather than just the one.
Rapoport: I am thinking of the picture on the right.
Brazier: On the right we see an enlargement of the squared-off section on the left.
Rapoport: They are mirror images. One is a positive and one is a negative. Therefore, what is being measured here is simply the potential at a particular site. What impresses me is the largeness of that site, 4 mm. apart.
Brazier: If you have got only one recording point in it, you cannot say how large the site is, can you?
Gerard: All it means is that it is between these two electrodes.
Brazier: Figure 17 shows another patient in whom the placement of the electrode was such that we think it went right through the cortex of the convexity, through the white matter, and to the cortex of the orbital gyrus. Again, we can see the voltage gradient from the surface all the way down to the fifth channel, and then we find fast activity, apparently unrelated to the other fast activity. In the sketch is a schematic suggestion of how we think that electrode was placed.
The point I am trying to make here is that the activity recorded between points 5 and 6 appears to me to be independent of the activity
recorded between 1 and 2. I would feel that this is supportive evidence that this is the reaction of the cortical cells.

_Hoagland_: I am not clear about the locus of the various electrodes. The point of the electrode is at 7 in the figure. Do you have uninsulated parts on the rod acting as other leads at different levels?

_Brazier_: The electrode has seven strands of copper insulated from each other, and then the whole shaft is insulated. Strand 7 is bare at the tip for 2 mm.; strand 6 is bare in the shaft, 2 mm. away from each of its neighbors, and so on. Dr. Delgado makes these electrodes.

In Figure 18 we see the electrode in place in this same patient as shown by x-ray. The trephine opening is ready for the leucotomy. All the wires are on the surface of the scalp, as well as the plug where the electrode wire is to be attached. The wire can be seen lying on the scalp and then entering the trephine hole and going down. Its point we believe to be in the cortical layers of the orbital gyrus. We think that is
probably responsible for the activity between points 6 and 7 in Figure 17, whereas in Figure 15 the cortex of the convexity is what we believe to be responsible for the activity between point 1 and 2.

**Figure 18.** X-ray of the skull of the patient whose electrical recordings are given in Figure 17. From Brazier, M. A. B., Hamlin, H., Delgado, J., and Chapman, W.: In preparation.
Magoun: That is very clear, but how are we to relate it to your earlier observations? Is this fast activity the same as what you described earlier as representing a phase of light anesthesia, or perhaps preceding anesthesia, when the subject is euphoric? Is it this same activity, observed 48 hours later, which you feel represents a persistence of the pentothal effect?

Brazier: I am sorry that I haven’t the records here to say how many days or hours this was postoperatively. I think this was recorded several hours after the operation ended. But the patient was certainly “conscious,” and probably out of his bed.

Magoun: What is the frequency of this activity? Is it double the α?

Brazier: It is usually from 25 to 35 per second, and a mixture rather than a single frequency. These are, of course, recordings only from the frontal lobe.

Perhaps now is a good opportunity to go on to some work on what happens to sensory impulses in the brain that have originated in the periphery, and what the effects are of anesthesia on the responses of the cortex to these impulses. Figure 19 shows the kind of response we obtain in the appropriate receiving area of the cortex when we stimulate a sensory receptor. In this particular case, and in most of the illustrations I was using single brief flashes of light as the stimulus. One of my reasons for this is that I am rather eager to examine physiological conditions, and when a nerve is stimulated electrically, we do not have a physiological condition. We are hitting all the synapses simultaneously with a big blow and forcing the synapses by a volley that starts out synchronously. This is certainly not equivalent to the physiological pattern of the serial bombardment of synapses that illumination of the retina gives; therefore in this work I have not used electrical stimulation, and I shall illustrate my talk in the case of the visual system with flash stimuli, not optic nerve stimulation, and in the case of the auditory system with clicks in the ear.

In the upper part of this figure is a classic response in the visual cortex. These are untouched pictures, but I think you can see where the flash occurs by the artefact in the baseline. This is a 200-cycle time line.

Scherrer: Where did you lead off from in this case?

Brazier: In this case, I had one electrode on the lateral gyrus of a cat, and the other on a coagulated (killed) cortical area, some distance forward; for example, the gyrus proreus, or sometimes a screw fixed in the bone over the frontal sinus. With this orientation of electrodes there is, after an interval of about 12 msec., an initial surface positivity followed by a longer lasting wave of surface negativity. The most usual interpretation of these potentials is that the initial component of the
Figure 19. A) (upper) Primary evoked response, recorded at the visual cortex under oil, in a cat lightly anesthetized with nembutal. The stimulus was a flash of white light 35 μsec. in duration, and was signaled by the artefact in the base line. Surface negativity recorded upwards. The time line is 200 cps. B) (lower) Primary and secondary responses recorded at the cortex after a single flash 35 μsec. in duration. The time line is 100 cps. Reprinted, by permission, from Brazier, M. A. B.: A review of physiological mechanisms of the visual system in relation to activating techniques in electroencephalography. EEG & Clin. Neurophysiol. Suppl. 4, 93 (1954).
Surface positivity is the approaching field of activity in the thalamo-cortical radiations—in this case, the geniculo-striate radiations—followed by the invasion of the apical dendrites of the pyramidal cells. The negative wave indicates propagation up the apical dendrites, making the surface relatively negative. That, in brief, is the usual interpretation given for this kind of picture. Its brevity makes it an oversimplification. I refer you to Bishop (25) for a more exact fractionation of these responses. As I am sure you all know, this is not the only event that happens in the cortex as a response to a single stimulus, even when the flash, as in this case, is only 35 μsec. in duration.

Kety: How does it produce the artefact initially?

Brazier: It is recorded by a photocell.

Kety: Is it not recording from the nervous system in any way?

Brazier: No, it is superimposed from a photocell onto the cortical trace. Now, as Forbes (26, 27) showed for sciatic stimulation a long time ago, if we use a longer time sweep, we find that the single stimulus has given more than a single response. In the lower part of Figure 19 I am using a slower time sweep in order to record over a longer time period. There are now 10 msec. intervals between peaks in the time-line instead of 5 as in the upper picture. There is the little artefact of the flash, and here is the positive response. I think you can see a jiggle in the baseline; it is very fine, and is superimposed on the trace.

About 12 msec. after the beginning of the downward deflection, the surface positive event is followed by the wave of surface negativity, and then something like 70 msec. later, is the response which Forbes described in 1936 (for sciatic stimulation) and which he called the secondary discharge (26). I prefer to call it the Forbes response because, as you will see later, there are some events that we can now find in between these two, so that “secondary” becomes now a rather misleading term.

Dr. Forbes and his co-workers were able to show a great many interesting things about their so-called “secondary” discharge: that it did not travel up the classical relay systems (in the case of sciatic stimulation, not through the ventral lateral nucleus of the thalamus which is the path of the primary one), and that it did not use the medial lemniscus. It was not restricted to the cortical receiving area for somatosensory stimulation, as the primary one. They found it spread much more widely over the cortex, and in both hemispheres on unilateral nerve stimulation, whereas the primary response, of course, is contralateral only. In the case of sciatic stimulation they were able to show that it came up through, or partially through, an extrathalamic route. They demonstrated some of its pathways and where it crossed into the opposite
hemisphere, finding a crossing at the level of the *inferior colliculus*, and another crossing pathway in the anterior third of the *corpus callosum*.

Hoagland: What level of anesthesia was used?

Brazier: They felt that this could not be recorded except in deep barbiturate anesthesia. There is some question as to their interpretation of why anesthesia had such an effect on this response, and whether they originally thought that the response was there in the unanesthetized animal but was masked by the background EEG, or whether (and I believe this was their view) it was something that was not there if one did not anesthetize the animal.

In this particular experiment, the animal was anesthetized. However, let me mention some of the work that is coming later. I now use two techniques in which the animal is not anesthetized. In one, under a preliminary anesthetic, gramophone-type needle electrodes are hammered into the skull and then the animal is allowed to emerge from the anesthesia. I find I still obtain the Forbes response. In a second we implant some electrodes in cats by screwing them into holes bored in their skulls under anesthesia, but this has been done so recently that findings are not yet available. In short, the response of Forbes is there in the absence of anesthesia.

Let me now show you the technique for these investigations that I am reporting in these figures. We have been very much influenced by Wade Marshall's work (28, 29). We always record under oil when we are examining the exposed cortex, in order to avoid the spreading depression of Leão (30, 31). After the craniotomy hole has been made, cement is built up around the edges of the skull and the hole filled with warm mineral oil before the dura is opened (Figure 20).

Fremont-Smith: What does that avoid?

Brazier: It avoids the spreading depression of Leão, these effects that Marshall has worked on so extensively, and the depression of electrical activity, as well as other phenomena that follow exposure of the pia to cold, to drying, to mechanical stimulation, or to some chemical change. The pia in our cats is never exposed to room air. In Figure 20 we can just see the fine wires going down into the pool of warm oil. The cat's nictitating membranes have been cut and the pupil has been dilated with collyrium or something of that kind. The cat is under anesthesia. A stroboscope faces it with a diffusion screen to illuminate the whole of both retinas uniformly.

I now come to the effect of anesthesia. Let me repeat that I do not take a global view of anesthetic characteristics, and when I mention properties or changes produced by a drug, I am really talking only about the specific drug that I name. What is true for nembutal is not true even
for dial, which one might think was so closely related as to give the same effect.

One of the last reflexes to disappear in a cat with deepening nembutal anesthesia is the ear twitch; when the hairs inside the pinna are blown upon, the ear twitches, and I found that to be eliminated a bit later than the corneal reflex. In Figure 19 we were just reaching a level of anesthesia at which one cannot work with the visual system because the eyeballs begin to roll. This is rather a light degree of anesthesia. Going to another experiment (Figure 21), on the top we see the responses at an anesthetic level just before the animal becomes unusable because the eyeballs roll. I did not wish to touch up these pictures, which are the actual traces, so I have put in a light mark about where the flash artefact appears, to draw your eye to it. Some of the flash artefacts actually show up clearly enough by themselves. I do not have to tell you the point I am going to make, because it stands out. Look at the Forbes response on the right at the top, and then see what happens to it below when
anesthesia has been deepened. Here the first deflection is the first sense-modality-linked response coming up to the lateral gyrus. These potentials are all recorded from the lateral gyrus, but the first one can be recorded only from the visual area of the cat’s lateral gyrus, whereas the later one can be recorded on both sides of the head in many areas of cortex, although not uniformly in all areas. There is a tremendous augmentation, as we see, of Forbes’ cortical response, although below the animal is in deeper anesthesia than in the top picture. It is the same animal. In spite of the cat’s being at this moment in deeper anesthesia, the message from his environment, shall I say, is leaving a more pro-

**Figure 21.** Comparison of cortical response to brief flash at two levels of barbiturate anesthesia. Effect of deepening barbiturate on cortical response to a single flash of light 35 μsec. in duration. Flash signaled as artefact on trace and emphasized by white line inserted above it. Note: Lengthening latencies and increase in amplitude of secondary response. Relative negativity at the exploring electrode is recorded by an upward deflection.
nounced trace in his brain in electrical terms. The primary surface negative response has very nearly gone.

I wondered whether this augmentation of a late response to a flash could be found in man during very light barbiturate administration. We can obtain a response to flash in an unanesthetized human being if we place the electrodes in the occipital region. In Figure 22 we see a subject exposed to flashes quite slowly so there will not be any build-up effect from repetitive stimulation. The flash rate is about one per second. There is a considerable latent period between the flash and the response. In my opinion, it is unlikely that this is the primary evoked response, because of its wide distribution and long latency. I think this is probably the equivalent in the human being of the Forbes response that I showed you in the cat. I should perhaps mention that I have

![Figure 22. Responses in man to slowly repeated flashes recorded from the scalp.](image-url)
recorded responses to flash in man with a short latency and discrete location that may well be primary responses.

One of my medical colleagues in the laboratory, Dr. George Gray, helped me with some experiments and we obtained the effect shown in Figure 23 with and without pentothal being run slowly into a vein.

Marrazzi: Are these effects difficult to obtain?

Brazier: No, if you mean the responses in unanesthetized man. If we search in the occiput, and especially in the midline above the inion, we nearly always obtain them. Here is a subject to which paired flashes are being given; the top record shows the response without any drug, and the lower one during the injection. We see the size of this subject's response in the two cases. Actually, less than 100 mg. of pentothal had been run in, very slowly, when this was recorded, and we can see the fast activity which we have been discussing, developing between flashes. I think you will agree with me that there is also a very marked augmentation of this response. The use of the paired flash is a technique that has been introduced by Dr. Gastaut (32) to emphasize evoked responses. His argument is that if we adjust appropriately the interval between flashes, we can facilitate the response to the second flash by impressing it in the supernormal phase of the recovery cycle from the response that the previous flash has induced.

<table>
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<tr>
<th>4 FLASHES AT 1 PER SECOND FLASH RATE</th>
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<td>BEFORE INJECTION</td>
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Figure 23. Effect of small I.V. dose of pentothal on occipital responses to flash in man. The amount of the drug is insufficient to induce anesthesia and the evoked response is still in the occiput. Note augmentation of the response with the drug and fast activity between flash responses.
I should like to go back now to another animal experiment (Figure 24), and show you more serial exposures demonstrating the point I made before. Here is a cat with the primary and the Forbes responses. On the left the animal is in very light anesthesia, and on the right added nembutal has been injected. There is the same enormous rise in the size of the Forbes response, but very little difference in the size of the primary.

Table XIII gives some of the measurements on 10 preliminary exposures followed by 20 more after added nembutal. As is well known, nembutal increases the latency of the primary response, as well as that of the secondary response, in very light anesthesia. The mean latency to the first downward deflection of the primary response was 12 msec.
## TABLE XIII

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<th><strong>Primary Response</strong></th>
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<th><strong>Secondary Response</strong></th>
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<tr>
<td></td>
<td>Mean Latency to First Positive Deflection (msec)</td>
<td>Percentage Increase Due to Drug (msec)</td>
<td>Mean Amplitude of Peak of Positivity (μV)</td>
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<tr>
<td>Very light anesthesia</td>
<td>12</td>
<td>22</td>
<td>368</td>
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<tr>
<td>After added nembutal</td>
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<tr>
<td>a) 1st 10 exposures</td>
<td>17</td>
<td>42 per cent</td>
<td>27.5</td>
</tr>
<tr>
<td>b) next 10 exposures</td>
<td>19</td>
<td>58 per cent</td>
<td>27.5</td>
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in the preliminary exposures. Actually the latency in every exposure was the same at this stage; they were all 12 msec. After the added nembutal, for the first 10 of those 20 exposures below the line on this slide, the mean latency for the primary was 17 msec. In the next 10 the mean latency was 19 msec. If we take the latency to the peak of the positive wave, it was increased from 22 to 27.5 msec. This was the very first early response; the amplitude had dropped very little. If we started out with a hypothesis that anesthesia depressed sensory responses, we might expect all the evoked potentials to decrease in amplitude.

Now let us consider the Forbes response on the right. We notice that the latency has also increased by about the same percentage as for the primary response. I might mention that of course there is a retina be-

**EXTREMELY LIGHT ANESTHESIA**

**35 MINUTES AFTER 60 MG. NEMBUTAL**

![Timeline and Graphs]

**Figure 25.** Responses from the visual cortex of a cat on being stimulated by a brief (15 µsec.) flash. Left column: very light nembutal anesthesia. Two right columns: consecutive exposures after the animal had been given more nembutal.
between the stimulus and the cortex in my experiments, and that is affected by anesthesia too. In the seventh column is the latency to the peak of positivity. But observe what has happened to the amplitude. That is really a tremendous change. In the last column we see the mean amplitude of the ten exposures before additional anesthesia. Then, after added nembutal, the mean amplitude of the first ten exposures, and finally the last ten. That is one effect of increased anesthesia (Figure 25). These are the original data from which the measurements are taken.

As we see, in some of the exposures there appear to be two responses, quite apart from the Forbes response. Figure 26 is an enlargement from another series, and shows what they look like. There is the artefact

Figure 26. Evoked potentials recorded from the lateral gyrus of a cat in response to a single flash 35 μsec. in duration. Time line 100 cps. Flash marked by fine line on trace (white mark added above to accentuate this). Surface negativity recorded upwards. The photograph shows the primary response beginning 12 μsec. the flash, then a second and longer lasting wave with a latency of 24 μsec., and finally the Forbes response at approximately 75 μsec. after the flash. Anesthesia is light nembutal and there is considerable EEG activity in a background. Relative negativity at the exploring electrode recorded by an upward deflection. From Brazier, M. A. B., Hamlin, H., Delgado, J., and Chapman, W.: In preparation.
signaling the flash. There is what we would all call the primary response. Immediately following it is another response, and then, a long time afterward, comes the Forbes response. The stimulus is a 35 μsec. flash. There is no question in my mind that this deflection immediately following the primary cannot be a Forbes response, for here there are all three. This is where I wish to draw Dr. Magoun into the discussion, because I am much interested in the work that is coming out of his laboratory. He has been able to show a response of approximately this latency after sciatic stimulation, and has picked it up from electrodes in the ascending reticular system on the way up to the cortex. This takes longer to reach the cortex than the primary evoked response, but nothing like so long as the Forbes response.

French, Verzeano and Magoun (33) published their results on these responses coming up through the ascending reticular system and arriving at the association cortex. In the case of sciatic nerve stimulation, the second delayed response that they followed up through the ascending reticular system, arrived 8 or 10 msec. later than the primary one.

Magoun: The time lag had about this interval in the brain stem; it could be later still in the cortex.

Brazier: Was there a similar delay for the auditory system, which you also examined?

Magoun: Yes. Modalities do not seem to be relevant here.

Brazier: I know that that paper did not include the visual system, so I thought it would be well to examine that. I also noticed that you did not mention—in a way, you specifically stated the opposite,—that this delayed response, which I will call the ascending reticular system response for the time being, did not come to the specific primary receiving area but to some other areas.

Magoun: I do not think we have precise enough data to generalize. Is this response to be identified with that traversing the central brain stem?

Brazier: I wonder if it is the counterpart, for the visual system, of a response travelling up by the same system. I have not yet had electrodes in the brain stem.

Magoun: Let me ask you some questions that might relate the two. First, does it disappear early in anesthesia? Second, does it have a long recovery time so as not to follow the last of a pair of rapidly spaced shocks?

Brazier: I have material on that from the auditory system. I am now very happily associated also with the Laboratory of Communications Biophysics at Massachusetts Institute of Technology, where Professor
Walter A. Rosenblith has a room that is not only soundproof but also anechoic.

In Figure 27 are some auditory system responses from the ectosylvian gyrus of a cat. The latency to the beginning of the first downward deflection is usually about 7 msec. In these photographs the start of the sweep is synchronized with the click. So the whole duration of the sweeps in this picture is about 45 msec., too short a time to record the Forbes response. The latency to the second response shown here is 16 msec. There is not so long a delay in the auditory system as in the visual because we do not have all the chemical changes that go on in the retina. On the left is the classical primary evoked response, and on the right the other response. There are many variables concerned in whether or not we record the second one, and one of them, of course, is anesthesia, which interests me very much. In the example from the auditory system the level of anesthesia is not as light as in the examples from the visual system in Figures 25 and 26. There is consequently less interference from the EEG. But in really deep barbiturate anesthesia we do not obtain it even while we are still getting the primary response.

Location must also be important, I think. I have at present no material of my own as to where on the auditory cortex one finds this, but Dr. Merlis’s laboratory at the Veterans Administration Hospital in Boston.

Figure 27. Evoked potentials recorded from the ectosylvian gyrus of a cat in response to a single click. Time sweeps approximately 45 μsec. in duration. Sweep triggered by the click. Relative negativity at the exploring electrode recorded in an upward direction. (Photograph by courtesy of W. A. Rosenblith, D. Raab and J. Macy, Jr.)
has published a map of responses that they made on a cat (34). In this case they found "double responses" only in certain locations which are very low down, in the middle ectosylvian gyrus. I do not know what the story will be with regard to the factor of location. I suspect that location in depth within the cortex at which the necessary degree of depolarization takes place will prove to be important, for I think this may indicate an involvement of apical dendrites. I am sure, however, that intensity of the stimulus has something to do with it, and so has anesthesia and frequency of stimulation. In fact, Mr. Josiah Macy, Jr., in Professor Rosenblith's laboratory, very kindly worked out intensity functions for me before I left and the results showed clearly that there was a greater incidence of these double responses with clicks 10 db. below reference level than with those 60 db. below. The results also demonstrate a falling off in incidence of double responses when the interval between clicks was less than two seconds. So the recovery rate in this system must be quite a slow one. Here may I add a reminder that I have dealt in this communication only with the effect of nembutal anesthesia on responses to single stimuli. As soon as the stimuli are repeated, we find that anesthesia has profoundly affected recovery rates.

I should like Dr. Magoun to tell us what he thinks these responses are, for he has far more experience in working with them than I have. I am of course interested in the fact that the primary sense-linked response, coming up in our classical systems, seems to be so resistant to anesthesia, and that the Forbes response is even augmented in anesthesia at a certain stage. But now we have something else, this other response in between, which I should tentatively like to call the "ascending reticular system response," although from my work I have no direct evidence of its using that pathway because I did not have an electrode there while I was recording from the cortex. This response is apparently vulnerable to anesthesia beyond a certain depth, and this raises the problem of whether this nervous pathway to the cortex is the one that has to be open if the individual is to be aware of the signals coming in from his sense organs on their specific routes. For "awareness" does he have to have activity in this ascending reticular system pathway, which is mixed for sense modality? Must that system be functioning, open and active for him to be able to "perceive" that signals are coming into his eyes and ears, for example?

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Physiological Evidence Concerning Importance of the Amygdaloid Nuclear Region in the Integration of Circulatory Function and Emotion in Man


Department of Psychiatry, Harvard Medical School,
Boston Psychopathic Hospital; Medical and Neurological Services,
Massachusetts General Hospital; Departments of Medicine and Neurology,
Harvard Medical School, Boston
Physiological Evidence Concerning Importance of the Amygdaloid Nuclear Region in the Integration of Circulatory Function and Emotion in Man


Department of Psychiatry, Harvard Medical School, Boston Psychopathic Hospital; Medical and Neurological Services, Massachusetts General Hospital; Departments of Medicine and Neurology, Harvard Medical School, Boston

Preliminary findings presented in this paper suggest that in man the amygdaloid nuclear complex, situated in the temporal lobe, may play a role in circulatory regulation as well as in emotional expression. The observations were made in five epileptic patients in each of whom a multiple electrode, consisting of four parallel needles, had been implanted in the amygdaloid region of one temporal lobe by a specially modified stereotaxic apparatus. Three of the needles were of equal length and spaced 5 mm apart in the position of an equidistant triangle, while the fourth was 3 mm shorter and was located in the center of this triangle. This electrode was used to record the electric activity, to stimulate this region, and finally to coagulate this nuclear area for therapeutic purposes. The amygdaloid area was localized by measurements derived from skull x-rays of the clinoids in each patient and from air studies of the tip of the temporal horn in all except one case.

Preliminary studies with the stereotaxic instrument in 11 cadavers using the same skull landmarks revealed that our centrally placed electrode needle entered the amygdaloid nuclei in nine cases and missed this structure by 1 mm in two cases. Since we have no tissue specimens in any of our patients for the determination of the precise location of the electrodes, we have defined the area studied as the amygdaloid nuclear region, meaning thereby, the area in or near the amygdaloid nuclei.

Three patients were diagnosed as having epilepsy with assaultive behavior of such severity as to necessitate confinement in a psychiatric institution. Two patients had a diagnosis of psychomotor (temporal lobe) seizures of incapacitating severity. All had electroencephalographic abnormalities in the temporal area before operation. The amygdaloid region was coagulated in the patients with assaultiveness in an attempt to modify favorably this behavior, and in the patients with psychomotor epilepsy, to avoid greater destruction by temporal lobe extirpation, such as is used in some centers in the treatment of that condition. In each case, a group of psychiatrists had recommended surgical treatment after all attempted medical therapy had failed. The extent of the lesion caused by the current parameters used for coagulation had been previously determined in 12 cats. The results of coagulation will not be reported until sufficient time has elapsed for clinical evaluation to be meaningful. Electric stimulation was employed in an attempt to obtain a clearer understanding of the functions of the amygdaloid region, including its role in our patients' illnesses. The effects of electric stimulation of the amygdaloid region on feeling states and the continuous recording of blood pressure and heart rate were studied, and the electric activity from this region and from the scalp was recorded at various intervals during a 7 to 9 day period prior to the therapeutic electric coagulation procedure.

Fig. 1. Electric stimulation caused a 50 mm-Hg rise in systolic and 33 mm-Hg rise in diastolic blood pressure and pupillary dilatation without producing mood or somatic responses. (1) Respiratory tracing, (2) blood pressure tracing; 60 pulses/sec, 1 msec pulse duration, 12 v.
Stimulation with a monophasic square wave at a rate of 20 to 60 pulses/sec, 1 msec pulse duration and 7 to 17 V for periods of 3 to 30 sec produced a variety of responses. In four patients, feelings of fear, anxiety, and at times a "weird" or "terrific" feeling in association with alterations in motor behavior were obtained. When the intensity of the stimulus was slightly increased or maintained for a longer period, the patients would show momentary confusion and unresponsiveness. Ability to count and the performance of a skilled act such as winding around a pencil would become impaired. In three patients, bilateral pupillary dilatation and a 20 to 100 percent increase in heart rate were elicited. In two patients, electric stimulation caused a 50 to 80 mm-Hg rise in systolic and a 30 to 60 mm-Hg rise in diastolic blood pressure, and, in one patient, widening of the palpebral fissure. The circulatory and pupillary responses could be obtained independently of, or in association with, alterations in mood, motor behavior, and changes in respiratory rhythm (Fig. 1). The time interval between the beginning of electric stimulation and the changes in the blood pressure or heart rate indicated that some responses were mediated directly by nervous pathways and suggested that others were perhaps mediated by the liberation of a humoral substance. All responses were readily reproducible. Voluntary motor movements simulating those induced by electric stimulation did not elicit the circulatory effects.

In the patients so far tested, stimulation that has not resulted in a psychomotor seizure has frequently been followed by increased muscle tension and eye blinking, which has obscured the electroencephalographic recording. This was found to take place even when the patient reported absence of subjective sensations.

In one patient with a diagnosis of psychomotor epilepsy who was having spontaneous seizure discharges confined to the area tapped by the deep electrodes, the only sign at the scalp electrodes was an occasional spike at the temporal tip on the same side. During these electric seizures the heart rate was augmented, and there was a great increase in blinking movements. In another patient in whom high voltage spikes were occurring randomly at the depth electrode, spikes at the temporal scalp electrodes on the same side were found but not always simultaneously with those in the depth (Fig. 2). Paillas (2) and Gastaut (3) have described similar spike activity recorded from the amygdala in two of their patients with psychomotor seizures.

The only complication known to have arisen from our use of the implanted electrodes was a temporary weakness of the contralateral facial musculature. This had disappeared by the time the electrode was removed.

The finding of striking elevations of blood pressure can now be added to previous studies in animals and man of the effects of electric stimulation of the amygdaloid region. Feindel, Penfield, and Jasper have reported (4) that electric stimulation in the region of the claustrumamygdaloid complex in the awake patient at operation frequently caused features of automatism, which probably included confusion, unresponsiveness, and abnormal motor behavior, as was noted in our patients. Pupillary dilatation, increases in heart rate, and behavior changes have been previously reported in amygdaloid studies in animals (5). Our observations may lend further support to the views expressed by the comparative anatomist that some portions of the amygdaloid complex may constitute a part of the brain concerned with visceral and somatic expression of internal states (6).

References and Notes

1. This investigation was supported by research grants H-568-C4, National Heart Institute, and M-595, Institute of Mental Health, National Institutes of Health, U.S. Public Health Service.


3. H. Gastaut et al., ibid. 88, 310 (1953).


5 August 1954.
I have been asked to attempt an account, from the neurophysiologist’s standpoint, of the transition from normal cerebral activity to seizure discharge. For anyone interested in research on epilepsy — and this group is the outstanding example — this is certainly one of the key problems. This transition is as difficult to investigate in those cases that have more or less readily identifiable lesions as in those where no visible structural defect can be demonstrated. It is in this area that perhaps the electro-physiologist’s techniques may shed some light.

In saying that electrophysiological techniques may reveal the mechanism of transition from normal to seizure activity in the absence of anatomically identifiable lesions, I am not implying that a neuronal tissue may exhibit a ‘functional’ disturbance in the absence of structural defect. I would assume that in modern science it is universally recognized that differences in neuronal function imply ipso facto structural changes, whether they be alterations of membrane impedance, accumulation of cations at a surface or any other submicroscopic change that can lead to a shift in the excitation threshold, whether reversible or irreversible. The structural change is there, just as in the grossly or microscopically visible lesion — it is a question of order of magnitude. This is merely a modern extension of Hughlings Jackson’s (23) insistence that no difference in underlying mechanism exists between idiopathic epilepsy and focal seizures.

What kind of submicroscopic shift in structure of cortical neurones could result in seizure discharges? What characteristics of the cells could this be? Hughlings Jackson described them as “highly unstable cells” but we would like to know what the physical substrate is of this “instability”. This is one problem.

A second problem is whether the instability of the cells whose discharge produces the seizure is due to a change in themselves or a change in other (and perhaps far distant) neurones which normally act on them as regulators. We find this concept in Gowers’ classic book (22) and we know how fruitfully it has been developed and substantiated by Penfield and his colleagues, as well as by many others.

So now we perceive some of the primary areas in which the electrophysiologist must search if he is to help — on the one hand he needs to examine the characteristics of neuronal structure to determine those which could lead to abnormal discharge and on the other he must find pathways through which influences from other centers might play upon these neurones to restrain them from giving seizure discharges at all times.

I shall not have time to discuss the latter problem — I think possibly some of the speakers who follow me may have pertinent observations in this field.

Let us consider neuronal structure and some of the known characteristics of such neurones as one finds in the cortex. Is there any anatomical peculiarity of cortical cells which could account for the epileptic spike discharge? All are familiar with the classification of compo-
component parts into cell body, axon and dendrites. Only recently has it been fully recognized that these component parts of a neurone have widely differing discharge characteristics (9, 16, 18, 37, 46). We owe this knowledge largely to those who work with microelectrodes. For example, in Bishop’s laboratory, Tasaki, using ultrafine electrodes, made extracellular unit recordings from axons, from cell bodies and from individual dendrites. He was able to confirm by this method that dendrites have characteristics in strong contrast to those of the cell body and the axon. I shall return to this later.

Tasaki made his measurements on dendrites of the Mauthner cell, and on dendrites of the lateral geniculate neurones and on those in the striate cortex of the cat. Several other workers have first-hand experience of microelectrode recording from the cortex, a technique in which I am as yet a tyro, and no doubt Dr. Jasper has much to tell us in the paper which follows this.

Returning to the question of the seizure discharge from the cortex — whether originating there or secondarily to release from below, the cells with which we are principally concerned are those that take the efferent impulses from the cortex to the muscles, that is: the pyramidal cells. Now these cells have a dendritic system unique to the nervous system in that they have the long apical shaft reaching up and branching towards the cortical surface. One of the prerequisites for recording potentials from the brain surface with large electrodes is that the contributing neurones should have some uniformity of geometrical arrangement or else the contributing potentials will cancel out. The pyramidal cells with their long dendrites are almost but not quite unique in fulfilling this condition. The recording of unit potentials is also favored by a geometry in which the dendrite is long. The role of the apical dendrite as a significant structure in the EEG potentials has been emphasized outstandingly by the work of Bishop* and has been suggested by many neurophysiologists: Adrian, Bremer, Gerard, O’Leary, Eccles, Chang, Tasaki to name a few only. The structure of this dendritic pattern is familiar to all from the drawings in the textbooks. Figure 1 is a photograph of a section through the visual cortex of the cat stained to show these sheets of apical dendrites reaching up to the surface layers.

The area of dendritic surface is very great compared with that of the cell body and any electrical characteristics that the membrane of these long processes may have can scarcely be negligible in the total picture. Sholl (42) working in Young’s laboratory, from measurements of many samples, has calculated that the dendrites in the cortex of the cat’s lateral gyrus occupy 20 - 30 per cent of the cortical volume. The dendrites then can hardly be considered negligible by the electro-physiologist, and the outstanding electrical characteristic that marks these structures when functioning normally is their extremely slow potentials relative to those of the axon spike or cell body discharge. Another significant property is that their parent cell bodies may discharge without any propagated response from these long dendrites, and vice versa (8, 9). This means that a change in excitability may result without activation.

The apical shaft of the pyramidal cell forms a long protoplasmic process with core-conductor properties favoring the spread of electrotonic depolarization from the cell-body up the dendrite. We are so used to thinking of dendrites as receiving synaptically transmitted impulses and conveying them towards a cell, that the peculiar properties of these particular long dendrites may be at first surprising. Bishop has emphasized that except at their junction with the cell-body they do not seem to have on them any synaptic endings that bring impulses from the specific afferent pathways. Synapsis on them of nonspecific afferents is another story (30, 9, 35) and one that perhaps we shall hear about from Dr. Jasper (24).

As Bishop has demonstrated, normal activity

*Since this communication was presented, three important papers have been published by Bishop and Clare. These have been added to the reference list at the end.
in these dendrites appears to consist very largely of non-propagated graded potentials spreading decrementally from the point at which the stimulus is received (9) and not of the all-or-none type of action potential. These non-propagated potentials are of long duration, are not all-or-none in character, have no refractory period and can sum with any consequent potentials that are set up before they die away.

Looking at the problem now from the opposite point of view: what can the neurophysiologist learn from the clinical electro-encephalographer's experience in recording from patients? One of the outstanding things that he learns is that the normal brain does not give spikes in recordings from the convexity of the cortex.

The spike of the epileptic discharge is not merely an excessive form of a normally occurring event, it is a new entity unknown to the normal brain.

The spike also differs from the well-known action spikes of axons and of cell-bodies. The duration in axons is less than 1 msec, that in the cells is of the order of 3 msec or less. In my experience the spikes one records from the epileptic cortex have not been less than 15 msec, in duration and are usually rather longer. Dr. Jasper (38) has given a duration of 20 to 60 msec. for these spikes. When recorded through the intact skull they are certainly of this order of duration as seen in Figure 2. There is, of course, the question as to whether the “epi-
leptic spike” recorded from a patient’s exposed cortex is in reality an envelope. The users of microelectrodes can help us here. We do know from Tasaki’s work with microelectrodes in animals that, when a dendrite can be induced to fire, the duration of its response is 14 msec. (46, 9) or more, whereas unitary cell discharges at any depth within the cortex are usually less than 1 msec. in duration. The dendrite’s response is then followed by a recovery period much longer than that of the axon (9). Another important property of these dendrites, in contrast to axons, is that when a dendrite is induced to discharge, the impulse is conducted decrementally in the antidromic direction (8) as the diameter decreases. Actual measurements of the decrease in diameter of the apical dendrites of pyramidal cells in the cat’s visual and motor cortices as they extend from the cell-body to the superficial layers have been made by Sholl (42). They taper from about 3 μ at their junction with the cell-body to about 1.4 μ at their terminal bifurcations in the plexiform layer.

One is tempted to suggest that in the normal cortex, parts of the dendritic structure unique to it, namely the long apical shafts, do not under normal conditions give spike discharges, and that their usual electrical activity is a slow fluctuation of electrotonic potential spreading along them from activity in their cell-bodies and from points on them where non-specific
afferents form synapses with them. Probably some of you who are neurophysiologists are wondering why I am shunning the term “synaptic potential”. It is because this term suggests to me more knowledge than we have at present, and all I wish to suggest is a local non-propagated change in polarization which implies also a change in excitability.

That in contrast to this, the epileptic spike represents a real action potential discharge of these dendrites may now be examined.

We can experimentally fire dendrites and make them discharge and when we do this we do indeed get an electrical response that we do not find in the “spontaneous activity” of the normal animal’s cortex. One way to fire the dendrites is by electrical stimulation of the cortical surface. Among the workers who have taught us what happens when one does this are Adrian (1), Bishop (9, 8), Burns (11, 12, 13, 14, 15), Chang (16), and Rosenblueth and Cannon (41). The initial response is a surface-negative spike of certainly not less than 10 msec. (8) in duration and more usually 15 msec. If the stimulus is increased in strength this will be followed by negativity in the deep cortical layers (recorded from the pia as a surface positive response). As long ago as 1936 Adrian (1) in examining this phenomenon drew attention to the differential contributions of cell-bodies lying in deep layers, their basal dendrites and their apical dendrites.

Burns (12, 14) has examined this surface negative spike with microelectrodes and has found it to have maximal negativity at a level 0.7 mm. below the pial surface in the auditory cortex of the cat. The main layer of large pyramidal cells lies much deeper than this and the maximal amplitude cell-body discharge of short duration lies well below this. I know that Dr. Jasper (27, 28, 29) has measurements and recordings pertinent to this problem. In my limited experience in microelectrode work the greatest amplitude short-duration extracellular unit cell discharges that I have so far recorded were at a depth below 1.0 mm. which in the cat’s visual cortex would be in Layer V where the large pyramids lie. Incidentally these unit discharges were independent of the response evoked by flash. Several other workers have previously found the same phenomenon (e.g., Li and Jasper (27, 28, 29), Jung (25, 26), Cohn (21), Thomas (47), von Baumgarten (5). I do not, of course, wish to suggest that unit cell discharges cannot be recorded in higher layers too, but there they are usually of smaller amplitude (48).

Figure 3, photographed in my laboratory by Dr. Max Dondey when he was visiting from France, illustrates how brief the unit cell discharge is compared with the dendritic potentials we have been discussing. The time line here is 100 c.p.s. so that 10 msec. elapses between its peaks. The spikes are approximately 2 msec. in duration and are recorded with negativity up. At this recording speed, such a measurement cannot be made with great accuracy. I infer that these are discharges of cell-bodies and not of axons or dendrites because of their duration and because they are apparently monophasic and hence reveal no sign of a travelling impulse such as one would record from an axon. I infer that they are extracellular recordings because they are of negative sign and I know that my fine electrode was too large to enter a cell (it was about 10 micra in diameter narrowing rapidly to about 1 micron at the tip).
Abnormally induced firing of apical dendrites would lead one to expect such a discharge to be propagated down the shaft in an orthodromic direction to fire the cell-body and in this case one would expect there to be some temporal relationship of the long duration strychnine spike and the short duration unitary cell discharge deep in layer V. This prediction has proved to be correct. Since the cell-bodies of these dendrites are the pyramids, whose axons are the main efferent routes from cortex, it would not be surprising that were a massed excitation to be initiated in this way, activity would spread and the result be a seizure. In fact, we know from Adrian’s experiments that when stimulation of the dendrites is sufficiently strong to discharge their cell bodies, impulses can be picked up in the pyramidal tract. Once the paroxysm starts, the short-duration cell-body discharges also enter the record.

This massed activation of cells through their apical dendrites can be mimicked artificially by repetitive electrical stimulation of the cortical surface for a few seconds. Shortly after the end of such stimulation a long-lasting afterdischarge develops that bears a strikingly close resemblance to the discharge of a focal seizure in an epileptic patient. It may later spread by axonal conduction to distant groups of neurons and become a generalized seizure. A strychninized cortex that is firing off individual spikes can be activated into a similar seizure pattern by bombardment with sensory impulses, such as in photic stimulation. Again the behavior of the sensitized cortical surface reminds one of the photosensitive epileptic patient. Of course afferent stimulation by routes other than the visual one can be effective in producing a seizure and stimulation of the cerebellum, as Moruzzi has shown, can evoke a seizure in an animal whose cortex has been topically sensitized by strychnine. No doubt Dr. Snider will tell us more about the role of the cerebellum later this morning.
In the human subject the flash of light as a general rule does not induce any massive efferent discharge but in some photosensitive epileptics, even though no seizure is evoked, the response to each flash may be so exaggerated as to resemble that of experimental animals artificially sensitized by strychnine.

Figure 5 presents an example of such a patient. Note the afterdischarge. In spite of the small percentage (perhaps 6 percent or less) of epileptic patients who are triggered into seizure by flickering light, all here are probably familiar with such cases.

Figure 6 presents the EEG of a patient with rare seizures — so rare that she had not been put on medication. She had not discovered sensitivity to flicker herself, as so many of these patients do.

The synchronous activation of many units by this intense sensory bombardment is paralleled in the neurophysiological experiment by induction in the apical dendrites of an abnormal propagated activity conducted orthodromically to their cell-bodies — a process probably initiated by impulses from non-specific afferents causing in them, by repeated bombardment, a summation of electrotonic potentials that eventually reach the threshold for discharge (8).

That the surface negative wave induced by afferent stimulation occupies the same neuronal structure as that produced by surface stimulation has been shown by Bishop (8). The structure in common is the apical dendrite.

In conclusion then, the hypothesis offered for examination is that the typical epileptic spike is an abnormal discharge of apical dendrites of

**Fig. 5. Exaggerated response to flash in an epileptic patient who could not be triggered into a seizure by any frequency used. The inset at the upper left shows the afterdischarge recorded by a unipolar lead from the mid occiput (reference on the nose). Duration of sample 13 seconds. Negativity up.**
pyramidal cells, in some cases fired from the cortical surface — as for example, by scar tissue and in others by triggering from lower centers via the non-specific afferents synapsing onto them in the higher layers of the cortex. I regret that I have not time to outline for you the recent work from Dr. Moruzzi's laboratory in Pisa (34) that suggests to me an explanation for the release of temporal lobe spiking by sleep. In brief, he has not only confirmed Jasper's evidence for non-specific afferents terminating in the layers through which the apical dendrites pass, but has also established that collaterals of the long axons of the pyramidal cells enter the reticular formation, so that a complete loop is formed that could play a regulatory role for the firing of the apical dendrites of these pyramids. The disruption of the reticular activating system by the sleep process would unbalance this control and this might thus explain the appearance of spikes in the EEG of these patients.

I need hardly emphasize to an audience such as this, that it is not the site of the epileptogenic process that this hypothesis is concerned with, but the site of one of its electrical signs. I believe both Dr. O'Leary and Dr. Jasper have laboratory findings directly bearing on this subject.

The observations to which I have alluded in this paper, with the exception of the few from my own work, have all been published and are available for inspection and evaluation. The hypothesis is however open to question — and I now would welcome suggestions for experiments to test it.

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REPLACES SINCE THIS PAPER WAS PRESENTED IN DECEMBER

CHAPTER 13

Electroencephalography

By MARY A. B. BRAZIER, PH.D.

This year has seen the formation of a new EEG society (the Austrian Society for Electroencephalography) which held its first meeting at Bad Ischl. Another group is forming in Australia. The Third International Congress of EEG, held last year, is to be congratulated on having all of its communications published within 12 months, as Supplements 3 and 4 of the EEG Journal. The papers and discussions of the Laurentian Symposium on the reticular activating system have now been published in full and a synopsis of the content has appeared. The reports given at the 5th International Neurological Congress last year are also now in print. A group from Tulane under the chairmanship of Heath has reported several years' work in the book, Studies in Schizophrenia. Electroencephalographers, familiar with the work of others with implanted electrodes in nuclear masses that send fibers to the septal region, will be dismayed at the interpretation given to the finding of spikes in the septum as specific to schizophrenia. A book by Dogulu on clinical EEG has appeared in Turkish. This covers essentially the same field as Schwab’s book from which some of its illustrations are taken, as well as the glossary. Unfortunately this reviewer cannot report on the text, but it seems to have been delayed in publication as there are very few references to work more recent than 1949.

A very brief but useful summary of the outstanding diagnostic characteristics of the EEG has been made by Schwab and compact reviews of many of last year’s papers have been written by Liberson and by Brazier. A descriptive article that may prove useful in teaching beginners is that of Game and Peacock. Chapter 15 of Penfield and Jasper’s book gives an excellent and detailed account of the EEG in epilepsy, while Gastaut’s monograph, in small space, covers the subject comprehensively and forms a useful teaching volume. Epilepsy in children is the subject of a new book by Livingston carrying on from the earlier volume by Bridge.

The symposium on Neurophysiology that was held at the 1953 meeting
of the Harvey Cushing Society has now been published. Fulton opened with a review of recent advances and was followed by Meyers's report on 34 human subjects and 6 cats in whom at operation he had searched for electrical suppression or motor suppression by stimulation or strychninization of area “4S”. No evidence of a suppressor mechanism could be found. Hanbery and Jasper gave a brief but comprehensive summary of their experiments demonstrating that responses carried by the nonspecific afferent system survive ablation of the specific thalamic nuclei. (A later paper by Hanbery gives in detail the pathways of the nonspecific projection system as established electrophysiologically.) MacLean described the production in animals of seizure discharges confined to the limbic system without alteration of neocortical potentials. He suggested a possible analogy to the psychomotor seizures of some epileptics (and in fact such independence of discharge has been demonstrated by recordings from electrodes placed in the amygdaloid region prior to the coagulation therapy in human subjects suffering from severe forms of this disease). At the same symposium observations were reported on human subjects having surgery of the “visceral” brain, Pool drawing attention to visceral representation in the neocortex as well as in the limbic system, and Scoville questioning the suggested role of this system in the mechanism of mental disease and of epilepsy. The impact of neurophysiological investigations of the reticular activating system on concepts concerned with mechanisms underlying impairment of consciousness have been succinctly reviewed by Pond and have been discussed in relation to anesthesia by Brazier. A most interesting paper by Gellhorn brings forward some more data bearing on the role of the reticulo-hypothalamic-cortical system in states of consciousness.

Among the papers on experimental work is one on the hibernating hamster who in the process of arousal shows no electrical activity at the cortex until its body temperature reaches about 20 C. Chatfield has now demonstrated that activity does appear subcortically before this—namely in the limbic system—although other subcortical structures, including the thalamus remain silent. The authors suggest that the site of this activity may account for the extremely agitated behavior of the just-aroused hamster. An incidental finding was a confirmation of Hoagland’s demonstration of the relationship between rise in temperature and frequency of the waves. In the non-hibernating warm blooded animal the effect of cooling on brain potentials has been studied by Ganshirt with the method devised by Geiger and Magnes for cats, in which a brain is perfused from another (uncooled) cat, in this way surmounting the difficulties of circulatory collapse and also of shivering. As in the hamster, the EEG became iso-electric at about 20 C. This paper contains an interesting discussion of the possible physiological mechanisms accounting for the observed changes above and
below normal temperature. These experimental studies may have some direct meaning for clinical work since the introduction of cooling technics in anesthesia. Fau has reported EEG's on 7 patients during this procedure.

This year several important papers have come from the St. Louis group on the steady potential drop across the cortex and on the various factors that have been found to influence it. To record these potentials one needs, of course, DC coupled amplifiers or a chopper device such as has been described by Kempinsky. Goldring and O'Leary have published in full the material presented by O'Leary at the 3rd International Congress (commented on in last year's review). Kempinsky has now added a study of the effect on pia-ventricular and on transcortical potentials of occlusion of the middle cerebral artery; he found a differential effect on cortical tissue and white matter of this gross interference with oxidative metabolism, the white matter being the more vulnerable, possibly because of its sparse capillary bed. Another report that neuronally isolated cortex exhibits no 'spontaneous' electrical activity has come in (Wright), and the influence on cortical activity in animals of sympathetic nervous system changes has been very well described by Bonvallet.

Exploration of the role of the amygdala continues, and an experimental study by Feindel and Gloor has appeared which compares the electrographic effects of stimulation of the amygdala and of the brain stem reticular system and emphasizes their similarity, not only on the electrical activity of the cortex, but on the activity of the opposite amygdala. Kaada too has published on the results of stimulation of the amygdaloid nuclei, using unanesthetized cats in order to observe behavioral responses (as a follow-up to his previous work on the electrographic effects). A differentiation can be made between responses evoked from the anteromedial division of these nuclei and those from the basolateral part. The author discusses the relation of these experimental findings to epileptic automatisms. Some preliminary observations from electrodes implanted stereotaxically in the amygdaloid region in man have been reported by Chapman. Stimulation of the hippocampus in man and the subsequent afterdischarges have been studied during operative procedures by Passouant with some results bearing on the connections of this area with the amygdaloid region and the temporal cortex. Recordings of respiration during subcortical stimulation in brain operations have been made by Dell. The regions explored included the thalamus, anterior hypothalamus and cingulate gyrus, and slowing or arrest of respiration was found to be evoked from widely different structures thus raising problems discussed by the authors.

A common problem in clinical interpretation of EEG records is the evaluation of focal depression of amplitude. A careful survey of a large number...
of records showing such depression led Friedlander\textsuperscript{39} to the conclusion that, although more common ipsilaterally to the lesion (especially when there was also a disturbance of rhythm), there was no good correlation with the type of lesion as assessed by clinical signs. Boxers are still yielding material for those interested in head injuries. In Sweden, Melin\textsuperscript{66} has had the opportunity of recording their EEG's both before and after bouts. Kaplan\textsuperscript{59} at a regional meeting reported observations made on boxers in New York.

Fischgold\textsuperscript{37} raises again the question of whether spike-and-wave should be taken as necessarily indicative of a thalamic disturbance and agrees with Jasper's\textsuperscript{41} statement that the electrographic picture alone is not sufficient to prove that such seizures originate there, although in animals they can be provoked by stimulation of the thalamic reticular system. Bearing on this problem are the studies by Cohn\textsuperscript{81} of the spike-and-wave in the human EEG which, when recorded on a multiple beam cathode ray oscilloscope, is revealed to be bilaterally asynchronous by intervals of the order of 5 to 20 msec. To this reviewer such time differences between any two areas might possibly be contributed by the cortical elements and be within the rather wide range of time necessary to activate an action potential in the apical dendrites of the pyramidal cells by synaptically transmitted impulses. This explanation would only hold were the present supporting evidence for two postulations to prove correct, namely that the nonspecific afferent system synapses onto apical dendrites, and that the spike of the 'spike-and-wave' is a discharge of these dendrites. The long duration of the spike found by Cohn would be in keeping with the latter suggestion. The evidence for the dendritic origin of spikes in focal epilepsy was outlined by Brazier\textsuperscript{8} at a symposium of the American League against Epilepsy. Some workers (e.g., Fuster\textsuperscript{42}), however, accept the diencephalic origin of spike-and-wave to the extent of concluding the triggering mechanism to be diencephalic in those cases of clinically typical automatisms that have this pattern of EEG abnormality. Neidermeyer\textsuperscript{86} and Schwab\textsuperscript{102} have both discussed this type of case. Passouant's\textsuperscript{89} note on 8 pairs of identical twins with idiopathic epilepsy is most interesting. Mann\textsuperscript{80} has reported 2 cases of status epilepticus in petit mal, and Vizioli\textsuperscript{110} has studied the EEG in a case of narcolepsy. An interesting report of 50 patients with temporal EEG foci and a comprehensive discussion of temporal lobe epilepsy has been published by Magnus.\textsuperscript{78} The illustrations include excellent recordings from nasopharyngeal leads as well as from scalp leads and electrocorticograms. In only a few cases did sleep accentuate the spiking.

Klingman\textsuperscript{64} finds the efficacy of ion exchange resins, as used in the treatment of epilepsy to influence electrolyte balance, to be reflected in the EEG. Great reliance is placed by Putnam\textsuperscript{95} on the relationship between seizures and EEG patterns and on this has been based a rapid method for choosing
for any given patient the optimum medication from 10 drugs. In 21 out of 27 patients clinical benefit came from a drug that fell among the 3 that had been most effective on the EEG. A new method\textsuperscript{*} for determining the threshold tissue concentration of a convulsant drug necessary to produce cortical spiking has been based on the fluorescent reaction to ultraviolet light of acridone—a convulsant overtly similar to Metrazol. It is known that the tertiary amines used in the treatment of Parkinson's disease are antagonistic to convulsants such as DFP and nicotine (but not to strychnine), and now an interesting report has been published by Longo\textsuperscript{75} which gives some clue as to the site of action of these drugs. The familiar arousal response in the EEG of an animal with an 'encéphale isolé' was obliterated by small doses of these drugs—this effect being evident whether the stimulus for arousal were auditory, or tactile to the head, or by activation of the brain stem. Lehmann\textsuperscript{76} has reported on chlorpromazine (Largactil) in human subjects and another study leading to the conclusion that this drug acts by depression of the reticular formation in the brainstem has come from Hiebel.\textsuperscript{56} These workers find that this is also the site of action of d-amphetamine\textsuperscript{57}, a drug which is notoriously alerting in its action.

The interest in reserpine (Serpasil) as a sedative and in its possible site of action has led to some studies on monkeys by Schneider\textsuperscript{100} that included EEG's. The conclusion was reached that although the animals became quiescent to a striking degree, there was no anesthesia or demonstrable hypnotic effect. The EEG changes were minimal. For a hypnotic Dormison has been compared with Seconal in the same subjects by Williams\textsuperscript{118} whose results essentially confirm the earlier ones of Henry. The effect of topically applied eserine and acetylcholine on evoked responses has been reported by Chatfield\textsuperscript{16} and that of intraventricular introduction of these drugs (and others) on the EEG by Cooke.\textsuperscript{23}

The current interest in geriatrics in a population with an increasing expectation of longevity is reflected in a crop of studies of the EEG of the aged. Obrist\textsuperscript{57} has reported on findings in a group of 150 men between the ages of 65 and 94, having no specific neuropsychiatric disease, but with the "normal" incidence of minor disorders for this age group. (The familiar difficulty of what degree of disability is to be deemed normal for the aged is a vexing one.) The predominance of slow alpha rhythms (usually 7–8 cps) and scarcity of 11–12 cps alpha was found to be characteristic, but delta activity was uncommon. This paper contains a useful bibliography on the EEG of the aged. Mundy-Castle\textsuperscript{55} has also published results from a group of 50 normal seniles and compared them with 104 patients with senile psychosis. The latter group showed a significantly higher incidence of diffuse delta and theta rhythms (4–7 cps). Both writers remark that normal seniles have more fast activity (above the alpha range) than young adults.
One regrets the information lost by omission of leads from the anterior temporal region, for Busse found a high incidence of focal disturbance in this region in his group of elderly people.

Ford has added another study to reports on increased amplitude of temporal lobe theta during mental calculation. He records only between a frontal electrode and an ear lobe and prefers to interpret the activity as coming from the frontal lobe. Muller, recognizing that electrodes on the ear lobe are highly active, finds them useful when used specifically as active electrodes for localizing lesions; when comparisons between hemispheres are to be made, he links them to both ipsilateral and contralateral electrodes on the scalp. The clinical importance of focal theta rhythms in the parietal regions as localizing signs of lesions has been emphasized by Cobb.

A review of 12 years of experience inducing chronic experimental epilepsy in monkeys by alumina cream has been brought together by Kopeloff. The peak time of onset of seizures is between 5 and 9 weeks after application, and the epileptic condition can last for years. In an investigation primarily designed to test whether alumina cream placed on the preoccipital cortex would affect visual discrimination in 3 trained monkeys, Chow also examined their EEG's. No detectable loss of visual faculties occurred in spite of the development of EEG spiking in all 3, and convulsions in 2 of the monkeys.

Increased fast activity has frequently been reported in studies of psychological disorder, and Kennard has demonstrated that automatic frequency analysis defines this more clearly than visual inspection, as well as emphasizing the greater scatter of frequency patterns in the patient group. Establishing a control group for studies of psychiatric patients is a major problem and the careful and statistical study of Ulett and his colleagues issues a much needed warning. In reference to the search for EEG signs in psychiatric disorders, Williams points up well the reasons why routine EEG records are unlikely to relate to the functional aspects of cerebral activity as a total picture (as reviewed, for example, by Ellingson), and he emphasizes that the response of the EEG to physiological and chemical changes together with a comparative study of the potentials of different parts of the brain relative to other parts is a more meaningful approach. The EEG changes accompanying inhalation of 30 per cent CO₂ 70 per cent O₂ have been followed by Friedlander in psychiatric patients receiving this therapy. The results are difficult to interpret in the absence of other physiological data (such as blood gas analyses). That psychiatric symptoms may be masking incipient brain tumors has been emphasized by Waggoner and Bagchi who urge the use of the EEG to detect focal lesions and make an early diagnosis.

The familiar effect on the EEG of barbiturate injection has been used by
Shagass to establish a 'sedation threshold'. His examination of amplitude changes in this frontal fast activity enabled him to establish a point of inflection in the rising curve of amplitude growth that could be used as an end-point; this end-point usually coincided with the onset of slurred speech. He found a significant correlation between a high sedation threshold, (expressed in mg. sodium amytal per Kg. body weight), and tension in psychoneurotic patients as rated by clinical assessments. Automatic frequency analysis confirmed his earlier work based on visual counting and measurement. In another study, Bergman found no differences between normal subjects and patients with organic brain disease in their EEG response to barbiturates (as assessed by simple inspection of the records), even though the latter group frequently reacted with marked mental disturbance.

Acting on Gastaut's original differentiation of the two types of reaction evoked by photic stimulation (the fronto-polar of muscular origin and the fronto-central of cerebral origin) Shagass studied the incidence and degree of the former (muscular) response in a large group of unselected psychiatric patients. Incidence of responses was not found to be a function of the type of psychiatric disorder, but to be related significantly to evidence in the patient's history of neurological brain disturbance (epilepsy, ECT, barbiturate poisoning) or familial relationship to epileptics. High incidence was also related to the presence of abnormalities in the resting EEG. Further cases of self-induced attacks in photosensitive epileptics have been reported, Graeme Robertson reporting on seven.

There has been some difference of opinion about the normal threshold for photometrazol activation in adults. In children it is an even more difficult problem, but Laufer having, in a group of 31 children, found a repeatable threshold in the same child, feels some confidence in a figure of 6.5 mg./Kg. as a normal standard for the ages 6-11. A demonstrably higher percentage of children with "organic syndrome" had thresholds below this. In neuropsychiatric patients, Lieberman has confirmed that catatonic schizophrenics and idiopathic epileptics have low thresholds to photometrazol activation but does not recommend it as a diagnostic test. Activation by chloralose for differential diagnosis in epilepsy is favored by Verdeaux.

An extension of photic stimulation tests has been made by Gastaut in the introduction of moving pictures as the activator. In a group of 80 subjects, 62 of whom were normal, the EEG findings could be classed under 4 headings: modification of alpha rhythm, appearance of occipital sharp waves, development of theta, and enhancement, when present, of the rolandic rhythm 'en arceau'. The latter rhythm was found more commonly in individuals with psychosomatic traits and is suppressed by voluntary movement, especially of the hands, such as clenching of the fists. Magnus finds sensory stimulation of the hand to be even more effective than voluntary
movement in blocking this rhythm. In this context Subirana's case\textsuperscript{107} is of interest: he reports a case with focal EEG abnormalities at the scalp over area 4, which disappeared when the patient made voluntary movements of his hand. Faure\textsuperscript{83} has used moving films with sound tracks to give a variety of types of stimulation while EEG's and ERG's were being recorded.

There has been some progress in devices for detecting evoked responses among the fluctuating EEG waves. Dawson\textsuperscript{28} has now published his method in detail and has demonstrated its success in picking out responses on the scalp to electrical stimulation of the ulnar nerve in man. As Dawson points out, the use of a mechanical rotating switch for sampling the EEG imposes certain limitations. The switch rotates 10 times per second and hence only a 100 msec. of record can be analyzed, longer lasting effects of a stimulus being, therefore, lost. In addition, only rhythmically delivered stimuli can be used. An electronic method working on analogue principles has been published by Barlow and Brazier\textsuperscript{2} that avoids these particular limitations and can also be applied to correlation studies of long samples of continuous EEG records. In experiments on cats it could be demonstrated (Szekely and Spiegel\textsuperscript{107a}) that in the cataleptic state produced by bulbocapnine, the reactivity of the cortex and various subcortical areas (hypothalamus, reticular substance of the midbrain, cerebellar cortex) to afferent impulses is preserved, or even increased. The interaction of peripheral and cortical stimuli with cerebellar potentials has been explored by Cooke and Snider\textsuperscript{24} who have shown the latter to contain slow components as well as the fast (300/sec) potentials.

Interest in models of neuronal organization in the cortex continues. Cragg and Temperley\textsuperscript{26} suggest one in which neuronal 'circuits' are secondary in importance to the effects of interaction caused by extracellular current flow. This hypothesis has the advantage of recognizing the nondigital character of some nervous system potentials and escapes from the confines of the all-or-none law. An ingenious model by Uttley\textsuperscript{108} for pattern recognition by the nervous system needs some modification to bring it up to date with our current knowledge of neuronal behavior, meager as that is. For his classification system by which pattern is recognized we are back at the "signal present" or "signal absent" concept—i.e., all-or-none. Also the assumption is made that when axons come within a given distance of dendrites, synaptic connection occurs. Only recently have we begun to understand synapsis onto dendrites and from what little is known, this assumption cannot be made in all cases. Brady's\textsuperscript{8} model for visual discriminatory mechanisms is again based on assumptions that some may question. One doubts whether Walter intended his stimulating suggestions all to be taken as experimentally established facts (as they have been in Brady's hypothesis). There is a great need for more work in this field in which Walter has indicated so
many promising openings. Of particular interest is a paper from his laboratory on stereognosis in which observations were made, in a test situation, of the EEG, EMG, respiratory rhythms and speech sounds.

Some interesting reports have come in on EEG changes in diseases that are not primarily neurological. The involvement of the CNS in collagen diseases has been studied by Lewis, Sinton and Knott by the use of 3 tests: EEG, CSF analysis and a psychomotor test. Of 51 patients suffering from a variety of diseases within this clinical grouping, 30 had abnormal EEG's, 13 of them having focal dysrhythmia. Fifteen of these 30 patients had CSF changes. The EEG in several cases of Addison's disease, diabetes and thyroid disease and in single cases of the rarer endocrine disturbances have been reported by Condon. Forty-eight per cent of the total group of 87 showed EEG abnormalities of various kinds. Further studies have come from Faure of the correlations between EEG and physiological fluctuations in endocrine function in menstruating and pregnant normal women as well as in psychoneurotics. Serial EEG's on tubercular patients treated with isoniazid have been followed by Winfield.

The in vitro metabolism of electrically stimulated cortical tissue has been investigated by McIlwain. A case of cerebral anoxia with unconsciousness for 3 years had EEG studies made by Lundervold and the findings in a case of hypopotassemia in a patient with periodic paralysis have been noted by Saunders. In a case of epilepsy partialis continua, Kugelberg finding a spike focus in the EEG, recorded simultaneously the electromyogram of the muscle twitch. Measurements on a cathode ray oscillograph showed the interval between cortical spike and muscle spike to be from 27 to 34 msec. The effects of carotid compression and of spontaneous carotid occlusion on the EEG have also received attention; in 7 cases of spontaneous occlusion of the internal carotid artery diagnosed by arteriograms, Feiring found only one to have a normal EEG, the usual finding being focal signs at the frontal and temporal electrodes on the affected side. Wise has reported the findings in cases of aneurysm in whom carotid ligation was performed, and Roberts on the EEG in essential hypertension and chronic cerebrovascular disease. The EEG in 80 cases of pernicious anemia and the effects on it of treatment have been followed by Walton who is of the opinion that the EEG reflects a specific defect in cerebral metabolism rather than the direct effect of anemia. A study in which the EEG was followed for several months in an epileptic having multiple blood and urine analyses before and during vasopressin and cortisone administration, has been made by Hatfield. Vasopressin and cortisone both caused water retention and exacerbated all symptoms. Improvement in the EEG paralleled decrease in severity of the seizures when fluid intake was restricted, but there was no decrease in their frequency. A report on the EEG and neurological
changes caused by X-radiation of the heads of monkeys while their bodies were protected to avoid radiation sickness has been published by Ross, and the related autopsy findings for this series by Clemente.

In the technical field there has been a description of a servo method for gaseous anesthesia, a circuit for synchronizing a time base marker for cathode ray work, and a statistical method for dealing with the information derived from automatic frequency analysis has been outlined. The medico-legal role of the electroencephalographer is one that is becoming increasingly important and this is reflected in a publication from France and in a symposium held in the United States.

In conclusion, it should be noted that these 118 references represent only a smattering of the EEG papers that have been published this year. The reports from this country on new aspects of the field tend to cluster in the EEG Journal but the electroencephalographer would be unwise to ignore other journals, especially those published abroad, since these contain more of the work of our colleagues overseas.

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CLINICAL AND LABORATORY NOTES

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SOME APPLICATIONS OF CORRELATION ANALYSIS TO CLINICAL PROBLEMS
IN ELECTROENCEPHALOGRAPHY

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In some previous communications from this laboratory (Barlow and Brazier 1954; Brazier and Barlow 1955; Brazier and Casby 1951, 1952) the principles and technique of correlation analysis as applied to electroencephalography have been described. The general principles of such application have also been discussed by Dawson (1954) and by Wiener and Brazier (1954). The present communication gives samples of the type of information made available by this method in some clinical cases. The apparatus and technique will not be described in detail here, as both an outline (Barlow and Brazier 1954) and complete construction details for the instrumentation (Barlow and Brown 1955) have been published. The latter publication is from the Research Laboratory of Electronics at the Massachusetts Institute of Technology, where the apparatus was developed and constructed in collaboration with R. M. Brown and W. A. Hosenblith with whom a joint project of research is in progress, of which this report concerns only a fragment.

CLINICAL APPLICATION

Examples of only two of the possible applications of this technique to clinical cases will be presented at this time: autocorrelation of the EEG, which extracts only periodic rhythms from the melee of brain potentials present, and, secondly, a special application of cross-correlation to the analysis of evoked responses by which those potential changes that follow the stimulus with a consistent time course receive especial emphasis.

AUTOCORRELATION

The EEG is recorded simultaneously on an ink-writing electroencephalograph as a voltage-time graph and on a 5-channel (frequency modulated) tape recorder. Autocorrelation is a series of comparisons of any one electroencephalogram with itself shifted in time, the comparison being taken for very many delay steps. This process, which is done electronically (Barlow and Brazier 1954; Barlow and Brown 1955) consists of taking the values of amplitude continuously along the curve of an EEG and of the same EEG displaced in time, multiplying them, integrating the products and normalizing. At each value of delay time used, an Esterline-Angus ink-writer records a pen deflection that is proportional to the correlation function at that delay step. Fuller explanation of this procedure will be found in previous publications as listed in the references at the end of this paper.

When a simple periodic wave (a sine-wave) is compared with itself in this way the resultant correlogram is itself sinusoidal (see, for example, fig. 1A). When only non-periodic (or random) potentials are autocorrelated, the result is an exponential-type curve rapidly decaying from full correlation (when the original is compared with itself without any delay) to zero correlation, without any periodically returning positive correlation (see fig. 1B).

When both classes of potentials are present, both periodic and aperiodic, as is usual in the EEG, the correlogram shows a periodically recurrent correlation, alternately positive and negative, riding on the initial decay curve caused by the aperiodic components, and usually outlasting it to comparatively large values of delay times (see fig. 2 below). In some subjects a periodically recurring correlation is also present that persists to delay times of considerable length. This phenomenon and some of its implications have been discussed by Wiener (1955) and will not be further described in this communication.

RESULTS

Figure 2 illustrates 2 autocorrelograms of the parieto-occipital EEGs of a normal subject, recorded
from the two hemispheres simultaneously. Mounted below each is a sample of the simultaneously recorded inkwritten trace. In this example the correlograms are of 1 min. EEG runs whereas, of course, only a few seconds of the ink trace can be reproduced. In all the examples shown, a time constant of 0.2 sec. was used for the EEG.

![Autocorrelation of known signal sources](image)

**Fig. 1**

Autocorrelation of known signal sources.

A. Autocorrelation of a 20 c/sec. sine wave. Length of sample 50 sec. The first and last few pen excursions indicate the baseline, i.e. the output of the correlator when there is no input. The figure indicates the relative degrees of correlation (positive or negative) of the sine wave with respect to itself at successively increasing delays (in steps of 1.25 msec.), beginning with maximum positive correlation at zero delay. The longest delay shown is 215 msec.

B. Autocorrelation of noise after passage through a low-pass RC filter with cutoff (i.e. half power point) at 50 c/sec. Sample length 20 sec., steps of delay 0.25 msec., maximum delay 30 msec. The figure indicates the approximately exponential form of the autocorrelation function of this type of noise.

These correlograms are from a normal man and they demonstrate that at small delay steps there is a periodic rhythm riding on the exponential curve due to his irregular waves and then persisting at longer delay steps in a more purely oscillatory form. The delay steps are at intervals of 5 msec., and since 18 pen deflections define a full cycle of each oscillation, the frequency of his rhythm is 11 c/sec. From the limited number of normal individuals whose correlograms have so far been run, it is clear that considerable variation exists as to the degree of persistence of oscillations beyond the decay of the exponential curve.

It is of great interest to us to note how similar some of our results are to the first published autocorrelograms of EEGs in man. In 1949 Imahori and Sahara published examples of their results obtained by mathematical calculation for delays out to 1.6 sec., and in the example shown (fig. 3B of their publication) the 10 cycle periodic phenomenon they found is still quite strongly present.

For comparison with the normal correlograms shown in figure 2, in which little difference between the two hemispheres is seen, some cases with brain lesions may be of interest to clinical electroencephalographers. From our series, two only will be reported here, with the object of familiarizing readers with this type of analysis and presentation of EEG findings.

**Case 1.** A 42 year old man with a 4 month history of headaches, episodes of weakness, dizziness and memory difficulties. Neurological examination revealed he had bilateral papilledema of 3-4 diopters with recent hemorrhage. The left corneal reflex was decreased, and there was weakness of the left face and arm. Decreased sensation to pinprick, touch, and vibration was noted on the left. The reflexes were more active on the left; and the left plantar reflex was extensor. There was a left homonymous field defect.

X-rays of the skull gave no evidence of a space-taking lesion. The standard EEG record showed diffuse slow waves from the right hemisphere but no clear focus. Some suppression of alpha was seen in the right temporal region. There was less following of flash frequencies on the right than on the left.

Autocorrelation analysis of the EEG indicated a more widely spread disturbance in the right hemisphere with involvement reaching posteriorly to the parieto-occipital linkage, thus being more closely in keeping with the neurological signs.

Autocorrelograms of four pairs only of the several leads used are reproduced in figure 3A. The pair at the top of the figure show the contrast between the temporal regions of the two hemispheres with a rather slow rhythm evident on the left and none of a periodic nature on the right. In the center pair on the left is the parieto-occipital record from the left hemisphere showing a clear 10 c/sec. rhythm (the delay steps are 5 msec., apart and 20 of these are seen to define a cycle). On the right is the correlogram of the homologous region on the right side (recorded simultaneously). The persisting 10 cycle rhythm is absent and an extremely low frequency
oscillation is present (as seen by the long swing below the baseline). This is approximately a 1.3 cycle oscillation.

In figure 3B is shown the effect of flicker at 15 c/sec. On the left the patient’s own 10 cycle alpha rhythm shows up at the beginning of the curve and then a 15 cycle wave obscured at the shorter delay times by the higher voltage (but less persistent) alpha becomes apparent and persists in undiminished amplitude to the end of the period of analysis. On the right however the effect of the flicker is only feebly superimposed on the slow oscillation detected in his resting record. This lateralizing of the flicker effect was in keeping with the visual fields.

The correlation analyses gave clear lateralization and suggested a more extensive lesion and disturbance spreading posteriorly to the occipital lobe, as did the neurological signs.

Autocorrelograms from 6 of the linkages used are shown in figure 4. A clear 10 cycle rhythm is seen on the left, maximal in the center strip. The contrasting records from the right are quite striking. In figure 5 is seen the effect of flicker at 10.5 c/sec. The difference in flicker response from the two sides, not remarked in the standard EEG, is brought out more clearly by the emphasis that autocorrelation gives to periodic potentials.

At operation an infiltrating tumor was found in the right temporal lobe extending posteriorly to the vein of Labbé and also into the operculum of the right frontal lobe. The tumor was an astrocytoma.

Case 2. A 61 year old man who entered the hospital because of weakness of the left arm of 3 weeks’ duration, together with blurring of vision and bifrontal headache. Two weeks before entry, the left leg had also become weak.

On neurological examination the patient was found to have a left hemiplegia involving face, arm and leg. There was also a left homonymous hemianopsia, and a diminution of vibration sensation on the left side. The left plantar reflex was extensor. Disc margins were indistinct.

X-rays of the skull showed calcification in the postfrontal region on the right reaching to the parietal lobe. The standard EEG record showed normal activity on the left and abnormal theta activity in the right central region with delta in the right temporal. Flicker did not show any lateralizing signs.

At operation a large meningioma was found in the right temporo-frontal region extending posteriorly into the parietal and occipital lobes.
time to the stimulus and tends to reject others that are independent of it.

The instrumentation differs from that used for the autocorrelations already discussed, in that an electronic device designed to sample the continuous graph of the EEG by constant amplitude impulses is employed. The sampling is accomplished by a gating and storage circuit whose technical details will be described elsewhere. An important feature of the method used is that the applied stimuli need not be periodic. The resultant correlogram gives the average form of the evoked potentials for the given number of samples taken. The more samples taken, the more clear-cut the form, but the physiological significance of exact details of waveshape may be questioned in the light of the known variability of response in the normally functioning organism. In our present series of subjects, the influences that tend to introduce variability of response are present, and none has been removed by anesthesia, sleep, sedation, or any other procedure.

An example of an average response to flash (from 70 samples) in a normal subject is shown in figure 6A. In this example the recording was a
bipolar one (with the occiput on the second grid) and the recording instrument was arranged to give deflections of the writing pen above the baseline when there was an increase in relative positivity at the occiput.

In this subject there is an occiput-positive deflection with its peak at 90 msec, followed by a large significance of the variations seen in the correlogram earlier than 90 msec, needs investigation by analysis of a greater number of samples. The physiological variability referred to above, is evident from the irregularities of the pen excursions for this number of samples. Only a wide survey of subjects will tell us how representative this illustration is for normal

Fig. 4
Case 2. Autocorrelograms of 6 samples of the resting EEG in a patient with a right sided cerebral tumor. The correlograms are analyses of 1 min. runs of which 3-sec. samples of the original trace are shown. Duration of delay increases from left to right in 5 msec. steps. Leads shown are (from top to bottom) parieto-occipital, posterior temporal to occipital, parietal to mid-occipital.

negative wave maximal at 145 msec. (The pen deflections are in steps of 5 msec. delay and the trough of the occiput-negative wave occurs at the 29th deflection.) There is a series of oscillations following this that are time-locked to the stimulus. It seems likely that these oscillations are the counterpart of the train of waves shown by Bishop (1933) to follow single flash stimulation in animals. The people. It is clear from our preliminary series that in some individuals the effect of each flash is not over in 850 msec, and that some brain potentials time-locked to the stimulus are still present.

In figure 6B the correlogram (similarly recorded) from a similar arrangement of electrodes is shown for an epileptic patient with unusual sensitivity to light. In this correlogram of an evoked response
without a seizure discharge, the initial occiput-
positive wave is very pronounced (with its peak at
95 msec.) and is followed by a conspicuous occiput-
negative swing (trough at 145 msec.) and then by

**COMMENT**

The purpose of this note is not to present results
of a specific research problem but to acquaint
electroencephalographers with this type of analysis

![Figure 5](image)

**Case 2.** Recordings and correlograms of parieto-occipital linkages during intermittent photic stimulation. Delay steps of 5 msec. 10.5 flashes/sec.

marked oscillations slower and of a less irregular
average shape than those of the control record in
figure 5A. The cycles are approximately 125 msec.
in duration or about 8 c/sec.

and the method of presentation used when this
technique is employed as an ancillary method to the
ink-recorded traces in clinical work. The emphasis
given to periodic potentials by autocorrelation an-

![Figure 6](image)

**A.** Evoked response to flash in a normal woman. Parieto-occipital recording with pen deflections above the baseline indicating relative positivity at the occiput. Delay increases in 5 msec. steps from left to right.

**B.** Similar recording from a photosensitive epileptic patient.
analysis makes this method especially suited to the study of the effects of intermittent photic stimulation since the stroboscope imposes a periodicity on the potentials of the normal brain.

The two examples of brain tumor cases were chosen because they have operative findings for checking those of the EEG and its correlograms. The example from the epileptic patient was selected because of her unusually sensitive response to light.

We would like to acknowledge the valuable help received from our many colleagues in the Electroencephalographic Laboratory at the Massachusetts General Hospital and in the Laboratory of Communications Biophysics at the Massachusetts Institute of Technology. We would also like to thank Mr. J. U. Casby for his continuing interest in this method and for many helpful discussions.

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"There is not always loss, but there is, I believe, always, at least defect, of consciousness co-existing with the overconsciousness ('dreamy state'). After some paroxysms in which consciousness has been lost there are exceedingly complex and very purposive-seeming actions during continuing unconsciousness; in a few cases the actions appear to be in accord with the 'dreamy state'.

It will have been seen that I do not consider the 'dreamy state' to be a 'warning' ('aura'), that is to say, not a phenomenon of the same order as the crude sensations of smell, etc. Hence my objection to the term 'intellectual aura', and adoption of the less question-begging adjective 'dreamy', one which is sometimes used by the patients. It is very important in this inquiry to distinguish mental states according to their degree of elaborateness — from crude, such as the crude sensation warnings of smell, etc., to the vastly more elaborate, such as the 'dreamy state' — in order that we may infer the physical condition proper to each. The crude sensations are properly called warnings; they occur during epileptic (sudden, excessive and rapid) discharges; the elaborate state I call 'dreamy state' arises during but slightly raised activities (slightly increased discharges) of healthy nervous arrangements."

HUGHLINGS JACKSON

_Brain_, vol. XI, 1888 p. 179
There have been many symposia this year in different countries but most of these will not see publication until next year. There is one new book on clinical EEG by Jus and his wife, written in Polish. Schwab’s book has been translated into Japanese; how faithfully, I cannot tell. Liberson and Brazier have written reviews of papers published in 1954. The new edition of Fulton’s A Textbook of Physiology (which has shed the name of Howell) has had several of its sections completely rewritten, including all those on the nervous system by Lloyd, and that on the EEG by Ruch. In the French medical encyclopedia, sections on the EEG have been contributed by Gastaut, with special reference to psychologic changes in the normal subject and the epileptic.

The papers given at the Symposium on Electrochemistry, in New York, have been published (with some modifications) as a book. Almost all these papers have a bearing on the basic processes underlying EEG potentials, although only two are directly on this subject. Jasper contributes a short survey of the EEG in epilepsy for those not familiar with the field. Bagchi gives a more advanced presentation of the EEG signs of brain tumors which many will find useful for teaching. O’Leary’s stimulating article is a valuable guide to the finer points of advanced clinical electroencephalography. Writing with extensive knowledge of his subject matter, he emphasizes the contributions EEG can make to the current trend in neurology, toward evaluation of symptoms and prescription of treatment. These contributions are deplored by Walshe who continues to release his barbs at electrophysiology and at EEG, despite their failure to impede progress in either of these sciences. "Le démon inventif des techniciens" (to use Fessard’s delightful phrase) perseveres undaunted.

The volume of Granit’s Silliman Lectures will interest electroencephalographers, especially his discussion of “spontaneous” activity in sensory receptors, for this has bearing on any hypothesis we may formulate about “spontaneous” activity in the brain. Granit emphasizes the centrifugal...
control of activity in receptors, such as the retina and cochlea as well as the well-known muscle spindle control; and he postulates self-exciting loops as the mechanism for this. This would suggest that the word "spontaneous" is a misnomer. As has been commented upon in previous reviews, the old dichotomy between sensory and motor systems is no longer so helpful a concept. We have become used to recognizing the controlling influence of afferent inflow on efferent phenomena (even if some do not like the word "feedback"), but now more and more evidence is mounting to show that the input to the central nervous system is under a degree of control exerted by the descending outflow from the brain stem and cerebrum. In this framework the simple "stimulus-response" approach to the study of the CNS is revealed as naive. In addition to Granit's book see, for example, the work of Rasmussen for such effects in the auditory system, Eldred in muscle spindles, and Hagbarth in spinal ascending systems. As Adrian has said, "We can see how even the most straightforward kind of receptor is subject to a constant adjustment by the central nervous system to make it provide the right kind of information."

Understanding of the physiology of sensory responses has become imperative for the EEGer because of the almost universal use of photic activating technics in clinical tests. This has focused attention on the intimate structure of the cortex in its relationship to the potentials recorded from it. A clear statement of Bishop's hypothesis as to the role of apical dendrites in specific evoked responses, together with a summary of the supporting evidence, has been published. The graded responses of these structures, and their lack of a refractory phase, give them characteristically prolonged fluctuations of activity adequate to account for the waves of the EEG. No explanation for EEG waves based on the brief explosions of all-or-none impulses in axons has proved satisfactory, and the recognition of graded response tissue in the cortex now suggests a medium for the continuous activity seen in the EEG. There is, however, still not complete accord among physiologists as to the structures responsible for the complex series of potentials evoked in the cat's cortex by stimulation of the optic nerve. Bremer refers all three of the spikes (that ride on the positive phase of the slow diphasic potential) to differences in conduction times within the visual system (unlike Bishop, who would place only the first spike presynaptically). Bremer finds this succession of spikes also in the transcallosal response, but only in the visual system. He does not obtain them with clicks. In the auditory cortex the transcallosal response (to geniculate stimulation) is a diphasic slow wave whose long latency Bremer allots to conduction time and synaptic delay in the transcallosal pathway.

An international colloquium on microelectrode studies was held this year in France, but the papers have not yet appeared in print. Among published
works is one by Buser, on lower vertebrates, which reports evidence for a multiple response to brief flash at the retinal level—a secondary emission of nerve impulses following the initial discharge, and recordable from the optic nerve as well as from the optic lobe. This finding would necessarily affect the interpretation of any excitability cycles that might be calculated for the optic lobe response to flash in these animals. Buser also finds in the optic lobes of these animals slow potentials at the unitary level that have the characteristics of the slow dendritic potentials described in mammals by Bishop. They have the physical attributes of dipoles oriented radially to the surface, and show a clear reversal of phase as the recording electrode penetrates the lobe. Lower vertebrates show a decrease in latency of optic lobe response with increasing intensity of light, as does the cat. In higher animals caution must also be exercised when calculating cortical excitability cycles, for the extracellular microelectrode studies of Eyre and Bickford clearly demonstrate late (in addition to the early) responses to flash of single cells firing in the geniculate as well as of single cells in the cortex. The late response may follow as long as one second after the flash. This phenomenon persists in the geniculate after removal of the ipsilateral hemisphere, the retina and the cortex, and therefore does not seem to be a simple reverberatory effect.

Microelectrode technics are being actively explored for the contributions they can make to these problems. At the meeting of the German Physiological Society Jung and Baumgartner discussed the action potentials they record from different types of single cells in the cat’s visual cortex in relation to single cell responses in the retina. The electrode arrangement they use within the volume conductor of the brain does not, however, record the electrotonic potentials of the dendrites, as they make clear. The advocates of unipolar recording (to a distant electrode) from extracellular electrodes in the CNS would do well to heed the warning from Donaldson and Matthews whose short note indicates with great clarity the errors latent in attempts to localize by that technic. At a symposium of the American EEG Society on microelectrode recordings, Amassian reported that the initial surface positive wave evoked by peripheral nerve stimulation showed maximal voltage change toward negativity at a level of the cortex superficial to 600 μ. In a few preliminary experiments by Dondey a similar level was found for the response evoked by flash. The measurements were made on the histologic section containing the electrode that had been left in place. Possibly this technic may account for the depth of reversal being different from that reported in the earlier work of Jasper and Li. Workers concerned with localizing their microelectrode recordings will be interested in reading Lehmann. At the Chicago symposium the hazards of generalizing about evoked cortical responses from observations on barbiturized animals were
once again voiced, as they have been in several recent publications, and specifically, by Schneider, in relation to topographic maps. The last paper gives an excellent review of the action of anesthetics on brain potentials, with a valuable bibliography (present in the reprints but cut out by the editors in the original journal). A further hazard in microelectrode work has been brought to light by the demonstration by Easton that a microelectrode internal to a single inactive muscle cell picks up potentials from adjacent active cells.

With extracellular recordings, Buser finds the spike to reverse in the cellular layer, but the 15 msec. potential to remain negative. On penetration of the pyramidal cell (as evidenced by change in resting potential) the 15 msec. potential remains negative in sign, thus substantiating the theory that it has its site in the long dendritic core conductors. In the sensorimotor cortex of the cat, Albe-Fessard finds a slow diphasic wave preceded by the fast spikes associated with cell penetration. These are, however, modified by stimulation. Li’s careful studies led him to the conclusion that the rapid repetitive discharge of fast positive spikes accompanying the DC shift represented mechanical irritation or injury of the cell membrane due to penetration of the electrode. The maximum amplitude he found for the action potential of the cell was 60 mV, and for the resting potential 87 mV. These positive spikes have a duration of a little over 1 msec. In the somatosensory system, Mme. Fessard has confirmed Amassian’s finding that in cats under anesthesia with chloralose (but not with Nembutal) there is an area where bilateral late responses to sciatic stimulation can be found. Her experiments show that these are not conducted by corticocortical fibers from the primary or secondary receiving areas, either ipsi- or contralaterally; the responses do not recruit, and the suggestion is made (on the basis of occlusion experiments) that some polysynaptic intrathalamic pathway may be involved.

The latency of the cortical response to flash is longer in man than in rabbits, and much longer than in cats. In the rabbit, Laue and Monnier find the first positive deflection to occur at 21, 27 and 28 msec. after the flash in the retina, geniculate and cortex, respectively. In man the latency to the retinal b-wave is 30, to the cortex 40 msec. They find the slow negative wave that follows this to have its peak at about 70 msec. in the rabbit and 115–128 msec. in man. In my experience, with a modified crosscorrelation technique for determining the average response, 90–95 msec. has been found to be the more usual latency for the peak of this event in man. Rémond has published an example in man in which his topograph shows a maximum negativity at the occiput at 100 msec. after the flash. Suenage and Noda have attempted a study of the effect on the EEG of the clicking of a metronome, but from their results one would conclude that the changes they re-
corded were not specific in kind, but caused by a change in alertness or tension on the part of the subject.

In the clinical application of photic stimulation as an activator, Leffman and Perlo\textsuperscript{115} made a comparative study of photic, Metrazol and combined photo-Metrazol in 150 patients. The threshold response (namely, spiking in the EEG) was accompanied in every instance by muscular jerks. Six patients, all epileptics, could be activated by light alone. The results confirmed Gastaut’s observation of low thresholds to photo-Metrazol in most epileptics and in many schizophrenics. The authors recommend this combined activation rather than Metrazol alone, and emphasize the differences in spike formation between responses in epileptic and nonepileptic patients. Fisher and Friedlander\textsuperscript{68} have undertaken statistic analyses of other workers’ (and their own) published figures on age in relation to Metrazol activation, and they conclude that it is not an operative factor among patients with convulsive disorders, although their analysis confirms Moore and Kellaway’s\textsuperscript{133} statement that more normal subjects under the age of 30 can be activated by the drug than those over this age. Epileptic patients who are triggered into seizures by photic stimulation without Metrazol are rather rare. Ardito\textsuperscript{10} has added five more to the literature.

Gozzano’s group\textsuperscript{68} has explored, in animals, the sequence of spread of Metrazol-induced seizure discharges in various subcortical centers in relation to the onset in the cortex. They have also made similar studies of photically-induced seizures after sensitizing with strychnine.\textsuperscript{58} Van Harreveld\textsuperscript{185} finds that photic or acoustic stimulation of rabbits (but not of cats) who received slow i.v. Metrazol causes a depression of cortical activity rather than a convulsion. He presents this slow DC shift as an example of spreading depression evoked by sensory stimuli. Arguing from the usefulness of cortical stimulation as an aid to localization in electrocorticography, Gozzano\textsuperscript{67} applied low voltage high frequency currents to the scalp through a diffuse electrode. He found them to have no effect on the EEG of normal subjects, but pathologic foci were sensitive, and their signs became augmented, while in some cases diffuse abnormalities became focal. Since the parameters of stimulation were too weak for direct cortical activation, Gozzano suggests that the effects may be indirectly mediated by vasomotor changes in the meninges.

The information gained from the EEG while the subject is asleep is getting wider recognition and application. For example, the desirability of psychotherapy in enuresis persisting beyond infancy is emphasized by Ditman’s\textsuperscript{62} finding that the EEG almost invariably returns to the waking pattern before wetting occurs. In the search for a sleep-inducing agent that does not itself affect the EEG, Ladwig\textsuperscript{113} tested one of the glutarimides now
on the market as a hypnotic. Although not chemically related to the barbi- 
iturates, it was found to produce fast activity, especially in the anterior part 
of the head. From an experimental study in rats of the behavior of artifi-
cially-produced spiking lesions, Caspers concludes that the activators of 
spiking are the changes in vegetative tone that take place in sleep and narc-
osis. The results are discussed in relation to spikes activated by sleep in 
epileptics.

Several studies of temporal lobe epilepsy add to our knowledge of the 
EEG signs. They have been described in the newborn, in unilateral cases 
and in a case of petit mal automatism rather similar to the one described 
by Penfield and Jasper, in that bilaterally synchronous spikes-and-waves 
were brought on by overbreathing, but different from it in that temporal 
lobe spiking was present before the seizure. There seems to be a very close 
but not absolute relationship between respiratory arrest and impairment 
of consciousness in petit mal attacks (rather than with electric seizure dis-
charge). Fischgold, using both mechanical and electronic methods for 
recording respiratory exchange, suggests that the associated “absence” may 
implicate a reticular formation influence not necessarily involved in the 
respiratory changes accompanying temporal lobe seizures. Some interesting 
cases in which temporal lobe spiking was inhibited by photic stimulation 
have been presented by Vizioli. Glaser has studied a series of 110 chil-
dren between the ages of 1½ and 16 with psychomotor seizures. It is not 
clear whether all were cases of temporal lobe epilepsy; several certainly had 
petit mal seizures as well, and 34 had bilaterally synchronous spike-and- 
wave. Eleven had unilateral temporal spikes when awake, but sleep added 
only four more to this number. Sleep, however, increased bitemporal spiking 
from one to nine cases, but tended to obscure slow wave foci.

The similarity of behavioral disturbances in temporal lobe epilepsy, and 
in some psychotic states, led Ervin to make a detailed study of 42 mental 
hospital patients selected on the basis of their showing either unilateral or 
bilateral temporal lobe spikes. Of them, 34 were classified as schizophrenics, 
and all but four of these were recognized as also having clinical epilepsy. 
Nine patients with temporal lobe spiking were not considered to be epilep-
tics, seven of them being diagnosed as schizophrenics with primarily cata-
tonic symptomatology. This study is interesting in that it offers a basis of 
comparison with Hill’s well-known observations on psychotic behavior as-
associated with signs of temporal lobe dysfunction.

The report from the Maudsley group on their experience with temporal 
lobectomy in cases of temporal lobe epilepsy is a fine example of medical 
writing—comprehensive, clear, yet concise, and comes just at a time when 
the style of scientific reports is under attack. The Maudsley workers 
have been outstandingly successful in their use of this treatment. Their
basis for selection (which relies heavily on the EEG) and their surgical procedure (which includes excision of the uncus, hippocampus and recently the amygdala) are felt by them to contribute to the high degree of improvement that results. The use of sphenoidal as well as basal electrodes, and barbiturate narcosis, are considered essential parts of the EEG technic.

Within recent years the amygdala has been a particular object of research for many widely distributed workers, and to all of these, Gloor’s careful analysis of the connections of this group of nuclei in the cat will be of special interest. Stimulation of both major divisions indicates (by short latencies) direct connection with the septum, the preoptic region and the anterior hypothalamus and the nucleus accumbens. From these “primary” projection regions there are widely- and more caudally-distributed multisynaptic connections (as indicated by longer latency of response), and evidence is presented for influence of the amygdala on the whole basal grey matter of the diencephalon and upper brain stem. It is not surprising that the effects of amygdaloid stimulation are diversified rather than specific, and though the amygdala influences the activity of many centers its destruction does not totally abolish their function. The direct nonsynaptic connections found by Gloor agree substantially with known anatomic pathways. These are extensively reviewed in his papers, which also include a discussion of the significance of the electrophysiologic data in terms of the demonstrable autonomic and behavioral responses to stimulation of the amygdala. One of the regions readily responding to amygdaloid stimulation, although only after long latencies, is the hippocampus. The multisynaptic pathway is apparently through the pyriform cortex, and the ease with which the hippocampus responds may be due to its low threshold for discharge (for a recent paper on this subject see Liberson and Akert).

MacLean’s scholarly article adds new material to our knowledge of the limbic system, and forms a bridge between the fields of behavior and neurophysiology. A brief summary of a longer report has come from India of some extensive studies with implanted electrodes, of the effects in awake animals of stimulation at various points in the limbic system. Evidence for a region in the first temporal convolution of the monkey, where stimulation produces suppression of electric activity, has been explored further by Huertas who has demonstrated an accompanying suppressor type of seizure with listlessness and loss of defensive reactions to attack. These results are discussed in their relation to psychomotor epilepsy.

The paper on the hippocampus by Cragg and Hamlyn gives the kind of correlation that is so much needed between electrophysiologic observation and histologic structure. With extracellular microelectrode recording in the rabbit, they find the response of the apical dendrites to weak synaptic stimulation to be 15 msec. in duration; with strong stimuli the dendrites
themselves yield a spike of shorter duration, but it is of low amplitude compared with the spikes of the cell layer. It is not clear whether a stimulus of physiologic strength could evoke this type of dendritic response. The all-or-nothing character of the response in the axons causes it to be abolished when the spike threshold is raised by anesthetics, but at the same anesthetic level the graded depolarization of the dendrites enables their 15 msec. response to persist. Velocity of conduction in these dendrites was found to be 0.3 to 0.5 meters per second.

A monograph on the hippocampus and epilepsy has been written by Cadilhac. This contains a great deal of original work as well as a review of previously published material. Liberson has brought together, in summarized form, many observations on rhinencephalic structures, and has related them to emotional factors in epilepsy. In about 12 per cent of epileptic children, behavior disorders vastly complicate the approach to treatment. Conclusions as to their management have been discussed by Pond on the basis of a detailed study of 50 cases.

In Symonds's lecture on the classification of the epilepsies, great stress is given to the EEG. He states that seizures may be accompanied by observed disorder of function in the neurones, and that, of this, the only example known at present is the physical disturbance recorded by the EEG. Some electroencephalographers may prefer to regard this as no less an inference than those made from the clinical signs. The controversy of the specificity of the wave-and-spike complex for petit mal has been considerably clarified by Clark and Knott's study correlating clinical aspects of seizures with the frequency of the components, the latter parameter being broken down into six subsections specified as single frequencies of 2, 3 or 4 c.p.s., or as specific mixtures of them. This refinement and extension of the variants, originally suggested by Lennox, has clarified some of the previous areas of disagreement, and tends to support the early findings of Jasper and Kershman. No evidence was found to support the suggestion that the classic three c.p.s. wave-and-spike pattern is indicative, and the slower variants contraindicative, of an inherited defect. The closer definition of the EEG concomitant of true petit mal epilepsy has therapeutic importance, for, as Cobb has emphasized, the presence of wave-and-spike in the EEG is not alone sufficient reason for giving Tridione, a drug peculiarly suitable to petit mal.

Howell reported a group of patients with classic three c.p.s. spike-and-wave discharges in whom the clinical seizure patterns were anomalous for the Montreal classification of centrencephalic epilepsy. This paper includes a discussion of how discharges may spread in such a way as to mimic focal cortical seizures. The great variety of spike-wave patterns has also been commented on by Ricci and Vizioli whose experience leads them to join
the ranks of those who warn against using this EEG pattern for differential clinical diagnosis. Fischgold\textsuperscript{67} made a detailed study of the changing location, from second to second, during the course of petit mal seizures of the highest amplitude spike, and also of the highest amplitude slow wave. He finds this parameter of each component to have moving fields and independent locations. Since the measurements of maximal amplitude for the two are not made at the same instant in time, the maps he derives are not strictly those of electric fields in the usual and exact sense of the term. Bates\textsuperscript{14} confirms Cohn's earlier finding of a focal DC shift toward negativity during episodes of spike-and-wave, a finding consistent with activation of dendrites. His finding that the spike is diphasic, and initially positive, would suggest that it is travelling toward his electrode and not being initiated immediately under it. A detailed discussion of abdominal epilepsy has recently been given by Jay\textsuperscript{103} in a paper which contains an extensive bibliography. Excerpts from the personal diary of an epileptic patient have been published by Passouant,\textsuperscript{148} recounting some subjective reactions to a complex of symptoms.

Theories as to a possible diencephalic pacemaker mechanism for the trains of three c.p.s. bilateral spikes and waves seen in the EEG in petit mal have been prevalent since Jasper and Kershman's first suggestion in 1941. As stated last year by both Jasper and Fischgold, one should not infer from animal stimulation experiments that all such wave-forms are triggered from the diencephalon in man. Recent observations by Bickford,\textsuperscript{22} with implanted depth electrodes in a patient having petit mal seizures, would also argue against a solely diencephalic origin for these specific wave patterns. In fact, their reproduction in animals is itself not easy, as demonstrated by a report from Ingvar,\textsuperscript{100} whose studies have brought out some essential differences between this response to electric stimulation and the classic recruiting response of Dempsey and Morison. Marsan\textsuperscript{2} demonstrated that not only do recruitment potentials wax and wane as the stimulus is continued, but the latency of the response also varies. These phenomena would appear to be caused by interplay between two sources (both activated by stimulation of nonspecific nuclei), since electrodes within the cortical layers reveal a different level of reversal in the waxing phase from that during the waning. This is of interest in comparison with Li's findings of a reversal level about four mm. below the surface for the nonspecific response, and one of seven mm. for the specific one.

The symposium sponsored by the Spanish EEG group has now been published. The papers are all centered around the physiology and pathology of the diencephalon. Outstanding among these is Bremer's paper,\textsuperscript{29} which covers the history (with bibliography) of corticothalamic connections, and presents his own data on the electrophysiologic properties of corticofugal
connections as well as those of the ascending system. Bremer has demonstrated (by occlusion) that sensory impulses from two different receptor areas can converge on the same reticular neurones and, moreover, that corticofugal impulses can also converge with sensory ones on the same neurones of the reticular formation. These findings throw light on the fact that cortical stimulation produces an "arousal" reaction electrographically similar to the more familiar ascending one. This demonstrated participation of the cortex in arousal may perhaps explain the familiar observation that calling a sleeper's name (with all the implied associations) may be effective in waking him, whereas a simple sound may fail. Bremer raises the question as to why, although the hypothalamus and subthalamus (together with the 1st and 2nd cranial nerves) are preserved in the cerveau isolé preparation, their presence apparently is insufficient to keep the animal "awake." He suggests that impulses from the more caudal part of the reticular core are necessary for this. R. Hess, in the same symposium, disagrees, and emphasizes that although stimulation of the posterior hypothalamus provokes desynchronization of the EEG (as shown long ago by Murphy and Gellhorn), this is its only similarity to reticular stimulation, and that, behaviorally, it has a far more powerful arousing effect.

The transections of the neuraxis that produce Bremer's classic encéphale isolé and cerveau isolé, respectively, are well known. Roger and his collaborators in Moruzzi's laboratory have brought the limits of the transections (critical for maintenance or abolition of the EEG and pupillary signs of vigilance) much closer by demonstrating that the critical locus is the sensory nucleus of the trigeminal nerve. With a pontine section caudal to this nucleus a cat appears "awake"; section rostral to this causes signs of "sleep." When the section is made at C-1, or just below the nucleus, the sleep pattern and pupillary changes can be produced by bilateral destruction of the gasserian ganglia. These results have been obtained in both acute and chronic preparations.

Moruzzi has brought together in summarized form the work from his laboratory that has been concentrated on the physiology of the reticular formation. Schiebel's extracellular recordings of single cells of the reticular formation add importantly to our knowledge of this system, but do not give the definitive evidence for ascending reticular neurones that is still so prominently lacking. Some of his experiments, in which reticular units fired before the onset of a cortical strychnine wave, may be evidence, but as Schiebel and Moruzzi point out, other explanations are possible. His experiments confirm that considerable convergence of afferent impulses takes place at this level, but indicate some topographic organization favoring certain sensory modalities. Of the afferent systems, the acoustic one proves to be an anomaly. The group at Pisa has continued to explore cerebellar-reticular relationships using surface-positive polarization of the an-
terior lobe of the cerebellum, and recording its effect on the spontaneous firing of reticular neurones. Not only are there differentially localized effects, but there is also a differential vulnerability to barbiturate (indicating, perhaps, the existence of both monosynaptic and polysynaptic pathways).

Jasper's paper, read for him in absentia in the symposium on the thalamus held at Montevideo, brings together the various pieces of evidence that the neuronal structures whose electric properties make them capable of rhythmic 8–12 per second potentials, lie in the cortical layers; that their state of excitability is maintained at an adequate level for generating this rhythm by impulses in afferents to the cortex; and that the intimate mechanism of these changes in excitability may be neurochemically mediated. The paper gives a concise summary of Jasper's views on the role of the thalamic reticular system in EEG potentials. Hassler, at the same meeting, presented his reasons for postulating that impulses from some of the nonspecific thalamic nuclei reach the cortex via relays in the corpus striatum. Bailey's discussion of the papers in this symposium, voicing his reservations, is an important critique of the current hypotheses as to the diffuse projecting system.

The comparatively recently-demonstrated role of the brain stem in states of impaired consciousness prompted Caspers to study the effect of brainstem stimulation on duration and level of anesthesia (in rats). His experiments indicate that deepening and lessening of narcotic effects can be mediated by neuronal mechanisms involving the brain stem. The evidence for the role of the reticular ascending system in anesthesia and "consciousness" has been summarized with great clarity by French, but this article presents no new material.

Spiegel has demonstrated that diminution of electric activity in the sensory cortex following destruction of the ipsilateral ventral posterior thalamic nucleus may be only transitory, and that, after an interval, "spontaneous" potentials may even be enhanced. An interesting finding is that in this sensitized cortex the secondary response to sensory stimuli is also augmented (the primary is, of course, abolished). These results point to a sensitivity of denervation, and give supportive evidence for the extrathalamic pathway of the Forbes response. The possible relation of these findings to problems of thalamic pain are discussed. In man, Monnier has analyzed, from a neurophysiologic point of view, some of the results he has obtained from thalamic stimulation. Of considerable interest are his observations on unilaterality or bilaterality of signs—sensory and motor—following stimulation of thalamic nuclei. Spiegel has made the interesting observation of confusion of time orientation as a transitory symptom in patients after dorsomedial thalamotomy.

Sem-Jacobsen has given an account of the types of rhythms found
by depth recordings in 94 psychotic patients. In the absence of recordings by similar technics from normal subjects, reports of the complex rhythms found have to remain at the descriptive level. An interesting finding in a subject with auditory and visual hallucinations was that these were accompanied by paroxysmal bursts of focal spiking in the temporoparietal leads. An opportunity\textsuperscript{53} has now arisen for this group to examine the degree of damage 38-gage electrodes may cause, for one of these cases died 19 months after the procedure, the terminal illness (pneumonia) being unrelated. The histologic changes, which were minimal, were traced down for each electrode. These workers have recently reduced the diameter of the individual wires still farther (to 46-gage).

The same authors\textsuperscript{67} recorded the response to odors recorded from electrodes in the olfactory bulb of man. They found so great a variation in responses that they were unable to systematize them. It occurs to me that they would ease their task by using pure reagents (instead of mixtures), since initially, at the peripheral receptors, olfaction depends on solubility of molecules in receptor membranes, and hence the number of C atoms in the reagent together with its molecular shape and flexibility are all-important. There is considerable evidence for three types of receptors, and it may well be that the temporal sequence and parameters of their excitation form the code that the olfactory bulb has to process for qualitative appraisal of odors. These recordings in man are interesting in comparison with those of Gozzano\textsuperscript{84} in animals.

Some further assessments of accuracy of EEG signs in cases of brain tumor have been reported. In a series of 120 cases of brain tumor, Castorina\textsuperscript{38} found the resting EEG to lateralize almost as well as the angiogram, but to fall far short in pinpointing the site. It should be noted however that no application was made of modern refinements of EEG technics or activation, such as have been demonstrated to increase the accuracy of localization. The group at the Neurological Institute in New York\textsuperscript{18} found the EEG to give either nonlateralizing or lateralizing signs that were correct (as established by ventriculography or craniotomy) in 67 per cent of 144 cases of increased intracranial pressure in whom focal neurologic signs were absent. Kubicki\textsuperscript{111} has made a follow-up study of 162 cases of brain tumor, and has studied the prognostic value of the EEG for duration of survival. The cases were broken down into tumor types (astrocytoma, glioblastoma and meningioma). The closest parallel was found in cases of meningioma. Millar\textsuperscript{31} has stressed the observation, familiar to EEGers, that infiltrating tumors are unlikely to give the focal slow waves seen with actively expanding lesions that cause cerebral edema. He attaches importance to intracranial pressure changes as contributing to this electric sign in cases of infratentorial tumors.
From a study of 18 cases with arteriovenous anomalies, the Mayo Clinic group considers routine recordings of the EEG to be of little help compared with angiography, but urge the use of activating technics, since these localize so successfully during the ictal and postictal phases. Potter reports disappointment with the EEG as a prognostic device for complications that may ensue from ligation of the common carotid. Terzian made an experimental study in dogs of the effects on the EEG of occlusion of the common carotid and middle cerebral arteries; his findings should be of clinical importance. Both Terzian and Macchi made detailed studies of the carotid sinus pressure test in large series of clinical cases. They find it to give distinct diagnostic information about vascular insufficiency, especially of the collateral circulation of the circle of Willis. An interesting example of periodic brief bursts of delta waves in a case with thrombosis of the anterior cerebral artery was reported by Andreani.

A considerable incidence of seizure discharges was found by Heyck and Hess in patients with migrainous or vasomotor type headaches, suggesting that cases with such EEG signs may lie on the borderline of epilepsy, especially since they respond well to anticonvulsive therapy. The careful study of Panzani and Boyer also raises this same question. In a series of 110 patients with migraine, they found 57 to have bilaterally synchronous, and 21 to have focal abnormalities. Murphy reported a case in which cerebral infarction followed a series of typical migraine attacks.

Leonhardt found conspicuous EEG changes in 33 of 50 patients examined during the days immediately following air studies. These were mostly in the direction of abnormality, but eight showed regularization of the alpha rhythm to an extreme degree—a finding that may interest the pavlovians. The revival of interest in the interpretation of well-known EEG phenomena in terms of pavlovian physiology is evidenced by the number of contributions on this subject at the Marseilles EEG colloquium in November (Rusinov, Morrell, Smirnov, Walter, etc.), and by various published papers. For example, Popov suggests a classification of EEG's according to the degree of spontaneous cortical inhibition (in pavlovian terms) evidenced by the waking record. By this classification, the high voltage regular alpha type would exemplify a minimal, and low voltage beta a maximal, degree of cortical inhibition. In the same paper she suggests a pavlovian explanation for differences between individuals in their alpha-blocking time.

The EEG is widely used in cases of head injury. From the examination of many boxers, Pampus concludes that a relatively mild head injury in one who has had many blows (which themselves produced no detectable injury) causes EEG changes of a severity that one associates with more intense trauma in the usual clinic patient. Grutzner and Koch, from their ob-
servations on a series of 29 infants and small children, consider the EEG of distinct value in lateralizing subdural bleeding in these difficult cases. The initial difficulty that the EEG meets in children's records, because of their wide variation within the physiologic range, is partly compensated for by the excessive abnormalities they frequently show after even quite mild head injuries. Some examples of conspicuous post-traumatic foci in small children have been published by Walkenhö̈rst. Head injury in children has also been studied by Ozek and Meyer-Mickelheit, with especial attention to the type of EEG abnormality (focal dysrhythmia, delta focus, alpha diminution, etc.) found in concussion, contusion and open head wounds.

This year there have been more papers on the EEG in childhood than is usual. Bickford's summarizing of the EEG findings in children, written for pediatricians, contains a schematic diagram of the changes in frequency bands and in amplitude with progressive maturation, including the rarely mentioned and transitory increase in alpha voltage seen in teenagers. The paper contains clear examples of the EEG in various neurologic disturbances in children, and the illustrations will be useful to teachers of EEG. The relationship of EEG potentials to neuronal structure is one of our unresolved problems. One line of attack is the ontogenetic one taken by Dreyfus-Brisac, in whose opinion the appearance of fetal brain potentials follows immediately on the development of dendrites (and their synapses) in the cortex. In premature babies she found the first EEG potentials at six months (of fetal life); none were present in two babies born at five and a half months; in seven month babies the EEG's began to resemble those of full-term infants. Her technic for recording from premature and newly-born babies has been described, and a monograph of results obtained has been written by Mme. Samson-Dollfus. This is interesting for comparison with the earlier monograph by Pichot.

Borkowski reported on the EEG's of two human fetuses within a few hours after removal from the uterus, and Bernstine has attempted to record EEG's by inserting vaginal electrodes, as well as having electrodes over the mother's abdomen. The usual finding was low voltage slow waves (1-2 cycles), occasionally with faster waves superimposed (12 cycles). Sherer continues his earlier studies of evoked cortical responses in newborn kittens, the development of which precedes that of the EEG potentials. The evoked potentials (at first purely surface negative, as previously shown by Hunt and Goldring) are of longer duration and have a longer refractory phase than those of the adult cat. These authors make an interesting comment on how these neuronal properties could affect the assessment of time-duration by the young, if the number of events the brain can discriminate per unit time is regarded as critical for a sense of time.
Concern among pediatricians about the severity of CNS damage, in the small percentage of cases that react catastrophically to pertussis vaccination, has led to a study by Low of the EEG of 83 children before and after this prophylactic procedure. Only two showed any EEG change, and in these the abnormality was both slight and transient. Thiébaut has published his findings in 25 children with convulsions showing the type of EEG record termed hypsarhythmia by Gibbs. In France, this clinical subgroup is, in Gastaut and Rémond’s classification, “myoclonic type B” and in Switzerland has been known for some years by the picturesque name of “Blitz, Nick und Salaamkrämpfen.”

With the universal interest in the galaxy of drugs now used in psychiatry there has been a concurrent increase in the number of studies of the EEG effects of these compounds. The French EEG Society devoted their annual meeting to this subject. A useful synopsis was prepared by Verdeaux on the EEG effects of a great number of drugs, together with a summary of their action on evoked cortical responses. The effect of LSD-25 on these potentials is elucidated in a report from Purpura who demonstrates the differential action of this drug on responses carried by the specific afferents, and those of the nonspecific afferent system. Individual drugs have been the subject of several studies. The EEG effects of chlorpromazine are interpreted by Bradley and Terzian as being on the brain stem, the cortex being affected only secondarily by the induced sleep state. The same opinion is held by Lebascle who finds that mixtures of such CNS depressants will obliterate the driving response to intermittent light in man. With intravenous doses of chlorpromazine (25 mg.) Shagass finds only the expected signs of drowsiness. Another report on chlorpromazine has come from Brazil, confirming the lack of effect of this drug on the EEG both in the normal and in the epileptic, so that its use as a sedative does not mask warning signs in the record.

There has been continued interest in the similarity between some types of psychotic behavior and the symptoms produced by such drugs as LSD-25 and mescaline. A conference of the Macy Foundation has been devoted to this subject. Adrenochrome, which is structurally related to mescaline, was found by Szatmari to accentuate the EEG abnormalities in a small group of epileptics, whereas, in general, nicotinic acid had the opposite effect. The site of action of some of these drugs, which have such potent effects on behavior, has interested many workers. Gangloff and Monnier found that intravenous reserpine raises the threshold for afterdischarge induced by stimulation in both the cortex and the thalamus, but not in the rhinencephalon of unanesthetized rabbits. The background EEG remains unchanged and shows no sign of sleep patterns. In a well-illustrated article, these authors have reported their studies of the comparative excitability
of cortex, diencephalon and rhinencephalon in normal animals. This gives them their base line for testing many drugs (e.g., Diamox,®* anticonvulsants,71 etc.).

Following up the old lead that acetylcholine is found in the CSF of cases with closed head injuries, workers at the University of Graz®* have studied the effect of the anticholinergic drug, Diparcol, on the slow waves seen in such cases, and have demonstrated considerable reduction of this abnormality. It has been suggested by Desmedt® that synapses that are dependent on pseudocholinesterase are involved in EEG activity, for its inhibitors not only block the surface positive element of evoked responses but also desynchronize the EEG. Perhaps some role has been found for the neuroglia, for it is known to contain a high concentration of pseudocholinesterase. EEG abnormalities caused by a cholinesterase inhibitor and the antagonistic action of atropine on them have been studied in animals by Duensing.59

Mendelow and Wright®® have added to the growing evidence against the existence of a suppressor area, 4-8. Their experiments with strychnine neuronography failed to verify such an area in monkeys. Previous conclusions concerning neuronal connections based on strychnine neuronography are due for reconsideration, not only on the controversial issue of trans-synaptic effects, but also in respect to the interpretation of the components and location of evoked potentials. The series of papers from Queen Square*®*®® on photically evoked strychnine spikes demonstrates that these are not merely potentiated specific responses, but that they behave differently on repetitive stimulation. During a train of flashes the specific response remains time-locked to the stimulus, but the evoked strychnine spike, initially superimposed, becomes separated from it by increasing delay as the train progresses. There is also a difference in refractory period. At flash rates above 3.5 per second, strychnine spikes soon fail to follow. They may then appear after alternate flashes only, or may block entirely, while the unpotentiated specific response continues. Apart from flash rate, the amplitude of the specific response appears to be critical for the firing of a strychnine spike. Cobb's* evidence suggests that the volume of cortex involved in an evoked strychnine spike greatly exceeds that involved in a specific response. This finding leads to grave doubts as to the validity of cortical maps made from strychnine spike distributions.

The spread of excitation from the visual cortex to other strychninized areas has been shown by Cobb and his colleagues® to travel within the cortical gray matter at a conduction velocity varying from 10 to 25 cm. per second, depending on the flash rate and distance between strychninized points. This spread is not impeded by undercutting the cortex, provided the gray matter is intact.

Interest is growing in the use of EEG as a monitor for efficiency of cere-
bral circulation during surgical operations requiring hypothermia or artificial heart-lung procedures, as is witnessed by the special section meeting held in connection with the annual meeting of the American Society of Anesthesiologists. The EEG is also advocated for checking on the post-anesthetic state of the patient. Bellville advocates the routine practice of recording the EEG during anesthesia, since he finds it a sensitive indicator of hypoxia, hypercapnia and depth of anesthesia. In pernicious anemia, Krump finds strikingly more severe EEG disturbances than in anemias of other etiologies. The complexities of the EEG findings in hypoglycemic conditions, including diabetes, have been discussed by Massmann who finds discrepancies between the degree of EEG abnormality and the clinical signs. The value of EEG in internal medicine has been stressed by Götze, who gives islet cell adenoma and uremia as examples.

A comprehensive study of hepatic coma has been added to the increasing material on EEG changes accompanying fluctuations in states of consciousness. Bickford found the EEG to be normal in patients having clear hepatic disease without mental changes, but, with the development of relatively deep coma, a characteristic slow triphasic wave (with the largest component-surface positive) was seen which appeared to travel over the head from the frontal region to the occiput. This would be a suitable phenomenon for examination by Shaw and Roth’s method for mapping moving potential fields. This wave configuration seems to accompany a reversible stage of coma and hence would appear to reflect the toxic condition rather than structural change of the brain.

Palthe has pressed for more emphasis on alterations in cerebral metabolism as the universal cause of EEG changes, arguing that at a cellular level the electric discharge must be linked to tissue respiration. He would impute metabolic changes (mediated by the autonomic system) as the cause of the EEG patterns seen in alterations of attention, alarm, somnolence and sleep; and the search for direct neuronal pathways for the reticular arousal response or even for photic “driving” seem to him unnecessary. His hypothesis, however, should receive attention in view of the observations of Ingvar that circulatory changes take place in the cortex on reticular stimulation, even in isolated cortical slabs. Purpura has confirmed Ingvar’s findings and has performed the critical experiment of using two cats with crossed circulation. Stimulation of the reticular formation in one caused EEG “activation” in the other. The recognition of an extraneuronal humoral factor seems inescapable. Sawyer found EEG changes paralleling hormonal rhythms in ovulating rats and rabbits. The hypothesis he presents is, however, not uniquely dictated by his findings, and several others will suggest themselves to readers.

The pressing need in some fields of EEG work for methods of quantifi-
cation and data reduction continues to stimulate the design of automatic analyzers. They fall into two categories: the familiar ones that seek information about the EEG in the frequency domain (i.e., as fluctuations of voltage per unit time) and the more recent designs that treat the EEG as a probability distribution and constitute a sequence analysis in the time domain. This year, in the first category is St. John Loe’s optical method, giving simultaneous analyses of two channels. It has the advantage of preserving information about phase and amplitude, but it does not constitute a data reduction system whose output is quantifiable in a form that can be led into computers. Knott has previously deplored systems designed to complement visual analysis that merely lead to further visual analysis, for as measuring tools they have their obvious limitations.

A method of automatic analysis of the EEG in the second category has been developed by Burch, founded on base line crossing measurements. It succeeds in meeting the usual criticisms of such systems by including base line crossings not only of the primary trace but also of the first derivative and of the second derivative, thus retaining some information about wave-shape. Although the system is more justifiable for DC recordings than for the routine R-C coupled EEG apparatus, the method (which is being used to study changes in the state of consciousness) constitutes an effective data reduction system and yields an output that can be handled by digital computers. An informed critique of some of the many methods for analysis of the EEG in the frequency domain, the time domain and the spatial domain has been written by Corriol, and another by Rémond in an article which gives a number of results obtained with his topograph. In its present form this instrument plots amplitude against electrode position, 600 times a second from an eight-electrode sampling on the scalp, and gives the position of a field at a glance. It has some features in common with the toposcope designed by Petsche and Marko, but has the advantage of being far easier to read and to quantify for computation than a toposcopic display. At the 8th Congress of physiologists and pharmacologists held in Kiev (and opened by Orbeli), Livanov described a toposcopic display rather similar to Lilly’s, and Yemtchenko discussed the effect of rhythmic stimulation by light and sound.

Among the studies using automatic frequency analysis is one by Corbin and Bickford on the EEG in childhood. Their results suggest gradual maturation and varying degrees of interplay between physiologically separate neuronal populations responsible broadly for the individual delta, theta and alpha bands, rather than a gradual shift in the frequency characteristics of a uniform neuronal population. Automatic frequency analysis has been used for a different problem by Kennard. She finds that schizophrenics show (individually) less homogeneity of rhythm from the various
parts of the head than either normals or psychopaths, and she suggests a schema by which degrees of EEG disorganization may be assessed for correlation with psychologic and psychiatric findings. At the annual meeting of the American Neurological Association, Heath presented graphs obtained by automatic frequency analysis of potentials recorded from implanted depth-electrodes in psychotic patients. The presentation gave the impression that the group using this technic had not quite understood the principles of Fourier analysis nor all the characteristics of their instrument, and had perhaps been misled into questionable interpretations.

The method for mapping EEG potentials used by Shaw and Roth (published last year) has been described in more detail. Examples have been given to show how such maps differentiate the fields of a stationary source from those of a moving one. A theoretic discussion of the assessment from potential fields of the depth of the source within the head is also given. Bipolar linkages give more reliable data for these localizing technics than unipolar, since potential gradients are obtained directly instead of having to be inferred by interpolation. It would be good to have Andrew’s account of the field of a dipole in a conducting sphere published, for although it is a restatement of classic theory it is expressed in a concise and clear form that would be helpful to EEGers.

In the field of apparatus, EEG amplifiers using transistors were demonstrated at the American EEG Society by Offner and at the EEG Society in London by Walter and Shipton. From Germany comes another design for radio-transmission of EEG potentials. Götze and Kofes have broadcast the EEG not only from one part of the building to another but over distances of up to two kilometers. The same workers have designed a head-holder for electrocorticography that appears rather similar to that made by Grass, except that the holder is made of a plastic manufactured in England that resists autoclaving, and the cord is insulated with siliconized fiber glass that is also impervious to autoclaving and to formalin. Among the technical papers is one by Lilly and his co-workers on the optimal wave-form for electric stimulation of the brain. Preferable to a unidirectional pulse is a balanced pair of positive and negative pulses with their brief interval held constant, irrespective of the frequency of the pulse-pairs, and with equal area under each phase so that the net coulomb flow is zero. A wave-form is described that has been found less injurious than a rectangular wave, as evidenced by threshold change with repeated stimulation.

Some essays have appeared that invade the philosophic reaches of the electroencephalographic field. Davis, in the memorial lecture in honor of John Kershman, discussed the representation of space and time in the central nervous system, and Schaltenbrand has considered the same problem...
from a rather different approach. Readers should not miss Lindsley's critical analyses of the several conceptual models for brain function that have current prominence (Ashby, Cragg and Temperley (1954), McKay, Walter, Pitts and McCulloch, Eccles). The role of the EEG in these highly theoretic treatises is conceived of in its relation to cycles of cortical excitability, and one is encouraged to find such a factual neurophysiologic foundation, though rarely is the original bricklayer mentioned (Bishop 1933).

Cragg and Temperley have published in *Brain* their hysteresis model for immediate memory. The analogy lies in the fact that the state of magnetization of a ferromagnetic substance depends not only on the magnetic field applied at any given time but also on past magnetizations that have left their trace (since the effect is not wholly reversible). It is suggested that assemblies of cortical neurones may exhibit hysteresis on receipt of sensory stimuli, that is similarly incompletely reversible, with the result that an engram is stored in the cortex. The memory trace would then not depend on a structural change in individual neurones but an alteration of the mutual interrelationship of an assembly of neurones. At the Third London Symposium on Information Theory, Taylor presented an electric model that simulates many of the electric properties of the nervous system far more effectively than any previously suggested. The circuitry works on analog principles and consists of combinations of basic electronic units that themselves imitate many of the classic characteristics of single neurones. Taylor has interconnected these models in ways that mimic the electric signs (familiar to us in the nervous system) of facilitation, inhibition, accommodation, potentiation and a type of primitive "learning by association." It is a step forward to see the old digital type models being abandoned for self-organizing systems that can exhibit adaptive behavior.

This review once more covers only a fraction of the papers published—of which there are far too many. If the journals that do not specialize in electrophysiology were to use better informed referees for the EEG papers submitted to them, there would be less chaff among the wheat. The psychologically-oriented journals are the worst offenders.

REFERENCES


182

188

188


A familiar characteristic of the electroencephalograms of patients under light Pentothal® anesthesia is the fast activity induced by this drug. This is readily recordable through the intact skull as well as from the exposed cortex at operation (1-10).

Some work undertaken by three of us (11, 12) in which electrodes were implanted in the frontal lobes of schizophrenic patients prior to frontal leukotomy has provided an unusual opportunity for study of these fast potentials. Not only has it been possible to study the distribution of these waves within and below the cortex while the patients were still under the influence of the drug, but it has also been possible to get direct recordings for as long as six days after operation, since the electrodes were left in place for periods of this length before being removed at the time of the leukotomy.

The implantation of electrodes in the human brain has been successfully achieved by investigators in many different centers (13, 14-27, 29) since the pioneer work of Bickford (24) and Cairns during the war. These workers placed electrodes in the track left by penetrating high-velocity missiles and made records over a period of several days.

In the present paper only that section of the investigation dealing with the findings as to persistence of the drug effect and its distribution within the frontal lobe will be reported.

Method

The method used has been previously reported (11) together with photographs of the electrodes designed by Delgado. In brief, the electrodes used to penetrate the brain consist of seven fine stainless-steel wires insulated from each other and bound together to form a single needle with an outside diameter of 0.5 mm. A new electrode of this type was constructed for each patient, studies being made with different interelectrode distances along the needle. The range of interelectrode distance investigated in this series of patients was from 4 to 8 mm. between adjacent exposed points. The leading point of this multiple electrode was ball-tipped as a measure of preventing damage to blood vessels during its insertion through the trephine.
opening. The seven leads from these electrodes were connected to a miniature socket under a bandage on the patient's head. They could be connected to a recording instrument at any time the observer wished: whether the patient was awake or asleep; eating, reading or talking; calm or excited. After implantation, x-ray films of the head were taken in order to determine the location of the electrodes.

A pair of another type of electrodes was also inserted at the same time. These were each in the form of an insulated plate, in the flat surface of which seven stainless-steel wires emerged at fixed distances. These two-plate electrodes could be laid on the orbital surface or the convexity of the lobe as desired. This report, however, will deal essentially with the material recorded from the needle since the activity recorded at the cortical surface is familiar to most workers.

**Material**

This report will concern itself with the findings on 5 of 6 schizophrenic patients examined at the State Hospital for Mental Diseases, Howard, R. I. The sixth patient underwent bilateral leucotomy in two stages six months apart. Hence two series of observations are available for this patient, although in his first operation no needle electrode was used, only plates on the surface of the orbital cortex. His electroencephalogram however was at all times so abnormal,
both pre- and postoperatively, that it is felt that no generalizations concerning the effect of anesthesia should be based on this record.

Anesthesia. In all cases the anesthesia used was 50 per cent nitrous oxide and 50 per cent oxygen initiated by Pentothal given by intravenous drip. The total Pentothal administered during the period of operation was as a rule 1,500 to 2,000 mg. and the duration of anesthesia was usually three hours. All patients were given 1/150 grain of atropine.

It will be noticed that Pentothal was not the sole anesthetic used. However, studies by others (28) of the effect of nitrous oxide on the electroencephalogram indicate that this drug does not result in fast frequencies within the range which we are studying here (that is, 20 to 35 cycles per second).

Results

Distribution of Fast Activity at Different Levels within the Frontal Lobe. In the 5 patients in which the needle type of depth electrode was used a clear gradient in voltage of the Pentothal fast waves, from the most superficial recording point downwards was found, confirming Bickford's early findings (14) but differing in some respects from his later observations (17) (figs. 1 and 6). From the records, the low-voltage fast activity picked up by the deeper points of the needle appeared to be the electrical field of activity having its origin more
superficially. This would seem to be a feasible explanation since the action of Pentothal resulting in fast waves is more likely to be an effect on cell layers rather than on the axons in the white matter.

In one patient (V. C.) in which the needle placement was such that the seventh and deepest point was not in white matter but presumably in a convolution of the orbital cortex, this last electrode point recorded high-voltage fast activity (fig. 2). In this tracing, in which bipolar recordings were made serially from pairs of electrodes down the length of the needle, the usual voltage gradient is seen as far down as point 6. When point 7 is reached, high-voltage fast activity is again found. It is of interest to note that the rhythms of this fast activity appear to be independent of that at the cortex of the convexity. This would suggest that the drug was having a direct effect on cortical cell layers and not acting through some integrating or activating system at a lower level.

In one patient (M. S.) in which both the degree of penetration of the needle and the inter-electrode distance between the two most superficial points were optimal, a phase reversal of the fast activity at the second point from the surface was a clear finding. This is illustrated in figure 3, a section of which has been enlarged. At points below this all activity is in phase. This is strong evidence that the generators of the fast waves in light pentothal anesthesia are cortical in location (unlike the activity recorded at deeper anesthetic levels).
That the cortical cells are directly affected by the drug at this stage is again suggested by simultaneous multiple recordings from plate electrodes on the orbital surface (fig. 4). There appears to be no common coordinating factor influencing the response to the anesthetic.
of the various areas covered by this type of multiple electrode, even though the recording points are within a few millimeters of each other. Such findings would be in keeping with the hypothesis that barbiturates at this light stage of anesthesia act directly on the cell bodies of the cortical neuron within the cortex or on their synapses.

There seemed to be considerable variation in the length of time that the electroencephalographic signs of the Pentothal anesthesia persisted although all patients received approximately the same amount of the drug over approximately the same length of time. In those patients in whom there appeared to be intrinsic fast activity present at the orbital cortex as recorded by plate electrodes it was extremely difficult to be certain when the drug effect wore off. An example of fast Pentothal activity persisting for fifteen hours in the cortex of the convexity as recorded by the superficial points of the needle electrode is shown in figure 5. In this case a control run on the 6th post-operative day provides a comparison with the intrinsic activity of this patient (M. S.). In another patient (A. K.) there appeared to be fast activity still present 29 hours after the end of the operation.

In figure 6 is shown the recordings taken after the operation at
EEG Effects of Pentothal®

intervals of eighteen and forty-eight hours, respectively. In this patient (A. N.) some fast activity is still seen to be lingering even after two days.

Our experience would lead us to doubt whether electrocorticograms during brain operations could be regarded as entirely free of all barbiturate effect if such a drug had been used during the opening procedures.

Summary

A brief report is given of the effect of Pentothal on depth recordings of the electroencephalogram made with implanted electrodes in man. The findings lend support to the hypothesis that, at light stages of barbiturate anesthesia when the electrical concomitant is fast activity, these potentials have their origin in the cortex rather than in deeper structures.

Considerable variation was found in the duration of the electrical effect of the drug in the five cases studied, but in all cases considerable persistence was noted.

References


Present Status of the Relationship of Brain Structures to the Circulation and Emotional Expression in Man

BY WILLIAM P. CHAPMAN, HARRY C. SOLOMON, HEINZ R. SCHROEDER, MARY A. G. BRAZIER, GEORG GEYER, CHARLES FAGER, JAMES POPPEN AND PAUL YAKOVLEV

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We have attempted by physiological methods to determine the relationship of certain brain structures to circulatory regulation in man. The procedure has been to record the effect on the blood pressure and heart rate of electrical stimulation of those brain regions which could be studied in the course of psychosurgery for patients with mental disease, intractable pain or epilepsy. At first the physiological observations were carried out during brain operations when the patients were under anesthesia. More recently, the development of indwelling electrode techniques which
are used to perform localized brain destruction through small trephine openings has made it possible to study the effect of electrical stimulation with the patient in the awake state over a 7-9-day period prior to the electrical coagulation procedure and electrode removal. In these awake patients we have correlated the effects of electrical stimulation on the circulation with the effects of this procedure on feeling states and motor (somatic) behaviour. In view of the consideration which must be given to emotional factors in the management of circulatory disorders, the attempt to study the integration of the circulation and subjective states or emotion seemed important.

_Slide No. 1._—Animal experiments and comparative anatomical data have been helpful in selecting the regions of the brain for study in our patients. These findings are summarized on these drawings of the human brain. In the anesthetized animal, principally the cat or monkey, changes in blood pressure and heart rate have been obtained in many laboratories by electrical stimulation of the posterior orbital surface of the frontal lobes, the anterior cingulate gyrus, the insula (Island of Reil) and the temporal pole. In the awake animal, Delgado and MacLean have noted an increase in heart rate from stimulation of the amygdaloid nuclei, lying inside the uncus. The importance of the hypothalamus and medulla in circulatory regulation has, of course, been recognized for a long time. It is of interest that these animal experimental findings are in essential agreement with the conclusions of the comparative anatomists. They maintain that the brain regions important for the regulation of internal states, including the circulation, are the more ancient midline brain structures that have become enveloped by the development or expansion of the cerebral hemispheres in higher mammals and in man. The location of these more ancient structures are indicated in black for the entocortex and as stippled areas for the mesocortex. The ectocortex or more recently developed areas are indicated in white. It can be seen that it is along the black and stippled areas that the circulatory responses have been obtained in the animal.

_Slide No. 2._—We have observed the effect on the continuous recording of blood pressure and heart rate of electrical stimulation of most of these areas in the anesthetized patient during the operation of frontal lobotomy but prior to section of the frontal lobe fiber tracts. These markers summarize the results in 23 patients in whom significant changes in heart rate or blood pressure were consistently obtained in 17. The red markers indicate that significant elevations of systolic and diastolic blood pressure were obtained from the posterior orbital surface of the frontal lobes, the anterior cingulate gyrus and the tip or antero-medial aspect of the temporal lobes. The black markers indicate that a significant slowing of heart rate was obtained from electrical stimulation of the anterior cingulate gyrus and the tip of the temporal lobes. The latent periods for these responses was from 2-4 seconds, which made it probable that they were mediated by nervous tissue. The green mark shows that a significant decrease in blood pressure was obtained from the anterior cingulate gyrus in one patient. In this instance, the initial change in blood pressure occurred
20–25 seconds after the beginning of the conventional 10-second stimulation period. Possibly this response was mediated by the liberation of a humoral substance. The white markers indicate the areas which gave no circulatory response from electrical stimulation.

As these patients were studied while under anesthesia, it was difficult to interpret the significance of these findings, particularly as they might relate to other functions. We therefore welcomed the opportunity to continue these observations in patients in whom indwelling electrodes were used to study the relationship of the electrical stimulation and electrical recording findings to the patient's illness and for the performance of the localized brain destruction for therapeutic reasons. We have used this technique in the frontal lobes in seven patients operated upon for schizophrenia and in six epileptic patients who were scheduled to have localized destruction of the amygdaloid region for "psychomotor" epilepsy or for intractable assaultive and overactive behavior. The epileptic patients had been unsuccessfully managed by medical treatment and had been confined to state institutions for periods of 11 to 22 years. In each case the decision for operation was made by the psychiatric staff of two separate institutions. It is hoped in the two cases of so-called "psychomotor" epilepsy that the destruction in the amygdaloid region will make unnecessary the more extensive operative procedure of removal of part of the temporal lobe which is a treatment used in some medical centers for this condition. As suggested by animal studies, it will be determined whether amygdaloid destruction in the assaultive and overactive epileptic cases will make them more manageable patients.

Slide No. 3.—The electrodes were implanted in the amygdaloid region by means of a stereotoxic apparatus designed for use in humans. This is a photograph of the apparatus and the four-lead electrode, together with the female socket which rests on the top of the scalp and which connects the four leads to the Grass stimulator and to the electroencephalograph. Measurements taken from the patient's skull X-rays of the position of the posterior clinoids and the tip of the air-filled temporal horn are at present being used to place the electrode in the amygdaloid nuclear region. More recently fine wires the thinness of one's hair and guided by the stiff needles shown in this photograph are implanted rather than the four-needle electrode, which is shown in this slide.

Slide No. 4.—The four wires may be seen in the left temporal lobe in this X-ray photograph of one of our patients.

Slide No. 5.—The data concerning the proper calculations for localizing the amygdala with the stereotoxic apparatus has been worked out in cadavers. The amygdala is a nuclear structure measuring about 15 millimeters, by 10 millimeters, by 10 millimeters and located in the temporal lobe laterally and slightly behind the posterior clinoids. As shown in this slide which is a sagittal section through the center of the amygdala, we were able to place the center lead of the four-parallel needle electrode into the amygdala in 9 out of the 11 first cadavers studied. The amygdala is encircled here and the holes represent our worksmanship in hitting this structure.
Subsequent studies in the cadavre indicate that still greater precision in localizing this region may be expected. The three peripherally placed leads of the electrode permit us to study and to coagulate about 50 per cent of this nuclear mass. Thus far, the use of this indwelling electrode technique over periods of 7–9 days has not been associated with infection or any neurological complications.

*Slide No. 6.*—The results in the six patients of electrical stimulation of the amygdaloid nuclear region which pertain to the subject of the circulation and the emotions may be summarized as follows:

1. Significant elevations of systolic and diastolic blood pressure have been obtained in four patients and significant increases in heart rate, in five patients. Feelings of fear and anxiety have been elicited in four patients and a state of euphoria, in one patient. The changes in the subjective state have always been associated with appropriate alterations in motor or somatic behavior. Bilateral pupillary dilation has been produced in five of the six patients.

2. The first response to appear with the lower intensities of current was usually bilateral pupillary dilatation. At this same or at slightly higher levels of current a 15–30 point increase in heart rate and or a small but significant rise in the systolic and diastolic blood pressure were obtained. Then by increasing the voltage 2–5 points or continuing the previous voltage for a longer period, the patient would experience fear or anxiety which was usually reported by the patient after the end and was usually evident from his gestures or bodily movements. When the subjective changes were elicited, there would occur greater increases in systolic and diastolic blood pressure and heart rate. This second phase in the circulatory response usually occurred 15–20 seconds after the beginning of the electrical stimulation and a few seconds after the terminations of the stimulations. The stimulus was purposely turned off within a few seconds after it was evident that an emotional response had been produced.

This tracing shows that pupillary dilatation and a 33 mm Hg rise in the systolic and a 25 mm Hg in the diastolic pressure were obtained with 60 pulses per second, 1 millisecond pulse duration and 12 volts. No subjective or behavior changes were elicited.

*Slide No. 7.*—When 17 volts were used in this same patient, feelings of fear and anxiety together with appropriate changes in motor behavior were elicited. These responses were associated within 7 or 8 seconds with an increase in pulse pressure and heart rate. The pupillary dilatation and subjective and behavior changes continued for another 60 seconds and it was about 60 seconds after this that the blood pressure and heart rate returned to the control level. In this tracing there was a 100 per cent increase in heart rate, a 60 mm Hg rise in systolic and a 40 mm Hg rise in diastolic blood pressure.

*Slide No. 8.*—This is a tracing from another patient showing an 85 mm Hg rise in systolic, a 60 mm Hg rise in diastolic blood pressure and a 100 per cent increase in heart rate associated with marked feelings of fear and anxiety and appropriate
changes in motor behavior. In this instance the major part of the circulatory response occurred after the end of the electrical stimulation. Because the needle moved out of the femoral artery we could not determine the duration of the circulatory effect.

The only other region of the brain in which it has been possible for us to study the effect of electrical stimulation on both the circulation and feeling states, is the orbital surface of the frontal lobes and that portion of the fiber tracts of the frontal lobes which was later sectioned by the frontal lobotomy operation. In these two locations of the frontal lobes electrical stimulation produced no subjective or motor behavior responses in any of the seven patients.

*Slide No. 9.*—In one patient an elevation of systolic and diastolic blood pressure was elicited in association with uncontrollable hyperventilation. Control studies in which this patient voluntarily hyperventilated indicated that the elevation in blood pressure produced by electrical stimulation of the posterior orbital surface was not due to the hyperventilation itself.

In conclusion, we feel that these physiological data indicate that there are areas in the cerebral cortex and regions in the amygdaloid nuclear mass which, when electrically stimulated, will modify the circulation. The findings in the amygdaloid region were much more impressive so far as the effects on the circulation were concerned than the results obtained from the frontal lobes. It was also clear that it was only from the region of the amygdala that emotional responses could be elicited. The 2–4-second latent period for the initial circulatory effects indicates that they are mediated directly by nervous tissue. The longer latent period for the second phase of the circulatory responses suggests but does not prove that this part of the blood pressure and heart rate changes may be mediated by the liberation of a humoral substance. There is anatomical and some experimental evidence from animal studies that suggests that there are direct connections between the orbital surface of the frontal lobes, cingulate gyrus, tip of the temporal lobes and amygdala and midline structures such as the hypothalamus or the reticular formation in the brain stem. More definitive information on this point will have to await further anatomical studies and animal experiments. We have made a preliminary examination of the case records and pathological material in patients with tumors or softening lesions of the brain in order to find out the effects of such pathology or circulatory regulation and changes in subjective and behavior states. Because of lack of adequate data about the circulation in such patient prior to these lesions and the extent of the influence of such lesions on neighboring brain structures it has been almost impossible to draw any definitive conclusion from this type of information. All one can say is that tumors involving the frontal lobes, medial aspect of the temporal lobes and more midline structures such as the third ventricle may be associated with clear-cut changes in subjective states and behavior.
CHAPTER 13

Electroencephalography

By MARY A. B. BRAZIER, Ph.D

There are no new books on electroencephalography this year, but for a comprehensive account readers are recommended to the chapter contributed by Hill to the volume on Recent Advances in Neurology and Neuropsychiatry, which outlines in a concise way the generally established knowledge in this field. A brilliant review of the somatic functions of the nervous system has been written by Dell and Bonvallet. Anyone who has attempted to write comprehensive reviews of this kind will immediately recognize the high quality of critical understanding that these authors have given to nearly 400 references in the space of 20 pages. That they have achieved this in a language other than their native tongue is a tour de force. Other reviews have been written by Brazier and by Liberson, and a description of EEG phenomena pertinent to anesthesia has been published by Schneider. It is good to welcome back into circulation (after a lapse of 20 years) the journal, Archives Italiennes de Biologie, under the editorship of Moruzzi.

At the International Symposium on Neurochemistry in Aarhus much of the material presented had direct bearing on the processes underlying brain potentials (for example, David’s review of synaptic terminations in the brain and Keynes’ report on the mechanism of nervous conduction). The International Physiological Congress in Brussels provided an opportunity to learn what the Russian neurophysiologists are doing. Kupalov, from the Institute of Experimental Medicine in Leningrad, discussed some experiments on unilateral secretory responses (stimulation of unilateral strips of transplanted tongue evoking unilateral parotid gland secretion). He reported that repetition enhanced the responses in a manner which he equated with the post-tetanic potentiation of Lloyd, though the time course would scarcely warrant this interpretation. He also reported asymmetric EEG activity in those animals in whom exaggerated unilateral responses had been developed by repetition and from this inferred cortical participation.
In contrast to this paper, that of Sarkisov (read in absentia) came closer to Western scientific thought and methodology. He presented studies (from the Brain Institute in Moscow) on the ontogenetic development of the various cortical areas (in monkeys, apes and man) in the prenatal and first years after birth. This paper presented actual data with histological studies of axo somatic and axo dendritic synapses and electrophysiological recordings from various cortical layers. (The implanted micro electrodes used for this work were later demonstrated to the group of American physiologists who visited Moscow). In Sarkisov's opinion the dendritic thorns play a major role in axo dendritic transmission. The ontogenetic studies showed these thorns to develop only in the eighth post natal months and to appear first in the pre- and post-central cortical areas. Electroencephalographers who read this paper (published in English) will be struck by the fact that this is where EEG potentials first becomes really clearly defined in the infant. Microelectrode recordings from electrodes chronically implanted in various cortical layers have also been used by Kogan, at the State University at Rostov-on-Don, to study sleep potentials and the influence of topically introduced narcotics into the cortex. Other microelectrode studies were reported by Kostyuk on intracellular recording of endplate potentials.

Anokin's paper of the role of the brain stem in unconditioned excitation of the cerebral cortex reported results of nociceptive stimulation and the blocking effect of chlorpromazine. Some of the statements he assigns to Magoun and Moruzzi are forgivable only if derived from mistranslation.

Another paper that presented data was that of Chernigovskii on cortical representation of interoreceptors in which he mapped cortical responses evoked by stimulation of the pelvic nerve. Other contributions included some results by Roitbak on rhythmic stimulation of the cortical surface which in light narcosis evoked a strictly localized cortical rhythm unrelated in frequency to the stimulus.

In view of the current surge of work on conditional reflexes by EEGers outside Russia, it is perhaps informative to go back to Pavlov's own concepts rather to those so often attached to his name. This has been made easier for us by an English translation of the stenographic records of his weekly research seminars which are included in a volume of his Selected Works published last year. These records reinforce the impression that Pavlov was not interested in the problems that now concern the neurophysiologist and the neuroanatomist, and was himself not bothered by lack of knowledge of a neuronal basis for these reflexes. In fact he came closer to the "black box" type of thinking that initiates studies of the input and the output of a system without concern about...
The connections that lie between. Indeed his use of the word "reflexes" is a far cry from that of Sherrington or Judson Herrick. (The reader should be warned that in this volume he will find Sherrington and Lashley ranked by the editor with the "lackeys of the imperialistic bourgeoisie.")

The use of EEG in the search for the neuronal basis of conditional reflexes has for some time occupied the current Russian electroencephalographers and is now attracting several workers in Europe, Asia, and America. Mme. Popov has published some records of the slowly repeating EEG changes that she finds in man during the minutes following a single stimulus and which she interprets by the hypothesis of Pavlovian inhibition. Morrell and Jasper (in an elaboration of Jasper's early work on the establishing of alpha-blocking as a conditioned response to sensory stimuli other than light) have added the interesting observation that the frequency response to photic driving can also be conditioned by non-repetitive stimuli. Unfortunately the records that have been reproduced were recorded on so slow a time-base that the reader cannot study them satisfactorily for identification of these frequencies. However, this work gives evidence that a frequency-specific response can be established as a transient conditioned response; this is followed, on continued reinforcement, by an activation localized to the visual cortex. The conditioning process is severely impaired by unilateral discharging lesions (alumina cream) of the cortical areas specific to the sensory systems involved, but can be restored to near normal by excision of the discharging foci. The authors suggest that abnormal electrical discharges are the deterrent to the formation of temporary connections in the brain rather than the absence unilaterally of cortical tissue. Morrell has followed this up by demonstrating interseizure impairment of alpha-blocking conditioned to sound in patients with focal temporal lobe epilepsy and infers structural rather than electrical responsibility for the disturbance. However, all who have experience with implanted electrodes in these cases will have been impressed with the magnitude of electrical seizure discharges that may take place during what (behaviorally, and by scalp recordings) may give the impression of a quiescent interseizure period. A quantitative study has been made by van Hof on the influence of flash intensity, flash duration and dark interval duration on the amplitude and latency of the primary response at the surface of the cortex. As the animals (cats) were under dial anesthesia, the amplitude measurements are mainly those of the surface positive component.

Some interesting observations have been made by Buser and Borenstein on responses evoked in association areas of the cortex by various sensory stimuli. These potentials are called "réponses secondaires" since they are found on spatially secondary areas, and they are not to be
confused with Forbes’ and Morison’s “secondary response” which was numbered for temporal sequence. These results include another example of the increase in area of cortical responses caused by certain anesthetics (in this case chloralose).

Among the studies of single cell activity is one by Creutzfeldt and his colleagues on the reaction of cortical units to electrical stimulation. Creutzfeldt has also made a study of experimental hippocampal seizures in cats and has outlined a schema of the connections by which they spread. The paper carries an almost complete bibliography of electrical activity of the hippocampus. More information is coming in about the relationship between unit discharges of cerebral neurones and slower potential changes. Last year Verzeano, Naquet and King, in a study of barbiturate spindle bursts, recorded from diffusely projecting nuclei of the thalamus, found that the bursts of unit activity caused by the drug were consistently followed by a slow wave which they interpreted as the summed positive afterpotentials of the discharged neurones. Schlag has found this same phenomenon on occasion, but in his experiments the relationship of the slow waves to the spikes was by no means constant enough in time or phase to warrant their being regarded as afterpotentials. Schlag leans towards the view that they may be summed synaptic potentials.

As the evidence continues to mount that the EEG is compounded of graded dendritic potentials and not of envelopes of all-or-none axon or cell spikes, it becomes imperative for the EEGer to familiarize himself with the properties of dendrites. A detailed exposition of the anatomy of these structures will be found in the book by Sholl with its fine photomicrographs of cortical structures (in man and cat). Dendrites have had considerable prominence in the neurophysiological literature for several years but only the papers bearing the dateline of this review will be mentioned. They are those by Bishop, Grundfest and Purpura. The elucidation by the latter authors of transmission through axo-dendritic synapses must influence our concepts of such EEG phenomena as the ascending reticular activating system and the diffuse projection system of the diencephalon, both of which appear to act on cortical neurones through this type of synapse. Synaptic transmission in the central nervous system is almost certainly chemical in nature, the transmitter being different for facilitation than for inhibition, hence the action of drugs on the EEG resolves itself into the effect on the usual balance maintained between these opposing influences. A comprehensive review of the pharmacological aspects of central and synaptic transmission has been written by Perry. The existence of an ascending reticular inhibitory system (in addition to Magoun’s activating system) is being invoked...
by more and more workers to account for their experimental findings.\textsuperscript{26, 41}
Since nembutal in light doses has an anti-inhibitory action\textsuperscript{9, 72, 73, 85} its
common use in animal experiments is probably the reason for this system's
having escaped notice earlier. It is interesting that Schlag found units
in the thalamus whose discharge-rate was augmented by nembutal in
doses of 5–10 mg./Kg. It will be remembered that apparently inhibitory
units have been found in the cortex by Jasper\textsuperscript{45} and in the nucleus ventralis anterior of the thalamus by Machne, Calma and Magoun.\textsuperscript{56}

The organization of the nonspecific afferent systems in the brain has
essentially been worked out in animals by electrophysiological techniques.
Papez\textsuperscript{82} has stressed the anatomical data in man that confirm the exist­
ence of fibers passing from the cells in the intralaminar nuclei to the
reticular nuclei of the thalamus. According to Papez the cells of the
latter nucleus are sparse, but their necessarily limited number of axons
are known (anatomically) to run into the internal capsule and are thence
presumed (from electrophysiology) to distribute diffusely to the cortex.
In the past some confusion\textsuperscript{7} has existed in the differentiation of the
augmenting response of Dempsey and Morison from the recruiting re­
response, the former being evoked by stimulation of specific thalamic
nuclei, and the latter of the nonspecific. The work of Brookhart\textsuperscript{12} and
Zanchetti\textsuperscript{94} and their associates on the former (and hitherto rather neg­
labeled) phenomenon has produced some interesting results. Accompany­
ing the positive component of the augmenting responses in sensorimotor
cortex there are simultaneous efferent pyramidal volleys. These efferent
discharges (and the cortical positive potentials) are abolished or reduced
by reticular stimulation. The negative components of the augmenting and
recruiting responses do however appear to share some neuronal mechanism
since some interference at a cortical level has been demonstrated.\textsuperscript{36, 83}

Connections between thalamic nuclei and the caudate and putamen
have been studied from retrograde degeneration in the macaque by Powell
and Cowan.\textsuperscript{71} The demonstration that the center median and N. para­
fasicularis relate with precise topical projection to the putamen, and N.
centralis medialis, N. paracentralis and N. centralis lateralis to the cau­
date, must surely be taken into consideration in concepts of the diffuse
projection system. An early finding of Starzl and Magoun was that re­
sponses could be recorded from the caudate nucleus on stimulation of the
intralaminar system. Recent experiments show that multiple impulses
from the thalamus are able to activate not only the striatum but also
the pallidum (Spiegel, Szekely and Baker\textsuperscript{91a}).

Rossi and his collaborators\textsuperscript{78} designed some experiments to determine
whether loss of vigilance in the \textit{cerveau isolé} was due to the interruption of the
activity of the reticular formation \textit{per se} or whether the important fac­
tor was loss of the ascending afferent (collateral) supply to the reticular formation. The important brain stem level that must remain intact for vigilance was found to be just in the region of the pons where the trigeminal sensory nerves enter, but this is also the site of the large reticular cells with long ascending axons. However, these workers established that bilateral Gasserian ganglionectomy abolishes vigilance and this is evidence that 5th nerve sensory inflow is the crucial factor, rather than intrinsic tonic activity of the reticular cells (thus confirming Bremer's earlier formulation). The authors satisfied themselves that the 5th nerve effect on the EEG was not indirectly mediated via cerebral circulation. In the cat the ascending trigeminal pathways have been studied electrophysiologically by Berry who found rapidly conducted potentials in both the lemniscal and extralemniscal ascending pathways (as well as the late potentials that one would expect in the latter system).

In view of the increasing interest in the role of vasomotor changes during EEG arousal patterns, Ingvar's new method for continuous recording of cerebral blood flow simultaneously with the EEG will be welcomed. His records illustrate that sensory stimuli which activate the EEG cause a marked increase in cerebral blood flow, a change that is independent of systemic blood pressure.

Physiological experiments on the powerful role of CO$_2$ in influencing brain potentials have been paralleled by clinical observations and recordings of respiratory changes during seizures. The work of Fischgold and of Torrigiani in particular has brought this into prominence. In the reviewer's experience in monitoring the EEG during operations in which hypothermia is used (for cerebral aneurysms, cardiac surgery, etc.), one of the danger signals for which the EEG is very sensitive is rise in CO$_2$ which should be counteracted by increasing the ventilation. A fall in pH is likely to be followed by ventricular fibrillation and the EEG usually heralds this danger by a general flattening. The biochemical studies of Boer$^5,6$ support the necessity for adequate control of the CO$_2$ in procedures involving hypothermia. In a long paper Morrice has reviewed the well-known effects of both hypocapnia and hypercapnia and has added new data of his own. Outstandingly missing from the many possible explanations he suggests for the disturbance these conditions cause in the EEG, is any discussion of the disruption of the time-course of the dendritic potentials that are in all probability the critical basic ingredient of the EEG recorded from the scalp.

In an attempt to elucidate the role of the reticular formation in coma following head injury, Foltz and Schmidt have recorded potentials from the brain stem evoked by peripheral stimulation before and immediately after experimental concussion. Responses from the reticular formation
were abolished after concussion whereas those from the lemniscus persisted unchanged. These findings form a rather dramatic confirmation of the conclusions reached by Magoun's group in regard to the relation to consciousness of impulses carried by the ascending reticular system.

Turrell and his group in an examination of 12 cases with ipsilateral hemiparesis due to unilateral subdural hematoma, found amplitude asymmetry in the EEG with reduction of amplitude and delta foci on the side of the hematoma. Chusid's experience with 55 patients with confirmed subdural hematoma leads him to give preference to cerebral angiography rather than to EEG or other diagnostic procedures in these cases.

A great help to clinical electroencephalographers will be the exhaustive study by Radermecker of the EEG changes associated with the encephalitides. Confirmation of his findings has come from several laboratories, among them a paper from Hamoen and his colleagues in Holland on subacute progressive leucoencephalitis. These workers found the EEG signs, first described by Cobb and Hill, (brief periodic paroxysmal bursts of slow waves) to be so consistent in this disease as frequently to be the first signpost to the correct diagnosis. Types of EEG abnormalities found in postinfectious encephalomyelitis have been illustrated by Ferrari.

Lairy's discussion and studies of reflex epilepsy are a welcome attempt to bridge the gap between the rapidly developing knowledge of the electrophysiologist and the observations of the epileptologist. The sensory stimuli travelling by the nonspecific afferent system are more frequently the trigger to reflex epilepsy than are impulses in the specific afferents (as originally envisaged by Amantea and Clementi), the localized seizure being set off by the resultant generalized activation of the cortex. Odd cases of focal spike and wave in the absence of overt epilepsy keep turning up. It is noticeable that they are usually in children. Zeigler reports a case of a child in whom the only complaint was headache and in whom the focus was pin-pointed to the right occiput. Glaser has also discussed focal wave-and-spike discharges. The hypothesis that petit mal epilepsy may have a diencephalic origin has been challenged by Wright who perhaps has more data than he presents here to support his strongly held views.

The patterns of propagation of epileptic seizures have been followed in monkeys by Walker and his associates. The seizures were evoked by cortical stimulation and their spread followed by depth as well as surface electrodes. The afterdischarges from different cortical areas spread to different subcortical nuclei, the basal ganglia being specifically involved.

Gastaut's essay on Van Gogh advocating a diagnosis of psychomotor
epilepsy rather than schizophrenia, brings the wheel round a whole turn, for the doctor who attended this tragic man when he cut off his ear, made the diagnosis of “une sorte d’épilepsie.” Van Gogh immortalized this young interne in a brilliant portrait, later discovered blocking a hole in the family’s henhouse (but now in the Museum of Modern Art in Moscow). Van Gogh’s case was one of those discussed at the European Reunion of EEGers held in October, the principal subject of which was EEG manifestations of episodic psychic disturbances among epileptics occurring during seizure-free periods.

The use of pentothal as an agent to bring out EEG abnormalities has proved extremely effective in the hands of Schneider. By studying, in the light of known neurophysiological data, the sequence of EEG patterns that follow slow induction he has been highly successful in incriminating the structures that must be involved to result in anomalies of wave pattern of each stage. Anomalies in the early stage of fast activity and the later one with K-complexes have given him the best localizing signs of sub-cortical lesions. A detailed examination of the K-complex by Roth has shown it to have three components whose fields and time characteristics have been mapped. Less has been written this year about metrazol activation. Freedman has investigated the effect of mesencephalic lesions on the response to metrazol injection in the cat. The changes in pattern resulting from this surgical procedure do not suggest an immediate explanation of the underlying mechanism.

Silverman has examined one thousand sleep records in order to find whether this type of activation is diagnostically helpful in diseases other than epilepsy. Only in posttraumatic disorders did he find sleep useful in bringing out abnormalities, but since the latter were similar in character to those of epileptics one wonders whether these cases deserved a separate category. Some had overt seizures and might well be classified as epilepsy (post-traumatic). It is interesting that sleep activation did not aid in cases of cerebrovascular accidents.

Perhaps some more optimistic assessment of the EEG as a localizer in cerebrovascular accidents than that found in most of the EEG texts is justifiable. Even in routine resting EEGs Feiring finds a high incidence of reliable focal signs in occlusion of the middle cerebral artery (unilateral delta activity, decrease in alpha most pronounced in temporal region).

The EEG has been used extensively by Meyer, Liederman and Denny-Brown in their examination of cerebrovascular insufficiency. By use of the tilt-table technique to induce ischemia they found the EEG to be a sensitive localizer of regional insufficiency, differential for occlusion
of the carotid arteries and of the basilar arteries. Some more material
on the EEGs associated with cerebrovascular accidents has been added
by Della Beffa and Torrigiani.25

Davidson and Watson21 have published the data on the 16 families
in members of whom they have found a sensitivity to photic stimulation.
They conclude that genetically determined disorder of the CNS under­
lies this light sensitivity. Rovetta82 has examined the effect on photically
evoked potentials of the psychotomimetic drugs mescaline and LSD 25.
The recording electrodes were concentric with the core at a different level
from the ring and hence the waveform of the potentials recorded differ
from those in the classic literature. Amplitude measurements were made
from positive peak to negative peak and hence no differentiation into
axo somatic and axo dendritic components was made. These technical
details make it difficult to compare the results with those of Purpura73
on the effect of LSD 25 in blocking the axo dendritic synaptic potential
of the evoked response, or with the conflicting reports of Evarts.28,29

It is impossible to review the plethora of papers on the effects of the
newer tranquilizing drugs on brain potentials as so many people have
jumped on this bandwagon. If the bewildered electroencephalographer
needs guiding to reliable information in this area, this reviewer would
recommend him to the publications of Dell and Bonvallet23 and to those
of the Killams.46-48

An attempt by Peacock66 to assess by EEG two drugs that are being
used as antidotes for barbiturate intoxication (diaminophenylthiazole
and methylethylglutarimide) proved rather disappointing. Too great in­
dividual differences were found for any clearcut conclusions to be drawn
from this small series (eight cases). Zimmerman102 has continued his
examination of Celontin as an antieconvulsant, reporting this time on its
use in psychomotor epilepsy in which he found a favorable reduction in
the incidence of seizures and only minor toxic side-effects. On the grounds
that pyridoxine deficiency in the CNS is a precipitant of seizures, an
acute deficiency has been produced by Pfeiffer68 in schizophrenics by the
use of hydrazides for therapeutic convulsions. The accompanying EEG
studies threw little light on the site of origin of the biochemical trigger­
ing action in man. A comparative analysis of Viadril and pentothal
anesthesia has been made by Schneider69 who has contrasted not only the
EEG changes in man but in addition the arousal responses and after­
discharge in the cat.

Depth electroencephalography has drawn a great deal of attention
this year, with special symposia (e.g., the Houston Symposium on Brain
Mechanisms83a and the Ste. Adèle meeting of the Eastern Association of
EEGers) and many papers on the topic. Delgado and Hamlin22 report
on recordings from the frontal lobes in five cases of schizophrenia, three of intractable pain, and one of anxiety neurosis. Of the several patterns of electrical activity found, none correlated with the clinical diagnosis but in general tended to be related to the region in which the electrode lay. No changes in the depth recordings were detected with change in mood, sensory stimulation or motor movement although at the motor cortex the blocking of activity on hand movement, first noted by Penfield and Jasper, was confirmed. Bickford's examination of the toxic effects of copper and of silver when used for implanted electrodes is important. He recommends stainless steel as minimally toxic.

Some of the recent surgical therapeutic measures in the treatment of extrapyramidal disease have stimulated interest in recording from the basal ganglia. Spiegel and his colleagues have published some interesting recordings from these structures, and Brazier and Barlow have reported some results cross-correlating the activity at the motor cortex with that in the basal ganglia in man.

A single simple type of depth electrode for use in acute experiments on artificially produced convulsions in cats has been employed by Kreindler. This involves minimal surgical procedures and makes it possible for the animal to be examined after the anesthetic has worn off. This paper carries an interesting discussion of the possible mechanisms underlying not only the triggering of the seizures, but also of their cessation.

A careful study of the EEG in unsedated children with mental deficiency has come from the Mayo Clinic. Among the total group of 74, those with hyperkinetic behavior had the most striking abnormalities in their EEGs, and possibly may represent a syndrome related to epilepsy. That the I.Q. per se does not correlate with the alpha rhythm might perhaps be expected if the role of the latter is a regulatory function related to consciousness rather than an information system. Those who work in pediatric neurology will welcome the publication by Dreyfus-Brisac and Blane with its analysis of the EEG patterns of infants during the first months of life, both awake and asleep and of the EEG responses evoked by sensory stimuli.

An unusual report on the EEG during hypnotic trance comes from Schwarz, Bickford and Rasmussen. They report alpha suppression during visual hallucinations with appearance of lambda waves (and their absence during hypnotic blindness). Their experiments led them to suggest that the influence of hypnotic suggestion on the triggering of seizures in epilepsy suspects was useful in detecting psychogenic factors. A study planned to quantify the amplitude changes in alpha that are known to accompany (unquantifiable) changes in visual activity and visual imagery has been reported by Walter and Yeager. By using
tests designed to allot degrees of visual activity and of visual imagery (as judged by performance tests) these carefully conducted experiments confirm the classic observations of the earliest workers in EEG and add some interesting observations on blind children. The application of EEG to problems of internal medicine has been stressed by Krump62 with examples of the EEG in Addison’s disease, coma of diabetic, hepatic or uremic origin, and poisoning by carbon monoxide and barbiturates, as well as in thyroid disease.

There have not been as many papers of a technical nature this year, though some interesting fragments have been published (mostly in the section on Technical Notes in Electroencephalography and Clinical Neurophysiology). Among unusual studies are those of Rohracher79 who has continued his interest in vibration potentials picked up from all parts of the body surface. In man these were found to have a frequency of 6 to 12 cps and an amplitude of 1 to 5 $\mu$V. Vibration potentials are not recordable in cold blooded animals, a finding which leads Rohracher to the hypothesis that they play a role in body-temperature regulation.

Again it has been possible to review only a sprinkling of the papers that deluge the electroencephalographer in the course of a year. The spreading interest in this field is welcomed but our reading task would be eased if editors were to be more severe on papers that give no new material or needed confirmation. An outstanding example this year was a paper on sleep in one of the most widely circulated scientific journals. The material it contained has been common knowledge to EEGers for nearly 20 years and the principal references it listed were of that age.

On reviewing the year, the developments most likely to have long-reaching effect on concepts of brain function important for electroencephalographers are the recognition of the role of dendritic potentials; the increasing knowledge of centrifugal control of sensory receptors (Granit, Galambos, Leksell11); the demonstration that animals with stimulating electrodes implanted in certain deep brain structures will almost incessantly stimulate themselves by pressing a bar to connect the current (Olds,63a Brady,18,63a Lilly); the direct demonstration from intracellular recordings from Betz cells that inhibition is a hyperpolarization phenomenon (Phillips69); and the separation from brain tissues by Elliott and Florey27a of $\gamma$-aminobutyric acid. Every one of these developing fields of knowledge imposes some reorientation of classical hypotheses.

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A STUDY OF THE LATE RESPONSE TO FLASH IN THE CORTEX OF THE CAT

BY

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In 1936, a team of workers (Derbyshire et al., 1936) in Professor Alexander Forbes' laboratory first described in the cat a cortical response to electrical stimulation of the sciatic nerve that was of long latency (40–80 msec.). They interpreted this as an effect of deep anaesthesia since they found it at deep levels of avertin and pentobarbital narcosis (though not with ether). They also found this late response with asphyxia. In a more detailed study from the same laboratory (Forbes and Morison, 1939) it was shown that the early primary response to sciatic stimulation preceded this later one, which therefore was named "the secondary discharge" by Forbes and Morison.

The findings that these authors established for this late response to sciatic stimulation were: 1) that it was of long latency; 2) that it could be recorded from all areas of the cortex examined, even from those where no primary response could be evoked; 3) that its sign at the surface might be negative, positive or diphasic according to location; and 4) that it had a long refractory period,

1) From the Neurophysiological Laboratory of the Neurological Service at the Massachusetts General Hospital and the Department of Neurology at Harvard Medical School. (Aided by a grant from the U.S. National Institute for Neurological Diseases and Blindness: B 369 Physiology) and from the Research Laboratory of Electronics at the Massachusetts Institute of Technology. [The work of this Laboratory is supported in part by the U.S. Air Force (office of Scientific Research, Air Research and Development Command), the U.S. Army (Signal Corps), and the U.S. Navy (Office of Naval Research)].
fading out at a stimulus repetition rate of about 3–4 per second.

Forbes and Morison restricted their observations to responses evoked by sciatic stimulation, but they expressed the opinion that the secondary response bore some relation to the slow waves found by Bishop and O'Leary (1938) on stimulation of the optic nerve. They suggested that they might be the sign of a centrifugal discharge.

In the same laboratory a few years later, Morison et al. (1941a and b) and Dempsey et al. (1941) from hemisection experiments reached the conclusion that the secondary discharge from unilateral sciatic stimulation had both uncrossed and crossed routes to the cortex, the decussations being at two levels, one caudal to the superior colliculus and the other in the anterior third of the corpus collosum. From ablation experiments these authors concluded that this response (unlike the primary) did not travel in the lateral part of the medial lemniscus or through the postero-lateral ventral nucleus of the thalamus. From experiments in which they stimulated subcortical structures they concluded that these responses passed upward through the subthalamus and the rostral pole of the amygdala, close to the temporal horn of the ventricle.

Since this early work was reported, many workers have confirmed the existence and characteristics of this late response to sciatic stimulation, but few have investigated other sensory systems. Gerbetzoff's experiments (1940) on vestibular responses are an exception. One author (Purpura, 1955) has reported a failure to obtain secondary responses from visual or auditory stimulation.

The present study reports the investigation of what, for brevity, will be called the late response in the visual system. Since in the original experiments of Forbes and his colleagues in the somatosensory system the experimental design had two features of a highly artificial nature, i.e. deep anaesthesia and a stimulus volley, it seemed interesting to explore the phenomenon in more physiological conditions. Light flashes have therefore been used instead of electrical stimulation, and recordings have been made from unanaesthetised cats with implanted electrodes as well as from animals lightly anaesthetised with a variety of agents.
This paper will report principally on the results of this latter group of experiments.

Some preliminary results have been published from this laboratory (Brazier, 1954a, b, and c). These results suggested that the failure of others to note late responses except in deep anaesthesia might be due, not only to the augmenting effect of barbiturates, but to the masking of responses at light anaesthetic levels where the background cortical potentials were still prominent. A method of averaging many responses has therefore been employed, using an apparatus designed and constructed by Dr. John Barlow. This technique is used as part of a correlator system for EEG which was developed by Professor W. A. Rosenblith, Mr. R. M. Brown, and Dr. John Barlow at the Research Laboratory of Electronics at the Massachusetts Institute of Technology.

A full description of this apparatus together with circuit diagrams has been published elsewhere, (Barlow, 1957) so that details will not be given here. The principle is a special case of cross-correlation (Brazier, 1952) in which the cortical potentials are compared at increasing steps of delay with a pulse generated by the flash. The resultant correlogram gives the averaged waveform and time course of all potentials that are time-related to the stimulus and minimises the background potentials not triggered by the flash. The greater the number of responses, the greater the rejection of random potentials and the clearer the waveform of the averaged responses.

METHODO

A) PREPARATION OF THE ANIMALS

For subcortical recordings the cat was placed in a Horsley-Clarke stereotactic apparatus and recordings were made under anaesthesia.

In the acute experiments, after preliminary atropine (0.15 mgm) nembutal was given intraperitoneally (40 mgm per kgm body weight). Occasionally more was needed for insertion of the earbars. This was usually added in doses of 6 mgm intravenously as required. Infiltration of the soft tissues of the mouth, orbit and scalp with 1 % procaine usually reduced the amount of
nembutal required. If the cat had any breathing difficulties a tracheotomy was performed, but this was rarely needed. A craniotomy was then performed, the dura removed and the pial surface covered with warm mineral oil. Care was taken to maintain the normal body temperature of the cat throughout the recordings. Horsley-Clarke co-ordinates obtained from the maps of Jimenez-Castellanos (1949) of Ingram et al. (1932) and of Jasper and Ajmone Marsan (1954) were used for placing the electrodes in the optic tract, superior colliculus, subthalamus, lateral geniculate, optic radiations and elsewhere.

The depth electrodes, made in this laboratory by Miss Elizabeth Peterson, consisted of 22 gauge steel hypodermic needles covered with a plastic insulation and an inner insulated wire passed through the core. The inner wire protruded from the needle by a predetermined length so that bipolar readings could be taken with a known inter-electrode distance. The most commonly employed inter-electrode distances were either 1 mm or 2.5 mm. Only the tip of the wire and the tip of the surrounding needle (cut transversely) were freed of insulating material. The cortical electrodes were made of fine jeweller’s silver wire wound into a helix which made them pliable to any pulsating movement of the brain. Occasionally wick electrodes were used. Later, enamelled stainless steel wire was used for the helices in order to avoid the photo-electric effect of silver.

The light source was a Grass stroboscope whose highest intensity saturates the retina. Total duration of the flash is 25 μsec, with a duration of effective intensity of 10 μsec, during which the candle power is 1.5 million at a distance of 10 inches. The pupils were dilated with atropine and both eyes were illuminated with the stroboscope at a distance of 5 inches.

At the completion of the acute experiments the deep electrodes were left in place and, with the animal still in the Horsley-Clarke apparatus, the carotid arteries on both sides were isolated, the superior vena cava cut and saline (90 cc) injected into each carotid. This was followed by 120 cc 10 % formalin. Nothing more was done until the next day when the animal was removed from the Horsley-Clarke, the needles withdrawn and the brain dissected out and placed in formalin. This procedure resulted in
preservation of clear needle tracks that gave not only data as to localisation but also the degree of shrinkage due to formalin. For example, the depth of penetration in the fresh brain as measured on the stereotactic instrument could be compared with the length of the track in the formalinised brain.

In some animals in which lesions were placed by ultra-sound irradiation trypan blue was injected before the formalin to mark those regions where the blood brain barrier had been injured. Only where the lesion is made does the dye pass out of the blood stream.

In the series of chronically prepared animals, whose results are discussed below, only dural leads were used. It is a pleasure to acknowledge the skilled help of Dr. Rosas Pena, visiting neurosurgeon from Colombia, in the preparation of these animals. Under sterile conditions 4 dural leads were placed, 2 on the lateral gyrus of each hemisphere, and a fifth electrode (for a reference lead) was screwed into the skull well below the occipital protuberance. A reference electrode in the frontal sinus cannot be used with flash stimuli since it picks up the potentials of the ERG.

The electrodes were stainless steel rods, blunted at the end that touched the dura and threaded at the opposite end. Each rod passed through the centre of a small nylon plug threaded to screw into a burr-hole made in the skull. The threaded end of the rod that protruded from the plug in the skull screwed into a nylon cap between experiments; when recordings were to be made the caps were removed and replaced by fitting sockets with wires leading to the recording instruments.

In some animals under inhalation anaesthesia phonograph needles were hammered through the intact scalp into the outer table of the skull over the appropriate gyri. The animals were then allowed to blow off the anaesthesia (ether, chloroform) and recordings were made in the natural awake state.

Experiments are being initiated with implanted electrodes in deep structures so that the observations can be taken from these regions in chronically prepared animals without anaesthesia but the results will not be completed in time for presentation here.
B) RECORDING INSTRUMENTS

Recordings were made simultaneously on an 8-channel III D Grass inkwriting oscillograph and on a 7-channel frequency-modulated Ampex tape recorder. The tapes were later analysed in Professor Rosenblith's laboratory at the Massachusetts Institute of Technology by the electronic averaging device designed by Barlow (1957) and mentioned above.

In addition to recording many responses on the magnetic tape for the purpose of averaging, sample responses were photographed either with a Polaroid or a Grass camera from a cathode ray oscillosgraph with 4 differential amplifiers and 4 traces (a Dumont double-beam oscilloscope with two electronic switches). The sweeps were triggered by a circuit that tripped off the flash approximately 5 msec. later, and the flash was recorded by a photocell. A Hewlett-Packard oscillator was used to provide the time-line.

RESULTS

The late response to flash, which is the subject of this article, is illustrated in Fig. 1. These are selected frames, picked because at the moment of exposure there was little masking by the background EEG. The notch on the second response is a common finding, sometimes appearing on the descending, sometimes on the ascending slope of the main response. It does not have as constant a latency from the flash as does the main deflection and therefore does not show in the averaged responses of most of our cats. Only occasionally have we found the notch to be sufficiently closely time-locked to the flash to emerge in the averaged record (e.g. as in the uppermost strip of Fig. 6). The main late deflection, however, has a relatively unchanging latency from the flash in any given animal provided the level of anaesthesia is held constant. As this level deepens the latency increases (as previously reported (Brazier, 1954a and b). The level of anaesthesia at which the responses in Fig. 1 were obtained was very light, as witnessed by: the amount of background activity; the short latency of the primary response; the fact that the primary response is of higher amplitude than the later one; and the size of the negative wave of the primary response.
This surface negative wave is very vulnerable to barbiturate anaesthesia, as many workers have demonstrated.

A typical averaged response is illustrated in Fig. 2. This record is from an animal under a moderate degree of nembutal anaesthesia as evidenced by the amount of EEG activity still present in the ink tracing recorded simultaneously. This correlogram is the analysis of a recording 1\frac{1}{2} minutes in length (i.e.

![Primary and secondary responses to flash](image)

Lateral gyrus
timeline 100 cps

35 μ sec flash

cat. # 29

Fig. 1.

Two consecutive frames showing response to a single flash (in this case of 35 μsec. duration) recorded at the surface of the mid lateral gyrus (F 2) Reference lead on the back of the neck. The flash is signalled by the photocell response on the trace (above which a white dot has been placed). Light nembutal anaesthesia. Time line 100 cps. In this and all subsequent illustrations in this paper, an upward deflection indicates relative negativity developing at the exploring electrode.
the average of approximately 50 responses). Space permits reproduction of only a 4-second sample of the accompanying ink tracing. The onset of the late response is at 72 milliseconds after the flash and the peak of maximum surface positivity is seen to be 85 milliseconds after the flash.

*Average of 50 responses to flash at surface of lateral gyrus*

![Average of 50 responses to flash at surface of lateral gyrus](image)

Sample of simultaneous EEG record

**Fig. 2.** Averaged response to approximately 50 flashes recorded from the lateral gyrus of a cat under moderate nembutal anaesthesia. The pen deflections are at intervals of 1 msec, increasing in length from left to right and the first of the continuous series is co-incident with the flash. (The first 3 pen deflections that stand apart are for calibration of the instrument). The positive peak of the late response is at the 85th pen deflection, and its latency is 72 msec from the flash. (The heavy lines of the chart paper are 20 msec apart). Below is the EEG tracing of a 4 second sample of the recording that was averaged. Aperiodic flash.

In the somato-sensory system, as noted above, Morison, Dempsey and Morison established that the secondary discharge did not pass through the thalamic nucleus specific for that sense modality. It therefore seemed of interest in the present work to determine whether a secondary response could be detected in the lateral geniculate nucleus.

Fig. 3 reproduces some averaged responses that are typical for the whole series. It will be noticed that a late response that reaches its peak at 91 msec after the flash is detectable in the
correlogram of the lateral gyrus. The optic tract response recorded from just behind the chiasm (Horsley-Clarke co-ordinates F 15, L 2, and 24 mm below the pial surface) shows the bimodal response described by many authors and the early electrotonic invasion by the retinal potential. There is no late discharge.

*Fig. 3.* Averaged responses to flash from 3 stations in the visual pathway of a cat, recorded simultaneously under moderate nembutal anaesthesia. Reference lead on the back of the neck. The numbers above the uppermost correlogram indicate serially the approximate latency in milliseconds: to the first deflection of the primary response; to its positive peak; to the peak of its subsequent negativity; to the onset of the late response; and to its peak. Numbers above the other correlograms indicate the approximate latency to onset and occurrence of peaks. At postmortem the geniculate recording point was found to lie in the upper edge of the nucleus, and the optic tract electrode on the tract just behind the chiasm. Pen deflections at 1 msec intervals. Flash coincident with first of the continuous series of pen deflections. (The heavy lines on the chart paper are 20 msec apart). Flash-rate 1 per 1.4 seconds.
There is no trace of a second response in the recording from the lateral geniculate. In contrast to the secondary response, the onset of the first surface positive deflection of the primary response at the cortex has the same latency as that of the geniculate and indeed represents activity in the axons of the same geniculate neurones. ¹)

Two frames of cathode ray oscilloscope recordings of responses, specially selected for clarity of responses to single flash are shown in Fig. 4, to illustrate this point. In the left-hand frame, at a sweep speed that allows 220 msec of the record to be viewed,

*Response to single flash*

(in optic tract, geniculate and cortex)

![Response to single flash](image)

Fig. 4.

Responses to single flash in a cat under nembutal anaesthesia. In both photographs the response in the optic tract is on the top beam, the lateral geniculate on the second, the cortex (lateral gyrus) on the third, and a timeline on the fourth. In the frame on the left, taken at a low sweep speed (5 msec time markers) a late response is seen in the cortex only. The primary response is present in all three recordings and is seen in more detail in the frame on the right, taken at a faster sweep speed (2 msec time markers). That the level of anaesthesia was light is evidenced by the background activity and the large surface-negative wave at the cortex. The incidence of the flash is marked by a black dot which has been re-inforced in the photographs. Further details in the text.

¹) For any study of exact latencies finer steps of sampling would of course be required (the present instrument will analyse at steps of 1/20th msec if needed) but since the emphasis in this communication is on late events, only steps of 1 msec are illustrated in order to present in the figures a sufficient length of the correlograms (i.e. about 150 msec.).
the primary response can be seen in the optic tract, lateral geniculate and cortex. Only in the cortex is a second response present, although the cortical site is one served by geniculo-cortical radiations. This point is brought out by the right-hand frame in which the sweep has been speeded up to give a finer look at the first 60 msec. The primary response from the optic tract is on the top beam and crosses the geniculate response in the middle trace. The latter (with a slightly heavier beam) gives a clear primary as does the cortex. The cortical response on the third beam does not cross the others, and incidentally, by its marked negative phase, gives evidence of the light level of anaesthesia that was used. The individual spike potentials that ride on the initial surface positive wave of the primary response can be seen in the photograph although, since they result from a flash, they are not as highly synchronised as those described by Bishop (1952) as the result of stimulus volleys to the optic nerve. The long lasting positivity that develops in the geniculate after the negative wave is unrelated in time to the late response at the cortex. (This positivity reaches a peak at about 120 msec in most of our cats under nembutal). (see Fig. 3)

Although sample recordings of this kind from electrode sites within a nucleus cannot positively rule out the possibility that some portion of it is traversed by the impulses responsible for the secondary responses, this result (i.e. absence of response in the lateral geniculate) is representative of 22 experiments in which recordings have been made in this nucleus within the Horsley-Clarke co-ordinates F 5 to F 9 anterior-posterior, L 8 to L 12 lateral to the mid-line and at depths from H 1 to H 5 above the earbars.

The response does however appear to travel in the white matter along with the geniculo-cortical radiations to the cortex of the lateral gyrus. In Fig. 5 are shown the responses obtained from two points on the lateral gyrus, 1 cm. apart in an anterior-posterior direction (reference lead on the back of the neck). The lowest strip is the averaged response of a simultaneous recording from the radiations which shows some evidence of an event simultaneous with the late response recorded from the surface 12 mm above. This distance is too great for the deflection to be-
assignable to a field effect. In this cat the radiation electrode was at frontal plane F 8. We have not found this late response at all anterior-posterior planes above the geniculate. See for example Fig. 7 where the electrode was at frontal plane F 5.

Averaged responses to flash
(cat. us. 118 Lt.)

Lateral gyrus
(posterior, left)

Lateral gyrus
(mid, left)

Radiations
(2 mm above geniculate on left)

Fig. 5.
Averaged responses to flash recorded simultaneously from two points on the lateral gyrus and from one in the white matter above the geniculate. Reference on the back of the neck. The numbers indicate the approximate latency to the onset and to the peaks of the major deflections. (Heavy lines on the chart paper are 20 msec apart).

When recordings are taken at different depths from an electrode penetrating the geniculate, a point is reached at which the geniculate response reverses sign, the peak of the primary response now appearing as relatively negative at the exploring electrode (see Fig. 7, fourth strip). On penetrating even deeper the electrode passes out of the geniculate body and into the
optic tract just where this enters the nucleus. At this point the recording shows the same bimodal response as is found in the optic tract close to the chiasm (compare Fig. 7 with Fig. 3). At none of these sites is any evidence found for a potential change comparable in time-course to the late response at the cortex.

Averaged responses to flash at cortex & geniculate (cat. 315)

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Fig. 6.
Averaged responses to flash at the cortex and in the geniculate nucleus. At the surface the onset of the late response has a latency of 68 msec and reaches its peak at 85 msec after the flash. There is no event in the geniculate with this time-course. The primary response on the other hand reaches its peak at 23 msec and reverses sign within the geniculate.

The responses evoked in the superior colliculus by flash were also recorded. Fig. 8 illustrates one of the experiments in which 2 recording electrodes were placed in the superior colliculus one
above the other (Horsley-Clarke co-ordinates H + 1 and H + 4.5 respectively, both at F2, L3). On the left are two consecutive frames showing single responses in the optic tract and in the lower point in the superior colliculus with both primary and late responses at the cortex. On the right is the response at the cortex.

*Responses in tract, geniculate, radiations & cortex*
(cat us. 110 Lt.)

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**Fig. 7.**
Averaged responses to flash in 5 stations of the visual pathway in the cat. Late response with peak at 100 msec after the flash. No similar component in radiations or geniculate. Note reversal of phase as electrode penetrates geniculate nucleus. The lowest strip is from a point just below the lower edge of the lateral geniculate and lies at the point of entry of the optic tract into the nucleus. Flash rate: 1 per 1.4 seconds.
upper electrode (illustrating the reversal of sign on penetrating deeper in the colliculus, as described by Bishop and O’Leary, 1942). The difference in latency between the colliculus and the

*Response to flash.*

Optic tract

superior colliculus
F2 L3 H + 1

Lateral gyrus
200 cps

Lateral geniculate
superior colliculus
F2 L3 H4.5

Lateral gyrus
200 cps
cat 321

Fig. 8.

On the left two consecutive frames of single responses in the optic tract, in the superior colliculus at Horsley-Clarke level H + 1, and at the cortex. At the right, a similar photograph but with a colliculus recording at level H + 4.5. Note the reversal of sign at the two levels in the colliculus, and the long latency of the response. Further details in the text.
primary cortical response can be clearly seen. The latencies to the collicular response agree with those of Ingvar and Hunter (1955) rather than with those of Fillenz (1953) who used microelectrodes. In the single frame below there is only a hint of the late response at the cortex (at 60 msec) but in the averaged responses from the same experiment (shown in Fig. 9) this is more clearly present and shows the notch referred to above. The data presented here are insufficient to assign this potential to collaterals from the retinogeniculate fibres, described by O'Leary (1940) as entering the stratum opticum of the superior colliculus in the cat, although this is one possibility.
There is a hint of some later activity (latency 80 msec) in the colliculus. The first potential swing in the colliculus (with its latency of approximately 21 msec) plays no part in transmission of the primary response to the cortex. The same may be said of the small late collicular potential seen at 80 msec after the flash, for the late responses at the cortex (recorded simultaneously) are over by this time. Ingvar and Hunter (1955), in a study of primary responses, have suggested that some brain stem potentials may be centrifugally evoked from the visual cortex. Presumably these would be the cortico-collicular connections involved in eye movements. The latencies for the responses from the optic tract, superior colliculus and cortex are seen more clearly in Fig. 10 from another cat. They are 10, 20 and 14 msec respectively.

The next step in the present studies was to record from the subthalamic region since it was here that Dempsey and Morison traced the Forbes response to sciatic stimulation. Fig. 11 illustrates an experiment in which electrodes were placed stereotac-
tically at Horsley-Clarke co-ordinates F 9, L 3, H. -2 (which on postmortem was found to lie in the H1 Field of Forel). The results are in striking contrast to the collicular responses.

In the subthalamus there is a double response suggestive of the arrival of impulses by two different pathways, differing in conduction rate or in number of synapses. Simultaneously in the geniculate there is only a single response, and at the cortex a primary response that reaches a maximum positive peak at 96 msec. (As mentioned above, for more exact information about latencies sampling steps of less than 1 msec. are used).

_Averaged responses to flash in the subthalamus, geniculate & cortex_

**Fig. 11.**

Averaged responses to flash recorded simultaneously from a sites in the subthalamus, one in the lateral geniculate nucleus and one at the surface of the lateral gyrus. (Aperiodic flash.)

Having reached these findings it was clear that several experimental procedures would have to be undertaken in order to define more clearly the nature of these delayed responses to flash. One of these is the placing of lesions to find the sites whose
destruction would abolish the responses. In this work we are experimenting with the use of ultra-sound in an attempt to produce lesions in deep structures without destroying the more superficial ones. In this work we are indebted to Dr. H. T. Ballantine and Dr. T. F. Hueter in whose laboratory the ultrasound technique is being developed. The results will form the subject of another report. Only one example will be given here to illustrate the effect of such lesions.

Fig. 12 illustrates the absence of both primary and late responses from the ipsilateral cortex in a cat whose geniculo-striate radiations were destroyed in the right hemisphere by ultrasound.

Effect on response to flash of ultra-sound irradiation of the geniculo-cortical radiations

![Diagram](Image)

Fig. 12.

On the left, the averaged response to flash at the cortex of the undamaged left hemisphere of a cat, whose right geniculate radiations have been destroyed by ultra-sound. The lesion in the radiations has abolished both the primary and secondary responses. Flash-rate 1/second.

The left hemisphere was not irradiated, and was used as the control. On the control side there were present both primary and late responses.

Another programme of work in progress is to investigate these late responses in animals under other types of anaesthesia and also in the absence of anaesthesia. In Fig. 13, for example, the ink traces are shown for the cortical response to flash in the same cat when under chloroform (upper strip) and when under nembutal (lower strip). A late response is seen in both. In both cases needles lightly hammered into the intact skull were used as recording electrodes, and the level of anaesthesia used was deep.
enough for the animal to tolerate this procedure and to abolish all scalp muscle potentials (in the case of the nembutal this was a stage of barbiturate spindling, as can be seen from the record). The presence of barbiturate is clearly not a specific prerequisite for obtaining late responses in the visual cortex. We failed to find the late responses under ether. Under light chloralose

*Responses to flash with two different anaesthetics*

**Cat. 319**

Chloroform

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Nembutal (40 mg/kg, I.P. 1 hour previously; 25 mg/kg more ½ hour ago)

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Fig. 13.
Ink-tracings illustrating the response to flash in the same cat under chloroform and under nembutal anaesthesia. (lateral gyrus).

anaesthesia the evoked potential was found to be rather different in waveform, but was again a double response. At the surface of the lateral gyrus there is an initial surface negativity into which break two surface positive waves, the second of which reaches its peak at approximately 75 msec after the flash (see Fig. 14). At this stage of chloralose anaesthesia there is frequently an accompanying muscle jerk with each response, a fact that suggests that the prominent surface negativity may be the sign of a massed efferent discharge. Further research into the effects of different anaesthetics will be reported in a separate paper, as well as the detailed examination of the unanaesthetised animals.
From the results reported above it is clear that the late discharge in the visual system, although having many features in common with the Forbes response to somato-sensory stimulation, has many important differences. The late response does not need barbiturate anaesthesia for its appearance, although at a certain stage of narcosis it is augmented. It seems likely that other anaesthetic agents have this same effect. As discussed in previous publications (Brazier, 1954a and c) this augmentation has the characteristics of a release phenomenon, as though the first action of the anaesthetic, at light levels, is to remove an ascending inhibitory influence before its depressive effect on excitatory synapses develops. The anti-inhibitory action of nembutal has been confirmed in another laboratory by Purpura (1955).

One of the most outstanding differences is that the secondary response to flash is not diffusely distributed over the cortex in the lightly anaesthetised animal. We have failed to find it in the ectosylvian gyrus, the lateral gyrus forward of the visual area, or the sigmoid gyrus. We have found a late response of low amplitude in the suprasylvian gyrus. Deepening narcosis undoubtedly increases the cortical area from which both the primary and the late responses can be recorded, and for a valid

*Response to single flash of cat under chloralose anaesthesia*

Top row: 4 examples of responses to single flash in a cat 2 hours after intraperitoneal injection of 40 mg/Kg a-chloralose. Bottom row: two spontaneously occurring chloralose spikes. Time line 200 c.p.s. (lateral gyrus).
comparison with other workers' findings in the somato-sensory system, larger doses of anaesthetic need to be used. At the light levels at which the present observations were made, the late response could represent the first wave of the slow cortical after-discharge. If the latter proves to be the case, it is surprising that this potential has a counterpart in the white matter 12 mm below the cortical surface. In none of the cats (without lesions) have we found the late response in an area that does not also give a primary one. As this work progresses it appears less and less likely that this response is carried to the cortex by a truly diffuse system of corticopetal projection.

**SUMMARY**

Single flashes of light evoke more than one response at the visual cortex of lightly anaesthetised cats. The second response does not travel via the lateral geniculate nucleus. The superior colliculus and subthalamus have been explored for late components in response to flash. The effect of various anaesthetics has been noted. The late response in the visual system does not appear to be diffusely projected to the cortex.

**ACKNOWLEDGMENT**

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**REFERENCES**

RISE OF NEUROPHYSIOLOGY IN THE
19TH CENTURY

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RISE OF NEUROPHYSIOLOGY IN THE
19TH CENTURY

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(Read in the Colloquium on the History of Neurophysiology held at the Annual Meeting of the American Electroencephalographic Society, June, 1956)

The 19th century was a golden age of neurophysiology and if, in the space allotted, we are to consider anything but the surface glitter, some radical selections must be made. Because of the special interests of this Society, emphasis will be given to electrophysiology, and particularly to that of the brain. Another contributor is to cover the peripheral system, and I am omitting discussion of Sherrington and of Pavlov since other speakers have these assignments. Growth of knowledge in the field of neurophysiology since the time of the Greeks came to a virtual standstill in the intellectually barren Middle Ages, and then followed only a slowly rising curve until the 19th century when it showed a sudden upswing. Along the way we come across some rather strange representations of the nervous system. I am indebted for Fig. 1 to the Keeper of Western Manuscripts at the Bodleian Library in Oxford. This drawing appears in a manuscript identified as a translation made by a monk in 1152 of a Greek manuscript on the structure of the human body. Only two nerves are depicted going to the brain, and these are shown to arise from the spinal cord at the level of the heart. Incidentally, the drawing also illustrates the consequences of having no abducens nerves. It was some years before the complexities of the nervous system were to be realized.

In the 17th century the long fight between science and dogma began to come out on the side of science. Science was first able to win territory away from dogma in the fields of astronomy and physics, and the foundations of modern science

Fig. 1. Early representation of human nervous system.
NEUROPHYSIOLOGY IN THE 19TH CENTURY

laid in the 16th and 17th centuries were in these subjects, Copernicus, Kepler, Galileo and Newton being the four great protagonists. The science of man’s physiology came so uncomfortably close to conflicting with dogma’s central core that its development hung back and, while Newtonian physics forged ahead, discussions of physiology remained very largely in the domain of the philosophers. Inevitably science was to invade physiology and to be accepted as its discipline, but it is noticeable that although the functioning of less controversial parts of man’s anatomy had been surrendered to the scientists long before (for example, the circulation of his blood in 1628), the “untouchable” sphere of man’s functioning—namely, his central nervous system—was the last to yield to science.

One of the greatest figures of early 19th century physiology, Johannes Müller, was himself a curious mixture of the scientific and the metaphysical and was a proponent of vitalism, although he was a powerful advocate of using the tools of physics and chemistry in the study of biology. The metaphysical concept of vital force hung on in Germany longer than it did in England and longer than in France, where revolutionary thought infiltrated all fields, not only government. Unorthodox thinking in Germany had been suppressed by the Carlsbad Resolutions of 1819, by which Metternich banned free expression of opinions hostile to existing institutions. In spite of the handicap that this intellectual climate must have been, Müller made great contributions, largely through crystallizing with great clarity the exploratory concepts and experiments of others. For example, he did much to gain recognition for the essential nature of the reflex arc being one of nerve conduction. When the century opened the role of nervous conduction had already been recognized by Robert Whytt (51) as the mechanism of reflexes, rather than irritability of the muscle fibers themselves—an older concept stemming from Glisson in the 17th century and Haller (32) in the 18th. However, Whytt did not conceive an arc, but postulated an unconscious influence that relayed the impulses from the sensory to the motor side. This influence he called the “sensient principle” and placed it in the spinal cord. The experiments of Marshall Hall (31) in the 1830’s on segmental reflexes in spinal animals established beyond doubt that the reflex was a purely nervous arc and laid the foundation for its importance in clinical neurology.

Müller is best known for his doctrine of specific nerve energies (46), although here again the concept was an old one. In 1786 John Hunter (36) had said, “It is more than probable that every nerve so affected as to communicate sensation, in whatever part of the nerve the impression is made, always gives the same sensation as if affected at the common seat of the sensation of that particular nerve. . . . A mechanical impression on the retina produces an impression of light; a blow on the ear the sensation of sound.” Thirty years later Müller was to reiterate this doctrine which was to become linked to his name. Müller was a great teacher and had a distinguished list of pupils to his credit. In 1840 he brought out his famous textbook, Elements of physiology (47). Two of Müller’s pupils were also to be outstanding in
the development of neurophysiology, von Helmholtz and du Bois-Reymond. Helmholtz’s knowledge of physics led him to use its tools for physiological experiments and to apply them to such problems as animal heat, conservation of force, and transformation of energy, and his classic books on optics (33) and on the sensations of tone (34) were major contributions to the physiology of the special senses. For neurophysiology another classic contribution (published in 1850) was the measurement of conduction velocity in nerve, an achievement of his younger days (35). This was in the days before the action potential of nerve had been discovered and his ingenious method was to stimulate a nerve at different distances from the muscle, noting the instant of stimulation on a galvanometer and the resultant muscle contraction on a smoked drum. He was so surprised at the low velocity that he pushed his stimulation point as close to the muscle as he could, and in this way discovered neuromuscular delay. He made measurements first in frog, and later in man, using thumb movement in response to stimulation at the wrist and elbow. He measured sensory nerve conduction by reaction times to stimulation at the toe and thigh.

It was du Bois-Reymond, Müller’s other great pupil and his successor in the Chair of Physiology at Berlin, who developed techniques for stimulating and recording that made electrophysiology a practical laboratory discipline. It was he who introduced the induction coil and the technique of faradic stimulation into biology and used a galvanometer to detect currents. In order to understand what du Bois-Reymond contributed, one needs only to consider the confused ideas of animal electricity that were prevalent when he entered the field. The famous controversy between Galvani and Volta had rocked the world of physiology at the end of the previous century. Each had tried to explain the twitchings of Galvani’s frogs as a single phenomenon (Galvani as animal electricity (27), Volta as currents of dissimilar metals (48)). Actually Galvani’s first observations were of a phenomenon with both these unknowns, a fact perhaps only first clearly recognized by von Humboldt. Even at the end of his days Volta only very grudgingly admitted the possibility of a biological source of Galvani’s electricity, but held that if it existed it must be due to the fact that there were two dissimilar tissues involved, muscle and nerve.

Knowledge of current flow in metals soon outstripped that of biological electricity, but in time Oersted’s discovery in 1819 of the deflection of a magnetic needle by a galvanic current led to the development of the galvanometer, du Bois-Reymond’s tool for detecting biological currents—so that, as he remarked, “metal electricity was enabled to atone for the wrong she had done to her more tender twin sister.” Galvani’s nephew Aldini (1) made many experiments in the early part of the century in an effort to demonstrate that electricity came from the animal and that it was not dependent on the presence of dissimilar metals. One of his more bizarre experiments is depicted in Fig. 2. The description reads, “The right hand of the experimentalist is placed in the ear previously moistened with salt and water, of
Fig. 2. An experiment by Aldini on animal electricity.

an ox's head, while in the other hand a prepared frog is suspended by the foot, and the sciatic nerves brought into contact with the ox's tongue. In the muscles of the frog convulsions are immediately produced." Later he was to find that he did not need the ox's head, which made the experiment simpler but less spectacular. Before du Bois-Reymond took up this work the great Italian schools of physiology had been the principal workers to follow the leads their countrymen, Galvani and Volta, had given them, and in almost every laboratory investigators were attempting to settle the notorious controversy. "The storm," said du Bois-Reymond, "which was produced by the appearance of the above-named Commentary among philosophers, physiologists and physicians can only be compared to that which disturbed at that time [1791] the political horizon of Europe. It may be said
that wherever frogs were to be found, and where two different kinds of metal could be procured, everybody was anxious to see the mangled limbs of frogs brought to life in this wonderful way.”

In 1825 Nobili, Professor of Physics in Florence, had improved Oersted’s galvanometer by compensating for the earth’s magnetism and with this instrument had demonstrated the electromagnetic action of frog’s muscle currents but had interpreted them incorrectly as thermoelectric phenomena. In the tradition of the great Italian schools, the study of animal electricity was taken up by Carlo Matteucci, Professor of Physics at Pisa. He first published in 1837, and devoted most of his productive years to study of the muscle currents of the frog, using the same name for them as suggested by Nobili, “la corrente propria della rana.” He also wrote much in French (39, 40), using the expression “courant propre”—mistranslated into English, where we find it referred to in all the journals of the time as “the proper current of the frog” (41).

Matteucci demonstrated the fallacies of Volta’s and Nobili’s theories but was himself hampered by a concept of “nerve force” which he appears to have regarded as a specific form of energy. Matteucci found his frog’s nerve-muscle preparation so sensitive to small currents that the muscle would contract if the nerve were laid across another contracting muscle (42). This is the “rheoscopic” frog of the physiology textbooks, although Matteucci called it the galvanoscopic frog (41). He used it to detect currents in the muscles of other animals. He deposited a sealed letter with Monsieur Dumas, the President of the French Academy (43), registering his claim to have recorded muscle currents in warm-blooded animals, and later (1845) he wrote a letter to von Humboldt (44) describing the currents he found in pigeon, rabbit and dog. In the same year he reported the existence of muscle currents in a man with an open wound. In addition to being an outstanding physiologist, Matteucci was one of the prominent figures of his time in the Risorgimento. A great liberal and a patriot, he made an attempt to coordinate the efforts of all the European liberals when the 1848 revolution broke out. When Italy was united, in 1859, he was appointed senator; he was one of the first Ministers for Public Instruction in Italy. He died in 1868 and is buried in the beautiful Composante at Pisa. The portrait in Fig. 3 is reproduced from the old yellowing photograph in the Scuola Normale Superiore at Pisa.

Matteucci’s observations really represent the stage that electrophysiology had reached when du Bois-Reymond entered the listings. He was a brilliant experimenter and a logical thinker, unhindered by the metaphysical concepts of vital force that had plagued his teacher, Müller, and he was much influenced by Matteucci’s work. To list extremely briefly his contributions to electrophysiology (24): He gave an unequivocal demonstration of what we now call the demarcation potential of nerve, showing the transverse cut surface to be negative to the longitudinal one. His term for this was Nervenström or nerve current. He extended these observations to the central nervous system, producing evidence for demarcation potentials in
the frog’s spinal cord and in its brain, between cut surface and convexity. This probably represents the first attempt made to find electrical currents of any kind in the brain. He went on to demonstrate that the negativity he found in nerve increased when an externally applied constant current was passed through it in the same direction and decreased when the current was reversed. He named this electrotonus. He made tests on himself to demonstrate muscle currents in man and gave the rather idealized picture of the experiment that is reproduced in Fig. 4. The finding that changed the face of neurophysiology was du Bois-Reymond’s discovery of the action potential of nerve. With short tetanizing currents he was able to show that the resultant “negative variation,” as he called it, was entirely distinct from the variations caused by the electrotonic state. He interpreted the action potential of nerve as a decrease in its demarcation potential—a view which held the board until the discovery of the overshoot by Hodgkin and Huxley and by Cole and Curtis in 1939.

Matteucci who had demonstrated demarcation potentials in muscle, had looked for them in nerve, but failed to find them. He reported, “Nous croyons être autorisés a conclure qu’il n’existe aucune trace de courants électriques dans les nerfs des animaux vivants, appreciable a l’aide des instruments que l’on possède aujourd’hui.” It is interesting that he made this statement

Fig. 3. Carlo Matteucci.

Fig. 4. Du Bois-Reymond’s experiment on muscle currents in man.
actually one year after du Bois-Reymond had, in fact, reported them in a publication (25). Du Bois-Reymond’s discoveries had a great influence on the development of neurophysiology, as did his famous book, Untersuchungen über thierische Elektricität (24).

The state of neurophysiology in those laboratories that did not yet use electrical techniques may be summarized briefly as follows: Charles Bell (11) had suggested the difference between sensory and motor roots. He had postulated that, although the anterior roots of the spinal cord were motor in function, the posterior roots were not, and Magendie (38) had independently demonstrated their sensory nature. Müller (45) had confirmed the Bell-Magendie law in frogs. Bell also held that muscles themselves had sensory as well as motor nerves and that these conveyed, to use his own words, “a sense of the condition of the muscles to the brain.” He spoke of “a circle of nerves” making a sensorimotor junction between brain and muscle. Perhaps this is an early glimpse of a hypothesis of feed-back circuits.

The inhibitory action of nerves was just beginning to be understood. The Webers (50) were establishing the inhibitory action of the vagus on the heart, and formulating a hypothesis to cover the previous findings of vagal influence on heart muscle. The discovery of other inhibitory nerves followed. Claude Bernard (13) demonstrated that stimulation of the chorda tympani caused vasodilation, and Pflüger (another pupil of Müller’s and also of du Bois-Reymond’s) found that splanchnic stimulation lessens intestinal movements. Electrical methods of stimulation had spread to the brain and the pioneer work of Fritsch and Hitzig and of Ferrier had proved Magendie incorrect in his claim that the cortex was inexitable.

Meanwhile, the intellectual climate in England was changing, owing largely to the influence of Darwin and Huxley. It now became respectable, not to say mandatory, to treat the brain as a physiological and not a metaphysical object for experiment. A predecessor of Sherrington’s in the Chair of Physiology in Liverpool, and the man for whom this chair was created, had in the early 1870’s examined the brains of rabbits to see whether the action potential that du Bois-Reymond found to accompany an impulse in peripheral nerve and in spinal cord could also be detected in the brain when impulses passed through it. This was Richard Caton, the pioneer of electroencephalography. Caton was a remarkable man who published widely in medicine as well as in electrophysiology—on acromegaly (his patient was the first to be operated on for this disease), on lead poisoning, on typhoid, on enteric fever. He was an amateur archeologist and a scholar. He was prominent in academic and public affairs, he was president of the Medical Institution and, at the age of 60, he was elected Lord Mayor of Liverpool in recognition of his work for public health. The illustration shows him in his mayoral robes. In 1874 Caton started his observations on the electrical currents of the brain and in the following August he demonstrated them to the British Medical Association (16) with Burdon Sanderson in the chair. He was either fortunate or wise in choosing the rabbit as his experimental animal, for in
These first experiments he used a Thomson's reflecting galvanometer with du Bois-Reymond's non-polarizable electrodes. This instrument was just able to respond to the slow waves of the rabbit's brain, whereas had he been using the rat he would probably have missed discovering the EEG because of the limited frequency response of his apparatus. It is interesting to note that this was before the EKG had first been recorded in man by Waller (49) and less than 20 years after the currents of the exposed heart had been observed in frogs by von Kölliker and Müller (37).

This was in the days before permanent records (I believe Burdon-Sanderson (15) was the first to photograph the movements of his electrometer) and Caton (Fig. 5), like other scientists of his time, had to demonstrate any claim he made. There were, of course, no electronic amplifiers and to give his demonstrations Caton had to use optical amplification. He used the same display technique by which he had demonstrated the effect of constant currents on the excitability of frog nerve to the Medical Institution in Liverpool earlier in the same year. Here is his description (17): “A graduated scale, some 8 or 9 feet in length being placed on one of the walls of the theatre, a beam of light from an oxyhydrogen lamp was thrown onto the mirror of the galvanometer, and thence reflected to this scale.” He set out in his experiments to detect potential differences between external surface and cut surface (as du Bois-Reymond had done in his frogs' brains) but went on to observe the presence of currents when both electrodes were on the cortical surface, or one on the cortex and the other on the skull. He was looking for changes with sensory stimulation, which indeed he found but, as all electroencephalographers know, he noticed that even in the absence of sensory stimuli he could not get a steady baseline. It would wobble, though the oscillations were small in comparison with the changes evoked by sensory stimulation. This was the discovery of the EEG and the foundation of the endeavor that brings us to this meeting today. Caton's own words in his first description were: “Feeble currents of varying direction pass through
the multiplier when the electrodes are placed on two points of the external surface, or one electrode on the grey matter, and one on the surface of the skull.” He attempted to relate changes in electrical potential to function and to use them to locate specific sensory and motor areas. He was more consistently successful with photic stimulation than with other sensory stimuli and failed to evoke any response with sounds.

In 1887 Caton came to this country to give an account of this work to the Ninth International Medical Congress in Washington, D. C. (19). Among other work that he reported on this occasion were the results of photic stimulation in rabbits and monkeys. His own words were, “I tried the effect of alternate intervals of light and darkness. . . . In those 5 experiments in which I was successful the relation between the intervals of light and darkness and the movements of the galvanometer needle was quite beyond question.” At this meeting in Washington, Caton reported for the third time (16, 18, 19) his finding of feeble currents when both electrodes were placed on the external surface of brain. He also mentioned their sensitivity to anesthesia and to massive hemorrhage, and their disappearance on death. This pebble that Caton dropped into the pool in Washington in 1887 was to produce no ripple in this country until 1930 when the first American publication on the electrical activity of the brain appeared. This was the article by Bartley and Newman (1a) in Science. In Europe ripples were to appear much earlier, but soon whipped up into a veritable storm.

In 1888 Adolf Beck, who was born in 1863 (Fig. 6), an assistant in the physiology department at the University of Jagiellianski in Krakau, asked his professor, Cybulski, for a subject for his thesis. (Cybulski was later to publish on brain potentials with his pupil (8, 9) and much later with another of his students (21), but the initial work was Beck’s.) The influence of du
Bois-Reymond and of his pupil Setchenow was very strong in Polish physiology; Cybulski, who had read his du Bois-Reymond (but not his Caton), suggested the following topic to his assistant, Beck: “The determination of localization of brain and spinal cord function by means of electrical phenomena.” By 1890 Beck had done his experiments and written his thesis (2). It appeared in full in the Polish language (2) in the proceedings of the Academy of Sciences in Krakau but, to broaden his audience, he also published a 3-page report of it (in the German language) in the Centralblatt für Physiologie, also in 1890 (3). He set out to find shifts in steady potentials due to sensory stimulation but he also found the brain-wave. He seems to have been absolutely unaware that both these phenomena had been demonstrated by Caton 15 years earlier. In his report of his own work he says: “Even in the very first experiment I noticed—and repeated experiments all confirmed it—that the difference in potential between the electrodes when applied to two given points on the cortex of the hemispheres was not a stable level of potential; there was a continuous waxing and waning variation taking place which neither was related to the respiratory rhythm nor was it synchronous with the pulse, nor finally was it in any way dependent on movement of the animal, since it was present in curarized dogs.” He published the protocols of all his experiments but had no means of making photographs or permanent recordings at this time (although he did of his later work). He used a Her-
mann galvanometer and gave the measurements of the spontaneous swings that he observed. Beck was to continue to contribute in this field in the present century and was to live on to the age of 79. As an old man, he was to meet a cruel and tragic death; he was killed by the Nazis in 1942.

Beck’s claim to priority evoked a number of spirited letters to the editor of the Centralblatt. The first, as most electroencephalographers know, was from Fleischl von Marxow (26), professor of physiology at the University of Vienna (Fig. 7), a communication in which he revealed the existence of the now famous sealed letter that he had deposited in 1883 with the University. The entries in the archives of the University of Vienna are in hand-

![Fig. 8. Entries in Archives of University of Vienna of Fleischl von Marxow's sealed letters.](image)

writing, and carry the heading: “Preservation of Priority.” There are records of two sealed envelopes from “Prof. Dr. Ernst v. Fleischl, Wien,” one deposited on November 7, 1883 (initialled E. F.) and the other on February 26, 1885. Both were opened at a session of the Imperial Academy of Science on November 20, 1890, and the first was published in the Centralblatt the following month (26). The entry for the first sealed letter lists it as a “Physiological discovery to be worked on further,” and that for the second entry: “Results of an experimental investigation” (Fig. 8). The original letter of 1883 makes it clear that Fleischl von Marxow had observed poten-
tial shifts following sensory stimulation in animals, had localized the visual responses and had attempted olfactory stimulation. He had recognized the importance of the technique for localization of sensory centers and had observed that responses were abolished by anesthesia. He made the interesting comment that this proved that anesthesia abolished sensation and not merely the memory of it. He did not observe spontaneous potentials (as had Caton and Beck) but he did comment that the evoked potential change could be led off from the skull, not only from the exposed cortex. It is interesting that he was looking so hard for evoked potential changes and finding them so successfully that he overlooked the EEG. He obviously wished his baseline to be flat and rather grudgingly says that there was "little or no movement of the galvanometer"—"Keinen oder einen sehr geringen Ausschlag."

Ignoring Beck's demonstration of spontaneous activity as well as of evoked responses, he claimed priority for the discovery of brain potentials. Beck answered with a flowery but firm letter (5) to the editor in which he pointed out that it is open reports that establish priority rather than letters sealed by professors. He mentioned that Cybulski reported the results orally in 1888 and that his own report was the first in print. At this point Gotch and Horsley (30), whose pioneer studies on the electrical activity of the spinal cord are classics, jumped into the argument and, again ignoring the discovery of spontaneous activity, claimed the priority for recording brain potentials with their publication of 1888. They were silent about the steadiness of their baseline. A rather quietly worded letter (20) from Caton to the editor of the Centralblatt ended these polemics.

It seems extraordinary that these English physiologists, Gotch and Horsley, were apparently ignorant of Caton's work although he had given a demonstration before the British Medical Association and this had been reported in such a widely read journal as the British Medical Journal. An added twist is that Gotch was later to succeed Caton in the Chair of Physiology at Liverpool. Gotch was himself to be succeeded by Sherrington. As a matter of fact another claim was to come from Danilewski in Russia who in 1891 (23) reported experiments that he had made on five dogs in 1876 before he knew of Caton's work. Danilewski was a pupil of Setchenow, who himself had experimented on the brainstem. Danilewski, working in the cerebrum, said in his 1891 paper that he had, in 1876, found changes in the steady potentials of the cortex as a consequence of various modes of sensory stimulation and spontaneous fluctuations when both electrodes were on the cortex. Danilewski did not pursue this line of work and his fame as a physiologist rests more on his work on the effects of stimulation of various structures in the brain on blood pressure, reflexes, and on respiration (22). An interesting footnote to history is that the abstract that appeared in Centralblatt f. Physiologie of one of his papers in 1892 is signed "Sigm. Freud."

Actually, as has been mentioned, Gotch and Horsley's chief contribution was in the spinal cord, where they had worked mainly with the demarcation potential, demonstrating that this changed when the animal's foot was
pinched, or the sciatic nerve stimulated (28). Horsley also demonstrated the descending influence of cortical stimulation (29) and adapted the method for localization of motor centers. Their conclusions were strongly opposed by Brown-Séquard (14) who remarked that one could make facial muscles twitch in laughter by tickling the foot, but this did not mean that the foot was a motor center. Horsley (29) was so heavily influenced by his work on spinal fiber tracts that, when his attention had been drawn to Caton's, Beck's and Danilewski's work, he advanced the opinion that their findings reflected the activity of the white matter rather than of the grey.

So what was known of brain potentials at the end of the nineteenth century when this survey ends? It was known that the brain had "spontaneous" electrical activity, that potential shifts could be elicited in the appropriate cortical areas by sensory stimulation, that these potentials could be recorded from the skull, and that anesthesia abolished them. At the turn of the century the focus of attention was still on localization of brain function by electrical methods, and Beck and Cybulski went on to pursue this, but the great era of the development of knowledge about "spontaneous" potentials that followed the invention of the vacuum tube was to wait until the second quarter of the 20th century, and to see its rise in Germany.

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M. A. B. B RAZIER,
D.Sc. 1960
Photograph of the contemporary oil painting (probably by Spagnoli) of Galvani that hangs in the University Library of Bologna. Several engravings have been made from this portrait, notably those of Sir Joshua Reynolds's pupil, Marchi. The engravings, however, unfortunately omit the frog.

(Reproduced by kind permission of Dr Giulio Pupilli, present holder of the Chair of Physiology at the University of Bologna.)
THE EVOLUTION OF CONCEPTS RELATING TO THE ELECTRICAL ACTIVITY OF THE NERVOUS SYSTEM
1600 TO 1800
MARY A. B. BRAZIER

This review of the development of ideas about the role that electricity might play in the activity of the nervous system begins at the opening of the seventeenth century and looks back from the viewpoint of an electrophysiologist to the early workers and thinkers in this branch of endeavour.

In the history of the electrical activity of the nervous system the outstanding figure is, without rival, that of Galvani, and it seems fitting that the first illustration should be of him (Fig. 1). This is a photograph of the oil painting in the University Library at Bologna. Many engravings have been made of it but they have the failing that they omit the frog, the animal that contributed more than any other to the electrophysiology of the eighteenth and nineteenth centuries.

In this essay, an attempt will be made first to outline what led up to Galvani’s discovery, and, secondly, to follow the difficulties that the scientists of the time had in reaching an understanding of the observations he described.

Three lines of knowledge converged to meet eventually in the concept of animal electricity. Their development will be traced quite briefly. One was the physical science of electricity, another was the knowledge that some animal forms, notably the marine torpedo and the electric eel, produced intrinsic electricity, and the third was the observation that animal tissues could be made to contract by electrical stimulation. Galvani had experience in all these fields.

Taking first the stage that knowledge of electricity had reached by 1791, the date of Galvani’s well-known Commentary. Static electricity had, of course, been known since the time of the ancients. Its differentiation from magnetism began when William Gilbert, the first modern scientist, undertook the studies that culminated in his famous book De Magnete.

Gilbert, scientist and physician to the Queen, was son of the recorder of Colchester. He was born and lived part of his life in his father’s house, a portion of which still stands and, at the time of
writing, is being restored. A tablet to him hangs on an ill-lit wall of the church there, and a nineteenth-century statue of him looks down from the façade of the town hall.

*De Magnete* marks a turning-point in science for it was the first book to advocate experimental methods, and in this way heralded the rise of empiricism in the eighteenth century. Gilbert declared the value to science of ‘trustworthy experiments and demonstrated arguments’ in place of ‘the probable guesses and opinions of ordinary professors of philosophy’. And if we overlook his final chapters, his book is a magnificent example for modern science.

In Gilbert’s time the only known form of electricity was the transient spark, and although the invention of a rotating sulphur globe by Von Guericke, a prominent citizen and scientist of Magdeburg, can be regarded as a step on the way to the design of machines for producing frictional electricity, he himself used it essentially for other purposes. It was still many years before electrostatic machines working by induction were to be available to physiologists.

Von Guericke noticed the attraction of light objects (which he likened to electrical attraction) and he also noticed repulsion. But neither of these phenomena was elucidated until the work of Du Fay in the following century. Du Fay’s pupil, the physicist Abbé Nollet, was one who employed a frictional machine for his many ingenious experiments, and a later type with rotating plates was used by Galvani in his famous series of experiments that began in 1780. (The date makes unlikely the popular story that Galvani’s discovery in 1791 was an accidental one, made while preparing frogs’ legs for his wife’s supper.)

Nollet, born near Compiègne at the opening of the eighteenth century, was to become its ‘savant à la mode’. In his theological studies the highest examination he passed was the Diocanat, but in science he was to achieve membership in the Royal Society and in the Académie des Sciences. Nollet’s gifts included intelligence, great manual dexterity and a flair for teaching. It was to his ability to interest the layman in science that he owed his recognition by Louis XV and his appointment to the chair in experimental physics at the College of Navarre.

In 1738 he published his popularized course on experimental physics in the second part of which he dealt with the laws of electricity. No doubt Nollet gained this knowledge from Du Fay and that in other branches of physics from his master, Réaumur, for he had
When Queen Elizabeth died in 1603, her Clarendon, William Camden, drew her funeral procession on a scroll many feet long (now in the British Museum). Depicted are all the mourners from the Lord Mayor of London to the scullery boys. In the group of four men labelled 'Clarks of Parliament Doctors of Physick', the one (third from the left) in the plain hat turning to face the artist has been identified by Silvanus P. Thompson as Gilbert, and indeed the features are in keeping with those in Clamp's engraving made in 1796 from the lost portrait of Gilbert attributed to Cornelius Kettle. This, the only authentic contemporary portrait, painted in 1591, hung in the Bodleian Library until 1796 when it was recorded as 'already decayed'. Clamp's engraving can be found in F. G. Waldron's *Biographical Mirror*, published by S. and E. Harding in 3 volumes in 1795-98. (The above excerpt from the Camden MS. is reproduced by kind permission of the British Museum.)

_Facing page 192_
Portrait of the Abbé Nollet from the pastel by his friend and neighbour, Maurice Quentin La Tour, exhibited in the Salon du Louvre 1753 and reproduced, in the catalogue of the sale by Princess Mathilde 1904. Engravings of this portrait were made by Molès and by Beauvarlet. Another portrait, exhibited at the Exposition Universelle in Paris in 1900, and since then frequently reproduced, shows a man without a wig and in a black skull-cap. It is, however, now thought to be a misidentification. (J. Torlais. L’Abbé Nollet, un Physicien au Siècle des Lumières. Sipuco. Paris, 1954, 220 pp.) The features of the Abbé reproduced above are similar to those in another authentic contemporary portrait, the oil painting by Jacques de Lajoue that hangs in the Musée de Carnavalet in Paris. This shows the Abbé in his study at the Chateau de La Muette.
had no formal schooling in science. He continued to experiment and teach all his life and among those who, as a young man, took his course (and praised it) was Lavoisier.

There was a period in the eighteenth century when interest in electricity was so keen that it was invoked to explain many natural phenomena not only of animals but also of plants.* Linnaeus’s daughter, Elizabeth, noticed that at twilight in her father’s garden near Uppsala some of the orange coloured flowers such as marigolds and firelilies appeared to give off flashes of light. (It was Goethe who showed this to be a retinal contrast effect and not an electrical flash.) But those who speculated about animals and man felt they were on surer ground. Did not the cat’s fur crackle when you rubbed it, and had not Theodoric, the Visigoth, thrown off sparks as he marched?

In the early part of the century it had been discovered empirically that the human body could be charged electrostatically, provided it was insulated. At first it was thought that a layer of air had to be present between the subject and the ground, for the characteristics of conductors and non-conductors were only beginning to be understood. Stephen Gray (who died in 1736) had discovered that the distribution of electric charges varied with the insulating or conducting properties of the material employed. These terms were not used at the time, nor was induction (which he had demonstrated) understood. His teacher, Desaguliers,? son of the minister of the French chapel in Swallow Street and demonstrator for Newton, was to clarify the distinction between conductors and non-conductors, showing them to be essentially the ‘non-electrics’ of Gilbert that conveyed electricity away, and the ‘electrics’ that could be charged.

In April 1730 Stephen Gray, writing from Charterhouse (where he was a pensioner), reported experiments he had made at Norton Court in Kent.

I made [he said] the following Experiment on a Boy between eight and nine Years of Age. His Weight with his Cloaths on, was forty-seven Pounds ten Ounces. I suspended him in a horizontal Position, by two Hairlines such as Cloaths are dried on . . . .

Gray goes on to describe how he charged a flint-glass tube by friction and demonstrated that if he held this near to the boy’s feet, the whole

* For example, l’Abbé Berthelon (De l’électricité des végétaux. Paris, Didot, 1783), von Kästner (Schwedischen Akademie Abhandlungen, 1762, 24, 291) and Goethe.
body became charged, so that a leaf-brass electroscope brought close
to the boy’s face was deflected.

Upon the Tube’s being rubbed [he reports] and held near his
Feet, without touching them, the Leaf Brass was attracted by the
Boy’s Face with much Vigour, so as to rise to the Hight of eight,
and sometimes ten Inches.®

This trick seems to have caught the popular imagination, for
Hausen,® Professor of Mathematics at Leipzig, demonstrated a
similar experiment in 1743. The irrepressible Abbé Nollet18 re-
produced it in his classes, attended by members of the court of
Louis XV, and amused them by drawing a spark from the nose of the
boy. (He had first tried this out on Du Fay in his garden at Tremblay
and had satisfied himself that it was harmless.)

Galvani employed not only these frictional machines to stimulate
his frogs, he also used the primitive forms of condensers known as the
magic square and the electrophorus, as well as the more efficient
Leyden jar. This last device, the first effective condenser, was the
invention of Petrus van Musschenbroek of Leyden. In the same year,
Von Kleist11 of Kamin in Pomerania, one of the indefatigable
company of eighteenth-century clergymen to whom science owes so
much, invented a similar device.

Van Musschenbroek,15 striving to conserve electricity in a conduc-
tor and to delay the loss of its charge in air, attempted to use water as
the conductor isolating it from air in a non-conducting glass jar.
However, when he charged up the water through a wire leading from
an electrical machine he found the electricity dissipated as quickly as
ever. His assistant, Andreas Cuneus, while holding a jar containing
charged water, accidentally touched the inserted wire with his other
hand and got a frightening shock. He had formed one ‘plate’, the
charged water being the other, and the glass jar the intervening
‘dielectric’. A condenser was born.

The physical experience was so alarming that letters flew out from
Leyden to fellow physicists; van Musschenbroek wrote to Réaumur,
and Allamand, his pupil, wrote to the Abbé Nollet. Nollet, recog-
nizing the spectacular value of this discovery, immediately published
excerpts,13 the descriptions losing nothing in horror by his transla-
tions from the Latin.*

* He quotes van Musschenbroek as saying: ‘le bras et tout le corps sont affectés
d’une manière terrible, que je ne puis exprimer: en un mot, je croyais que c’en était
fait de moi.’
The portrait of Petrus van Musschenbroek when he was Professor of Physics at Utrecht, painted by J. M. Quinkard. The portrait hangs in the Rijksmuseum of the History of Science in Leiden, and I would like to thank Dr Storm van Leeuwen, collateral descendant of van Musschenbroek for this photograph. In the foreground can be seen a compass, a loadstone, a barometer and a pyrometer.

(Reproduced by permission of the Rijksmuseum voor de Geschiedenis der Natuurwetenschappen, Leiden.)
Fig. 5

Early Leyden jars (though not the first ones made). These can be seen in the Rijksmuseum of the History of Science at Leiden, and are much larger than the ones depicted by Galvani or Nollet. They are too large to hold in the hand.

(Reproduced by permission of the Rijksmuseum voor de Geschiedenis der Natuurwetenschappen, Leiden.)

Fig. 6

The portrait of Abraham Bennet that hangs in the vestry of the church at Wirksworth in Derbyshire. It has been suggested that this may be the work of Joseph Wright, but it is certainly more primitive in treatment than most of this painter's works. In the original, written on one of the pile of books on the left, can be seen the title: Experiments in Electricity, and on a scroll: 'Rev. Abm. Bennet F.R.S.' The tablet to Bennet's memory hangs on the south wall of the nave at Wirksworth.

(The author is indebted for these photographs to the Reverend G. Busby, Rural Dean of Wirksworth.)

[Facing page 195]
The name, Leyden jar, adopted by Nollet, has persisted, although never so called by its inventor. When later Du Bois-Reymond came to Berlin and gave all his working life to the elucidation of animal electricity he revived the German name, referring always to the 'kleistsche Flasche'.

The Leyden experiment (also Nollet's term) was repeated by him and fully described. His illustration shows a brass rod, suspended by silk ropes charged by an electrostatic machine, the charge being accumulated in the Leyden jar that the experimenter is holding. On touching the bar with his finger, the man draws a spark which is dramatically portrayed in this engraving, and he gets a shock described by the Abbé as 'une commotion très forte et très subite dans les deux bras, et même dans la poitrine et dans le reste du corps'.

The instruments so far described were devices for the production of electricity, and could be used to demonstrate that animal tissues react to applied electric shocks, but the instruments available for detecting electricity were still quite limited. Up to the time of Volta the most sensitive instrument available was the modification of Cavallo's electrometer¹⁴ perfected by the curate of a rural parish in Derbyshire.

The Reverend Abraham Bennet of Wirksworth, a village on the Derwent, designed and constructed the delicate instrument that carries his name.¹⁵ He replaced the silver wires used by Cavallo and the gilded straws of Cavendish¹⁶ by strips of gold leaf. It was the movement of strips of gold leaf when charged, that had earlier made Newton¹⁷ so sceptical of the theory of electricity prevalent at the time, namely that the electricity that could be drawn from a charged body was an emanation or effluvium produced by that body. This appeared to contradict the law of gravitation, for there was no loss of weight.

In the little medieval church where he spent so many of his years there hangs a small portrait of the Rev. Bennet. The portrait is not by a very skilled hand which makes unlikely the suggestion that it is by Joseph Wright (a friend of Bennet’s and a purchaser of his book). Bennet’s famous book (*New Experiments in Electricity*) appeared in 1789, a copy being bought for his local scientific society (the Derby Philosophical Society) in two cautious instalments of two shillings and sixpence each, one made before publication and one after, the payments being authorized by Erasmus Darwin. Some interesting and unpublished manuscripts of Bennet’s are in the possession of the Derby Public Library.
Galvani\textsuperscript{18} himself had the straw electrometer designed by Volta, but used this instrument for detection rather than measurement, and, in fact, frogs' legs were a more sensitive detector of electricity than any of the electroscopes available in his day.

Following this brief account of the electrical knowledge that led up to Galvani's work, an outline will be sketched of the knowledge scientists had at that time of intrinsic animal electricity as exemplified by the electric fish. The ability of these fish to deliver electric shocks was, of course, known to the ancients, as it must have been to anyone who swam in the Mediterranean. The fish received its name from the torpor it can induce in its victims and has handed it on to a more lethal weapon. The first really systematic studies of the marine torpedo were those carried out at the Île de Ré by John Walsh\textsuperscript{19} and reported to the Academy of La Rochelle in 1772. Walsh conceived of the shock as being due to the release of a compressed electric fluid.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{image}
\caption{Matteucci’s drawing of the electrical organs of the Marine Torpedo and his experiment to show that its discharge in air produces a spark. (From Matteucci, C. Leçons sur les Phénomènes physiques des Corps vivants. Paris: Masson, 1847, 407 pp.)}
\end{figure}

The identification of electricity with the torpedo's discharge was not immediately accepted and possibly the anonymous notes scribbled in an eighteenth-century hand in the margins of the copy now in the library of our university may reflect an average reaction of the time to Walsh's notions. 'Into what absurdities', says one of these notes, 'will some men run, to support a favourite hypothesis!' And later: 'Had
these shocks been electrical, they would certainly have been attended with both light and sound.’ This touches on a common stumbling-block in the early acceptance of biological electricity. Frictional electricity had led observers to expect a spark and a crackle. Almost a century passed before Matteucci\(^9\) demonstrated a spark from the discharge of a torpedo. For success, the procedure is as follows: The unfortunate fish (and Matteucci tells us it must be ‘une torpille

\[ \text{Fig. 8} \]

Galvani’s notes on an experiment he made in 1795 on the marine torpedo. The notes read: ‘Giorno 16 Maggio. 26. La Rana senza far arco colla superficie della Torpedine fra nervo e muscolo ma toccando coi soli nervi crurali la Torpedine, in qualunque luogo, ma più col dorso, o spora, o in vicinanza de’ corpi elettrici cade nelle solite convulsioni a qualunque scossa.’

(I am indebted to Dr Giulio Pupilli of Bologna for this photograph of the manuscript preserved in the Biblioteca dell’Archiginnasio di Bologna.)

très vivace’) is placed on an insulated metal plate, while another metal plate held by an insulated handle is lowered over it. Attached to each plate is a wire from which hangs a strip of gold leaf. When the fish discharges its shock, the gold leaves move towards each other, and if separated by exactly the right distance, a spark leaps across the gap.

Walsh’s observations received almost immediate confirmation from
John Hunter. But Hunter argued that the electrical organs are controlled by nerves and hence that 'the will of the animal does absolutely control the electric powers of its body; which must depend on the energy of the nerves'.

At the present day when so much time has been given to the design of electrical models of turtles and bar-flies, it is interesting to recall that that eccentric Englishman, Henry Cavendish made in 1776 an artificial torpedo of wood and leather which would give shocks when submerged in salt water, its supply of electricity being a Leyden jar.

Galvani himself studied these electric fish on the Adriatic coast of Italy (in 1795), and left some manuscript notes. In Fig. 8 is a facsimile of Galvani's handwriting on a page from his notebooks which are preserved in the Library of the Archives of the City of Bologna, and I am indebted to Dr Giulio Pupilli for permission for reproduction. Unlike the famous Commentary which was prepared for publication in Latin, these jotted notes by Galvani are in Italian. This one records the observation that the frog was convulsed with every discharge from the torpedo when only its crural nerve touched the fish, even though the surface of the torpedo was not making an arc between the nerve and the muscle. Galvani notes that the effect was greatest when the nerve touched the back of the fish and when it was over or close to the electric organ.

For many years before Galvani's day it has been known that the limbs of a frog could be convulsed by an electric shock to the muscles, but before there could be recognition that electricity might be a factor in the natural transmission of nervous activity, a hypothesis had to be dislodged that had been held, almost unquestioned, for over 1500 years. This was, of course, Galen's theory that the nerves were hollow tubes carrying the animal spirits from the ventricles to various parts of the body. This is only one example of the almost paralysing effect the authority of Galen's work had over the scientists and physicians of the Middle Ages and even into the eighteenth century.

Animal spirits were supposed to flow from the brain down the nerve into the muscle, expanding it during contraction. So sacrosanct were Galen's statements that no one seems to have tested this experimentally until Borelli, in an ingenious experiment, slit the muscles of a struggling animal while its limbs were submerged in water and

* All the early electrophysiologists use the term crural nerve presumably by analogy from comparative anatomy, but in the frog it is essentially the sciatic nerve that features in their experiments.
demonstrated that no gaseous spirits bubbled out. He argued that, since the muscles were in violent contraction an excess of animal spirits should have been present had this form of the old concept any validity. However, he unfortunately concluded that a liquid flowing from the nerve evoked a fermentation process in the muscle that caused it to balloon. This experiment was only one of Borelli’s many ingenious designs, among which was a diving bell and a boat in which the occupants could row themselves about under the surface of the water, a forerunner of the present enthusiasm for underwater exploration. Borelli was a Cartesian, though his mechanistic approach was essentially an experimental one rather than the theoretical one of Descartes. Borelli’s book, published posthumously, was so much admired by Chirac (professor of anatomy at Montpellier), that in 1772 he left 15,000 livres to the University of Montpellier for the foundation of a chair to study Borelli’s works. The will was never executed.

The next to test Galen’s postulate experimentally was Francis Glisson* who demonstrated by immersion of the arm that muscles do not increase in volume on contraction, and thus he ruled out the presence of excess animal spirits in either gaseous or fluid form. From this developed his suggestion, not too crisply formulated, that tissues had an intrinsic irritability, an idea to be developed later by Albrecht von Haller into a concept that was to dominate physiology for more than a century. Glisson was Regius Professor of Medicine at Cambridge and it is possible that the Statutes governing these professorships may have led him to re-iterate the ideas of Galen more than he would otherwise have done, and may account for some of the residual vagueness of his statements.

The concept of irritability was to be raised next by Jean de Gorter, Dutch physician to the Empress Elizabeth of Russia, though its most prominent developer was Haller, the student of Boerhaave. At the opening of the eighteenth century the dominating figure on the continent was the influential Boerhaave of Leyden, then the leading medical centre of Europe. This renowned physician taught the Galenist doctrine that

The Ventricles of the Brain have also many Uses or Advantages in Life, such as the perpetual Exhalation of a thin Vapour, or moist Dew.

* Glisson differentiated three stages of irritability in fibres: ‘primam, a sole perceptione naturali, secundum a sensu externo, mediante positiva ratione perceptionis naturalis, tertiam ab appetitu interno, phantasia dirigente.’
Boerhaave in his famous Institutiones Medicae gave many pages to considering 'the Juice or Spirit of Brain and Nerves'. More of a chemist than a physiologist, Boerhaave supported his arguments with the experiments of others and taught that

Tho' the nervous Juice or Spirits separated in the Brain are the most subtile and moveable of any Humour throughout the whole Body, yet are they formed like the rest from the same thicker Fluid the Blood, passing thro' many Degrees of Attenuation, till its Parts become small enough to pervade the last Series of Vessels in the Cortex, and then it becomes the subtile Fluid of the Brain and Nerves.

This conception of nervous fluid and its formation had not progressed a step from that of Galen.

Boerhaave considered and rejected the only rival hypothesis of the time, namely that the nerves were elastic cords causing muscles to contract by their vibrations. Boerhaave bluntly stated: 'There is therefore no Face of Truth in that Opinion, which asserts the Nerves to perform all their Actions by Vibrations, like those which arise from striking a tense Chord or Threat: Since this is repugnant to the Nature of the soft, pulpy, and flaccid Nerves which have so many Inflections and Incurvations.' Boerhaave delivered his lectures in Latin, but these excerpts are from an eighteenth-century translation.*

On his own initiative he published only infrequently, but was plagued by a nuisance that modern lecturers experience. From time to time someone who had heard him teach would publish the lecture notes he had taken, attaching to them the name of Boerhaave. So exasperated was the latter that he finally petitioned the government to make this practice illegal, and wrote a strong letter to the local paper (the Leyden Courant) denouncing the booksellers for printing his name for (as he put it) 'the sake of lucre only'.

Two of his pupils, however, are to be thanked for collecting and publishing Boerhaave's teachings after his death: these are Haller who brought out the Praelectiones in 1740-2 to be followed by the Primae lineae physiologiae in 1747, and Van Swieten who took shorthand notes in Latin (the tongue in which Boerhaave lectured). Van Swieten who as a Catholic had little chance of advancement in the

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University of Leyden, went to Austria and founded the Vienna School basing it on the sterile physiology of Boerhaave. He spent many years of his life writing Commentaries on his master's sayings. It was presumably these that were used by Goethe, since copies of them can be seen in the library of Goethe's house in Frankfurt.

Facsimile of a letter from Boerhaave.

Boerhaave was very generous to the work of others and was responsible for getting Swammerdam's writings into print. We are told that intense application to his work had made Swammerdam 'a hypochondriac and unfit for society' and that he plunged 'into the depths of mysticism...'. He so injured his constitution by mortification, that he died in 1680, at the age of 43.

We have a contemporary description of Boerhaave's habits and also of his looks so that he emerges for us as a person in the round. With such an influential teacher as Boerhaave in the famous school of Leyden championing the cause of fluid coursing down pipe-like nerves, it was indeed a hard task for scientists to refute this entrenched
hypothesis. The concept, as has been said, had reigned for over 1500 years in spite of there being no experimental proof whatsoever.

It might be thought that once the microscope had been invented, the question of whether or not the nerves were hollow pipes might have been quickly settled. Indeed in 1674 Leeuwenhoek specifically sought for cavities in the nerves of a cow but his reports did not settle the issue, for he found them in the vagus but not in the optic nerve. Because he was told that Galen had seen canals in the optic nerves merely by holding them up against the sun, he redoubled his efforts, but again reported them absent. He then engaged in special pleading, arguing that in the case of the optic nerves it was unnecessary to have nervous fluid flowing from the eyes to the brain.

Meanwhile in German science there was the stultifying influence of Stahl to be overcome. Stahl, ‘the sour metaphysician’, as Haller called him (‘acris homo et metaphysicus’) revived animism, teaching that the soul was the vital force that caused muscles to contract and tissues to secrete. The metaphysical approach of Stahl later came under criticism from Vicq d’Azyr who suggested that the invention of an imaginary soul to resolve those phenomena that could not yet be explained by the laws of physics and chemistry was merely a cloak for ignorance. Van Helmont did not escape the same criticism.*

Stahl’s doctrine of vital spirits, harking back to the dark ages, was a more metaphysical version of the popular views on animal spirits that had been invoked by so many to explain the phenomena of body and mind. In the early eighteenth century the functions of the brain and nervous fluid were viewed essentially by analogy with the heart and blood. Nicholas Robinson in 1729 in his delightfully written treatise on ‘the Spleen, Vapours and Hypochondriack Melancholy’, speaks of the systole of the brain, signifying ‘its Contracting Power, whereby the animal Juices are forcibly driven into the Fibres of the Nerves’. He had, however, also the idea of Machinulae, or ‘small Corpuscles of Matter, that vary their Distance and Motion in every Contraction or Distraction of a Fibre, Muscle or Organ’. The degrees of ‘Elasticity

* Pour découvrir le mécanisme du système vivant, il faut rechercher parmi ses effets quels sont ceux qui se rapportent aux lois bien établies de la chimie ou de la physique, et les distinguer soigneusement des effets qui n’ont point avec ces lois de liaison immédiate ou au moins connue, et dont la cause nous est cachée. Ce sont ces derniers que Van Helmont et Stahl ont fait dépendre d’une archée ou de l’âme, sans réfléchir que leur nature n’étant point approfondie, ce qu’ils attribuaient à un seul agent dépendait peut-être de plusieurs. En recourant à des causes imaginaires, ne semble-t-il pas que ces grands hommes aient voulu cacher leur ignorance sous le voile de la philosophie, et qu’ils n’aient pu se resoudre à marquer jusqu’on s’étaient leurs connaissances positives?’ Vicq d’Azyr. Oeuvres, vol. IV, Paris, 1805.
or Springiness' of the nerves were held to depend on how tightly packed these Machinulae were. And to the degree of elasticity of one's nerves, Nicholas Robinson allotted the cause of all nervous and mental disease as well as differences in temperament and in intellectual achievement. In respect to the latter he was bold. He says:

Were I permitted to give my Opinion concerning the different Inclinations observable between the People of the French and English Nations, in relation to the Improvements of the Arts and Sciences, it should be, that the French, being generally more biliose in Habit, are more ready at Inventions, from the Quickness and Changeableness of their Tempers, that seldom suffer them long to dwell upon any one Object; but that the English, being of a slower Temperature, are fitter for Improvements, which demands a deeper Attention to the Ideas of those Objects they would improve upon.

This is a rather different view from that of his contemporary, Montesquieu, who felt that the climate was responsible for the English temperament.* Even if we are not today willing to incriminate the weather in quite this way, it is possible that the early English scientists who studied static electricity may have envied Ben Franklin the less humid air of Philadelphia.

In England the prestige of Thomas Willis** was also a deterrent to the development of more scientific hypotheses of nervous action, for he added to a basis of Galenism the bizarre concept that the soul had two parts — a flame in the vital fluid of the blood and a light in the nervous juice. The sparks drawn from an animal's fur by friction were thought by Willis to be evidence of the inner flame. Thomas Willis comes alive for us in the brief contemporary glimpse that John Aubrey*** gives us of him learning his craft from the wife of the canon of Christchurch.

He was first servitor to Dr (Thomas) Iles, one of the canons of X Ch. whose wife was a knowing woman in physique and surgery, and did many cures. Tom Willis then wore a blew

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*Dans une Nation à qui une malade du climat affecte tellement l'âme qu'elle pourrait porter le dégoût de toutes choses jusqu'à celui de la vie, on voit bien que le Gouvernement qui conviendroit le mieux à des gens à qui tout serait insupportable, serait celui où ils ne pourroient pas se prendre à un seul de ce qui causeroit leurs chagrins, et ou les Loix gouvernant plutôt que les hommes, il faudroit pour changer l'état les renverser elles-mêmes." L'Esprit des Lois. 3 vols. Geneva, 1749, vol. I, 237.

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**Thomas Willis

***John Aubrey
livery-cloak, and studied at the lower end of the hall, by the hall-dore; it was pretty handy, and his mistresse would oftentimes have him to assist her in making of medicines. This did him no hurt, and allured him on.

Yet even in the seventeenth century a few dissenting voices had been raised against the Galenist doctrine of nervous activity. Niels Stensen, the great Danish anatomist, writing from Florence as early as 1667 had remarked that ‘Animal spirits, the more subtle part of the blood, the vapour of blood, and the juice of the nerves, these are names used by many, but they are mere words, meaning nothing’. He made experiments, as Glisson had done before him, proving that muscles did not swell in volume during contraction. Swammerdam and Verheyen in Holland, and Robert Whytt in England were later to add their confirmation.

To the greatest scientist of the time, though not himself a physiologist, the concept of animal spirits flowing in hollow nerves was not acceptable. Newton, in the General Scholium which he added to the second edition of the *Principia*, had suggested an all-pervading elastic aether and, in a query added to the second edition of the *Opticks*, asked:

Is not Animal Motion perform’d by the Vibrations of this Medium, excited in the Brain by the Power of the Will, and propagated from thence through the solid, pellucid, and uniform Capillamenta of the Nerves and the Muscles, for contracting and dilating them?

This suggestion was immediately embraced by many contemporary physiologists. One of them, Bryan Robinson, was so enthusiastic that he claimed that ‘Sir Isaac Newton discovered the Causes of Muscular Motion and Secretion’ and went on to argue that ‘the agent by which the nerves propagate to the muscles the power of will is no less than Newton’s aether’. In this way he could account for the invisibility of the nervous force and the speed of its action. Another writer, William Smith, granted that this aether is so fine as to be invisible to man, but suggested that cats and owls may be able to see it.

Reluctance to accept the view that the force of the blood could

* Smith, who lived in Carey Street and later in Red Lion Square, was an M.D. though not a Licentiate or Fellow of the Royal College of Physicians. This fact suggests that he may have given his time to writing (in which he was prolific), rather than to the practice of medicine.
ELECTRICAL ACTIVITY OF THE NERVOUS SYSTEM

produce muscular motion was expressed by Stephen Hales who wrote:

From this very small Force of the arterial Blood among the muscular Fibres we may with good reason conclude, how short this Force is of producing so great an Effect, as that of muscular Motion, which wonderful and hitherto inexplicable Mystery of Nature, must therefore be owing to some more vigorous and active Energy, whose Force is regulated by the Nerves; But whether it be confined in Canals within the Nerves, or acts along their Surfaces like electrical Powers, is not easy to determine.

Impressed by the work of Stephen Gray, Hales went on to say:

That a vibrating electrical Virtue can be conveyed and freely act with considerable Energy along the Surface of animal Fibres, and therefore on the Nerves, is evident from curious Experiments made by that Skilful and indefatigable Experimenter Mr Stephen Gray.

A later dissenting voice was that of Alexander Monro, Professor of Medicine and Anatomy in the University of Edinburgh, a pupil of Boerhaave and first of the great dynasty of Monros. He wrote in 1729 rejecting, as had his master, the oscillatory theory of nervous conduction. But unlike his master, he was unhappy with the hypothesis of nervous fluid in pipe-like nerves, for he noted that no such cavities could be seen in nerve, no drops of fluid came out when a nerve was cut, the nerve did not swell when ligated, and above all, no known fluid could move as fast as nervous action must demand. Rather cautiously Monro skirted the possibility of electricity playing its part in the phenomenon.

We are not sufficiently acquainted [he says] with the properties of aether or electrical effluvia pervading everything, to apply them justly in the animal oeconomy; and it is difficult to conceive how they should be retained or conducted in a long nervous cord. These are difficulties not to be surmounted.

This discouraging prediction happily did not deter others from considering the possibility and later testing it including (much later) his son Alexander Monro Secundus.
But these first fumbling steps towards a concept of nervous activity in which electricity played a role were to be overshadowed by the introduction by Albrecht von Haller of a dichotomy of irritability and sensibility. The first expression of Haller’s ideas of the relationship of contractility to irritability is found in 1739 in his Commentaries on Boerhaave’s lectures and a fuller development of them in his 8-volume text-book (Elementa Physiologiae), but it is in his Göttingen lectures given in 1752 (and published the following year) that the concept was most fully crystallized and here supported by 190 experiments. There is a useful contemporary French translation of his dissertation by Simon Tissot, and one was made from this into English in 1755. The following quotations are mostly from the latter.

Haller’s own definitions for the dual properties of irritability and sensibility were as follows:

I call that part of the human body irritable, which becomes shorter on being touched; very irritable if it contracts upon slight touch, and on the contrary if by a violent touch it contracts but little. I call that a sensible part of the human body, which on being touched transmits the impression of it to the soul; and in brutes, in whom the existence of a soul is not so clear, I call those parts sensible, the Irritation of which occasions evident signs of pain and disquiet in the animal.

One sees immediately the bogey of the early physiologists raising its head: the necessity, on invoking the soul, for differentiating processes in man from those in animals. Haller describes his technique for determining sensibility as follows:

I took living animals of different kind, and different ages, and after laying bare that part which I wanted to examine, . . . I examined attentively, whether upon touching, cutting, burning, or lacerating the part, the animal seemed disquieted, made a noise, struggled, or pulled back the wounded limb, if the part was convulsed, or if nothing of all this happened.

As one reads through his series of experiments one cannot escape some revulsion at their cruelty, and Haller himself felt some apology due on this score. He speaks of it as ‘a species of cruelty for which I felt such reluctance, as could only be overcome by the desire of contributing to the benefit of mankind’.
Haller recognized that nerves are, as he put it, 'the source of all sensibility', but applied his dichotomy of irritability and sensibility to various types of nerves, noting that all nerves are not irritable according to his definition (with its insistence on resultant contraction). He thus approached the differentiation of motor and sensory nerves. He envisaged a nervous fluid within the nerves and as his teacher, Boerhaave had done before him, he rejected the alternate concept that nerves were cords that communicated sensation to the brain by their vibrations.

In considering how a fluid could possibly flow as swiftly as nerves can be observed to act, Haller proposed that it must indeed be a very subtle fluid imperceptible to the eye yet more substantial than heat, aether, electricity* or magnetism. In another comment he granted that electricity was a most powerful stimulus to nerves, but that he thought it improbable that the natural stimulus was electrical.† Thinking always in terms of electricity flowing as down a wire, Haller, like so many physiologists after him, felt the lack of insulation around the nerve to be a critical argument against its having any electrical properties. The velocity that a nervous fluid would have to have in order to act swiftly enough gave the early physiologists pause. Haller estimated that it would have to be 9000 feet per second; De Sauvages, on the other hand, calculated that no less than 32,400 feet per second would suffice.

Whytt,* who tangled with Haller on so many aspects of the problem, did, however, agree in rejecting electricity as the agent. He says:

And as of late years there has appeared a fondness in some, to explain almost every hidden operation in nature by electricity, I thought it might not be improper to shew that the electrical aura, even supposing it were the MATERIAL cause of muscular contraction, will not enable us to account for the motions of muscles whose fibres or membranes are pricked, torn, or otherwise stimulated.

* From Elementa Physiologiae (Haller), vol. IV, p. 381. 'Si vero cogitata nostra de ipsa natura spirituum proferre juberemur activum ad motum a voluntate et a sensu concipiendum aptissimum, celerrimum, omni sensuum acie subtilius tamen hactenus igne, et aethere, et electro, et magnetica materie crassius faceremus elementum, ut in contineri vasis et vinculis coerceri aptum sit.'

† 'Ab electrica scintilla nervum emoveri certum est, quae sit stimulorum potentissim. Naturam, quam electri, nostrorum spirituum esse, non est probable.'
It went much against the grain with Haller that his demonstrations of irritability were interpreted by some, and especially by de La Mettrie (another pupil of Boerhaave’s and a translator of some of his work) as evidence against the existence of the soul. In a spirited refutation, Haller took the line that indeed irritability has nothing to do with the soul nor can it be controlled by the soul, but it is the nerves, said Haller, that are ‘the satellites of the soul’. Haller never worked himself quite free of his master’s galenist influence as had de La Mettrie. The treatise ‘L’homme machine’ in which he argued that mind was a function of the brain, was to cause de La Mettrie’s expulsion from Holland and the burning of his book. It was his insistence on the lack of essential difference between animals and man and his denial of the immortality of the soul that caused offence.

Haller in his rebuttal which came after de La Mettrie’s death at the early age of 42, attacked his views as an ‘impious system’. He said:

The deceased M. de La Mettrie had made Irritability the basis of the system which he advanced against the spirituality of the soul; and after saying that Stahl and Boerhaave knew nothing of it, he has the modesty to assume the invention to himself, without ever having made the least experiment about it.

Haller himself was a great experimentalist and one reads with interest his own accounts of his many laboratory procedures, but in his criticism of de La Mettrie for his failing in this respect he noticeably does not suggest an experiment that would establish the existence of the soul.

It was against this background of physiology dominated by Haller that Galvani was to introduce his experiments and concepts of animal electricity. For although Haller was dead, his influence was still powerful. He had represented a break-away from the systematists and as such had appealed to the more progressive philosophers. Condorcet, the optimistic and romantic philosopher who, like Lavoisier, lost his life in the French revolution, wrote a eulogy of Haller extolling him for removing the prejudice and distrust with which the science of physiology was regarded by natural philosophers.

In 1761 a discovery was made that was not to be understood for nearly forty years. Johann Georg Sulzer (the 25th child of Swiss parents) reported to the Academy of Sciences in Berlin some experiments in which he described the sensation produced by the contact of
FIG. 10

A contemporary portrait of the Abbé Felice Fontana.
(I am indebted to Dr Giulio Pupilli of Bologna for this photograph.)
two different metals on the tongue. He described the taste as ‘assez approchant au gout de vitriol de fer’. He interpreted this by the current hypothesis that sensation was produced by vibration, but realized that the junction of two metals was all important. This was, in fact, the discovery of the generation of electricity by dissimilar metals — a phenomenon to be stumbled on again by Galvani and to lead later to Volta’s design of the battery.

One of the few prominent scientists favourable to giving electrical phenomena some importance in the animal body was Galvani’s countryman, Fontana,®* physician to the Archduke of Tuscany and professor of Physics in the University of Pisa.

The mechanism of muscular movement [he said] is unknown, we cannot even imagine how to explain it, and it seems as though we will be compelled to adopt some other principle — if not of ordinary electricity, then something analogous to it.

He thought in terms of an electric fluid and said the nerves would be the organs destined to conduct this fluid and perhaps even to excite it (‘et peutêtre encore à l’exciter’). This is, perhaps, the first suggestion that the production of electricity might be excited by the nerves rather than merely conducted by them as by wires. Fontana’s use of the word ‘irritabilité’ was related to contractility. Since nerves did not contract in length or change shape when pricked they could not be irritable — even though this manoeuvre led to contraction of the muscles they served.

At this time electricity and its effects on the human body were a favourite subject for theses. In the collection of unpublished manuscripts by Jacques de Romas® that is preserved in the City Archives of Bordeaux, there is one on electricity that includes observations on electrification of two paralytic patients. Another example is in the thesis collection at the University of Montpellier, and was written in 1750 by Jean Thecla Dufay,® who restricts himself to the electrical nature of the nervous fluid and does not discuss therapy. Montpellier was at that time a centre of great interest in electricity, and it was here that Boissier de Sauvages® endowed a convent hospital solely for electrical therapy (1740-60). Dufay examines the arguments for and against the nervous fluid being electrical, and comes out unequivocally for its electrical nature. One notices that the President of the board of his examiners was De Sauvages. In 1748
On the left the title page of the first commercial reprint of the 1791 (Bologna) edition of Galvani's commentary, and on the right the title page of a copy of the 1792 (Modena) edition inscribed 'ex dono auctoris' (in the Silvanus P. Thompson Library at the Institution of Electrical Engineers). In the folder in which this is preserved, Silvanus Thompson has entered a note that this is the copy Volta received from Galvani and that this is Volta's handwriting.

A copy of the 1791 edition with the same inscription (but written on the fly-leaf) is in the Burney Library, Norwalk, Connecticut, where the handwriting is thought to be that of Galvani.

(The above photographs are reproduced by courtesy of the Institution of Electrical Engineers.)
De Sauvages had himself received a prize from the Académie Royale des Sciences at Toulouse for a dissertation on hydrophobia. In this, in what he terms a ‘Digression sur l’électricité’, he champions the existence of animal electricity. De Sauvages evolved a bizarre hypothesis about nerve and muscle activity in hydrophobia. It went as follows: given that muscular movement is proportional to the force of the nervous fluid, the venom of rabies, on mixing with it, doubles the velocity and also doubles the density of the nervous fluid—hence the nerve force and the resultant muscular movement are eight times stronger than normal. By this tortuous piece of arithmetic De Sauvages explained the violent muscular spasms in hydrophobia.

Academies were generous with prizes on medical uses of electricity which no doubt accounts in part for the plethora of such theses at this time. Another winner was Jean Paul Marat, who was to meet such a violent death in the French Revolution. His essay won the prize of the Paris Academy but drew the rebuke that his criticisms of other workers were too forcefully expressed. Deshais went on to publish his work on electrotherapy, thus joining a company too large to be numbered. Many absurd claims for electrotherapy were made by physicians, and at their doors must be laid the blame for much subsequent quackery. A contemporary critic ridiculed these claims but published only anonymously. However, his gay and witty touch betrayed his identity to Nollet as that of another gentleman of the Church, the Abbé Mangin. Nollet, who had himself gathered acclaim through his use of electrotherapy (though he had also done his bit to expose the quacks) scolded Mangin for ‘d’avoir confondu les temps, les lieux, les personnes et les choses’.

Into this atmosphere of quasi-quackery Galvani launched his famous Commentary. In his early work he had been influenced by Haller’s ideas on irritability and indeed had read a paper on them before the Academy in Bologna in 1772 entitled ‘Sull’ irritabilità halleriana’. But it is, of course, his experiments on animal electricity that made Galvani famous. These are so well known to all who are interested in the history of science that they will not be described here in detail, and only his main observations will be outlined.

The original experiments established four main points. Stated in their briefest form they were as follows: first, that a frog’s nerve-muscle preparation although at a distance from an electrostatic machine would twitch when touched by an uninsulated scalpel held by an observer. He reported that this happened only at the moment
when the machine was actually sparking.* Secondly, he observed he got the same result when a long wire was substituted for the observer. His third observation was that atmospheric electricity could also act as a stimulus to his frogs, and the fourth (which at the time he misinterpreted) was that a nerve-muscle preparation would twitch if connected in a circuit with two dissimilar metals, in his case a brass hook and an iron railing.

It took him many experiments and much argument with the opposition, led by Volta, before he reached anything approaching a correct understanding of these observations, all of which he attempted to explain at first as being due to intrinsic animal electricity. This he thought to be secreted in the brain and conveyed from it by the inner core of the nerves, the outer fatty layers acting as insulation to prevent loss, and the muscles receiving and storing the electricity in a similar fashion to a Leyden jar. Discharge of this accumulated electricity was thought by him to be the stimulus to the muscle fibres which then by virtue of their irritability, contracted.

Although the experiments he had made up to this time did not justify a hypothesis of intrinsic animal electricity, his suggestion that the muscles acted like a Leyden jar, being negative on their surface and positive on the inside, was the first time anyone had conceived the electrical potential of animal tissue to be disposed in this way. (Galvani’s use of the term ‘positive’ was intended to signify a collection of electricity.) With the exception possibly of Fontana, all previous considerations of electricity as a factor in either nerve or muscle had been framed in terms of conductors analogous to wires, and in fact Galvani still thought of the nerve as a wire-like conductor. It was many years before the transmembrane potential of both the nerve and the muscle fibre was finally recognized.

Galvani’s initial observations — those reported in his Commentary — did not warrant his interpretation and it is arguable whether the concept of animal electricity may be regarded either as an inspired guess or the prise-de-conscience of a genius. Galvani had been working on animal electricity for some years before the Commentary

*‘... quin uella tamen scintilla tune temporis ab aliquo eliceretur; at nulli omnino visi sunt motus.’ The observation is sound, and its modern explanation is as follows: A charge had been transferred to the insulated nerve muscle preparation by induction at a distance. When the machine discharged by sparking, the nerve-muscle also discharged through the observer’s scalpel to earth. This was the stimulus for contraction. It was known in the textbooks of the time as the ‘returning stroke’. Galvani was the first to observe it in a biological preparation in a laboratory setting and failed to recognize it as such.
was published, for Matteucci\(^{63}\) tells us that a notebook was found after Galvani’s death describing experiments carried out in 1780, and further experiments were published in 1786.

![Casa Galvani Settembre 1786.](image)

**Fig. 12**

The picture that Du Bois-Reymond had made by an artist from his own original sketch. This shows Galvani hanging up frogs' legs on the railings of his house in Bologna.


Volta’s proof that dissimilar metals in a circuit were in themselves a source of electricity led to his own invention of the Voltaic pile, but caused Galvani, and, more especially his eager but less prudent nephew, Aldini, to press on to experiments omitting the dissimilar metals. Finally, one experiment was evolved in which no external source of electricity was present. A twitch was demonstrated when the cut end of a frog’s spine fell over on to its muscle. In this case the source of the electricity was what we now recognize as the current of injury. This experiment was published in the supplement to the famous anonymous tract of 1794,\(^{64}\) thought by such authorities as
Gherardi and Silvanus P. Thompson to be indubitably the work of Galvani.

The exploration and exploitation of this phenomenon were taken up by physiologists all over Europe and as Du Bois-Reymond wrote,

It may be said that wherever frogs were to be found, and where two different kinds of metal could be procured, everybody was anxious to see the mangled limbs of frogs brought to life in this wonderful way.

Galvani’s experiments were mostly carried out at home although he was Professor of Anatomy at the University of Bologna. In 1852 Du Bois-Reymond made a pilgrimage to Bologna to see the house where these famous experiments had taken place; he made a rough sketch which he later had perfected by an artist. The resultant picture of Galvani’s house shows the great man hanging up his frogs’ legs for stimulation by atmospheric electricity. Du Bois-Reymond described the house as being near the two leaning towers (Bologna is a city of towers and one of these leans towards another giving the illusion that neither is upright. It is in the locality of these two that Du Bois-Reymond found the house).*

Galvani and his wife lived on the third storey of the house at the back of which was an addition with a wing built on to it. This had a flat roof surrounding an area. At the bottom of this was presumably the garden of which Galvani writes,† It was on these iron railings that Galvani hung his frogs’ legs (as shown in the picture), and here he noticed their twitchings during a thunderstorm and also even in fair weather. And it was the iron of these railings together with the brass of the hook from which the frogs hung that formed the bimetallic source of electricity mistakenly thought by Galvani to come from the tissues themselves. The later experiments in which no metals took part were carried out inside the room. Du Bois-Reymond states that it was in the room with the glass door on the left that the electrostatic machine stood. He tells us that the woman artist, whose name he does not give us, took pains to make the likeness of Galvani authentic and the costume correct for the period.

Today we can see that it was Galvani’s interpretation of the

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* The address was 96 Strada San Felice.
† ‘... praeparatas ranas in ferreis cancellis, qui hortum quendam pensilem nostrae domus circumdabat, collocatas uncis quoque aereis in spinali medulla...’
experiments reported in the Commentary, rather than the actual observations that caused the stir. For it was known that a frog's nerve-muscle preparation was a sensitive electroscope and of Galvani's observations, each in its turn had been previously demonstrated for non-biological systems. That objects could be charged at a distance had been foreshadowed for a century from the work of von Guericke and was explained in textbooks of Galvani's time (e.g. Mahon's Principles of Electricity). In 1753, the Abbé Beccaria had experimented with sparks from the sky on the roof of San Giovanni-di-Dio in Turin. Nollet, who visited Beccaria in 1749, described him as 'sec et bilieux', but granted that he wrote 'avec élégance et s'occupe spécialement d'Électricité'. The electrical nature of lightning had been elucidated by Franklin. As an historian of the early nineteenth century puts it, Franklin was 'the first who, rivalling the boldness of Prometheus, dared to light the torch of science with fire taken from heaven itself'. The stimulating action of dissimilar metals had been observed by Sulzer and is often quoted as having been demonstrated on frog's muscle-nerve preparations by Swammerdam in 1658. To the physiologist, however (as Du Bois-Reymond pointed out), neither the text nor the illustrations necessarily merit this interpretation. Swammerdam's illustrations are extremely clear. Although his book was published posthumously by Boerhaave, the drawings had been prepared in his life-time (some can be seen in the Museum of the History of Science in Leyden). Copper plates had also already been made from the drawings and were found after his death by Boerhaave and used for the book. In any case this demonstration by Swammerdam caused little attention for, he plaintively reports, 'I demonstrated this, in the year 1658 to the most illustrious Duke of Tuscany, now regnant, but he was at that time not in the mood to favour me'.*

Another much quoted report is that from Cotugno in 1786. One of his medical students had stumbled on the same phenomenon when he got a shock from a mouse he was dissecting. This report was criticized fifty-two years later by Müller who said the sensation must have been caused by repugnance.

One of Galvani's less frequently quoted experiments, to which he makes only passing reference, was an attempt to see whether stimulation of the brain would produce a muscle movement. The

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* "... prout olim jam, anno 1658, Illustrissimo Ducii Hetrusco, cum maxime regnante demonstravi; quem Is immerso sane favore ad me invisere non dedignaretur."
experiment failed.* He was not the first to try, for both Caldani (in 1754) and Fontana (in 1757) had made attempts.

The story of the great controversy stirred by Volta is well known. Only its outline will be given here. Galvani's findings were confirmed by Volta, as they were by everyone who repeated his experiments. There are not many experimental scientists of whom this can be said. Volta's first private letter to Carminati in April 1792 accepted the existence of animal electricity and was fulsome in praise of Galvani. However, he was soon to change his mind.\textsuperscript{76} Volta's explanation was that the electrical charges on metals ('conductors of the first class') were greater than on tissues ('conductors of the second class') so that when these touched electric fluid circulated. It should be noted that Fowler's book\textsuperscript{71} in which he reported experiments with various pairs of heterogeneous metals and their action on frog preparations had already been published in 1793. From them Fowler had concluded that Galvani was justified in allotting part of the electricity to an animal source. Valli's book\textsuperscript{72} had also been published testing the effects of such various metals as a shilling, a silver spoon and a guinea, and Valli was to develop a controversy of his own with Volta over priority. Valli was, however, primarily a pathologist and a pioneer in experiments on vaccination against the plague and yellow fever (from which he died).

Volta, a much superior scientist, at this time was abandoning the idea that equilibration of charge between metal and tissue was responsible and hotly denied any electrical property to nerve or muscle.\textsuperscript{74} He dropped the expression 'elettricità animale' and from then on used 'elettricità metallica'. From then on and in twenty memoirs and a number of letters written between 1793 and 1800, he strove to explain all the frog experiments on bimetallic currents, insisting that to produce electricity three substances were always necessary: two (heterogeneous) metals and a third conducting material to complete the circuit.\textsuperscript{74} If this third material were a frog's muscle, it would by virtue of its irritability, react to the flow of bimetallic electricity, but its role was solely that of an electroscope. It was in no way a generator of electricity. When Aldini\textsuperscript{75} demonstrated by dipping ends of nerve and muscle in mercury that the same effect could be obtained with a single metal, Volta replied that the surface in contact with the air suffered a change that made it heterogeneous with

\* 'Si enim conductores non dissectae spinale medullae, aut nervis, ut consuevimus, sed vel cerebro ... contractiones vel nullae, vel admodum exiguae sunt.'
the depth. This specious argument was disproved by Humboldt, and indeed by the experiments of Galvani in which no metals were present, the cut end of the spine falling over on to the muscle to complete the circuit. Volta then adopted an explanation based on the two different tissues (muscle and nerve) being unequally charged. In fact by 1796 Volta had concluded that to produce electricity his three substances could all be moist conductors provided they were heterogeneous.  

In all his attacks on Galvani, Volta exhibited a failing against which Claude Bernard was later to caution his students: setting out to experiment with so deeply rooted an idée préconçue that it became an idée fixe prejudicing all interpretations. Yet from Galvani’s having stumbled on bimetallic electricity, Volta was to go on with brilliance to the development of the electrical battery, one of the most outstanding gifts of technology, and for this achievement Volta’s name stands out in the first rank of scientists, not only in his own times but in history. After the description in 1800 of the details of his pile, Volta made no further publications of great note although he lived to the age of eighty-two.

Von Humboldt is the first great name in support of Galvani, for he recognized that both protagonists had made discoveries of real phenomena, and that Volta’s brilliant development of the current flow between dissimilar metals did not preclude the existence of animal electricity. The design of Humboldt’s experiments and the clarity of his reasoning are a pleasure to study in the welter of acrimonious controversy that greeted Galvani’s findings. Without bias towards either protagonist Humboldt repeated their experiments, examined their interpretations, designed new experiments to test their hypotheses and came to the conclusion that Galvani discovered two genuine phenomena (bimetallic electricity and intrinsic animal electricity) and that these were not mutually exclusive. Humboldt demonstrated that both great scientists erred in their interpretations of their experiments, but both had made important discoveries from which were to grow the science of electrophysiology on the one hand, and on the other, the brilliant development of the Voltaic pile. Not only did he expose the erroneous parts of Galvani’s and Volta’s interpretations but also those of the writers who rushed in so precipitately to take up arms for one or other protagonist, Pfaff, Fowler, Valli, Schmuck— they each received their rebuke. He tells us that he thought some of these problems out while sitting at the foot of Mt.
Bernard reading De Saussure’s *Voyages dans les Alpes*. He was a great traveller, but did not let this interfere with his experiments, for he took his apparatus along with him even on horseback. But Von Humboldt’s dicta did not appear until 1797 and in the meantime many workers, including those he criticized, had entered the fray. Their publications succeeded Galvani’s *Commentary* with great rapidity, two in Germany appearing in the following year (1792) but adding little. The next year saw many, the most important being those of Pfaff, Professor of Physics at Kiel, who supported Volta, and Richard Fowler, who backed Galvani. The Medical Society of Edinburgh made animal electricity the subject for one of its prizes given annually, and allotted it to Crève of Mainz. These early salvos represented a rushing into print, rather than careful experimental examination of the pros and cons of the great controversy. This, of course, was to take longer.

With the close of the eighteenth century this review ends. In the fifty years that followed, many great scientists were to search for the explanation of Galvani’s findings, their work finally culminating in the detection of electric currents in nerve by Du Bois-Reymond and the elucidation by Hermann of what we now call the demarcation potential or current of injury. Du Bois-Reymond used a galvanometer to detect nerve currents, an instrument whose development he owed to Oersted’s discovery in 1819 that a magnetic needle was deflected by a galvanic current. Using the terminology of the great controversy, it may be said that he utilized metal electricity to demonstrate the existence of animal electricity. He acknowledged this debt by remarking that thus ‘metal electricity was enabled to atone for the wrong she had done to her more tender twin sister.’

To list all the many secondary sources and their authors to whom the writer is indebted would exceed the allotted space. The most valuable have been the physiological textbooks of the early nineteenth century which evaluate the new contributions in the setting of the then available knowledge. Histories of medicine written in the eighteenth and early nineteenth centuries have also been a useful source, for they have followed closely enough on the events to avoid hyperopia of hindsight. The primary sources have been listed, and for effortless access to the majority of these the author is indebted to John Goodhue Treadwell, physician of Salem, Massachusetts, whose library came to the Massachusetts
General Hospital on his death a hundred years ago. She is in addition grateful to the Institution of Electrical Engineers for the opportunity to work with the copies of the Galvani writings and the De Magnete of Gilbert in the Silvanus P. Thompson and Roland Libraries.

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222 THE BRAIN AND ITS FUNCTIONS


THE CONTROL
OF INPUT FROM SENSORY RECEPTORS
BY OUTPUT FROM THE BRAIN.

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One of the concepts lying at the core of cybernetic theory is that of a recurrent feed-back by which some of the output of a system returns to modify or control future input. That a degree of control of this kind may operate in the central nervous system has many times been suggested. In fact the latter suggestion goes back in neurology at least as far as Charles Bell who, in 1811, when trying to puzzle out spinal reflexes, recognized that muscles had sensory as well as motor nerves which "conveyed a sense of the condition of the muscles to the brain", and he spoke of a "circle of nerves" making a sensory-motor junction between brain and muscle.

I would like to speak today of some more recent work on circular paths of a different kind within the nervous system, work which gives neurophysiological evidence for control over peripheral receptor response to sensory stimulation. This is a type of control exercised over the information that is allowed to proceed from the receptor into the central nervous system, rather than a central control introduced at a higher level of sensory integration. Many types of central control, by facilitation and inhibition of nerve impulses have, of course, been known for a long time.

The sense organs within the muscles are familiar to all who know Sherrington's [1] work and the experiments in which he demonstrated that the fine fibers from the muscle spindles enter the spinal cord along with other sensory fibers in the dorsal root. Muscle spindles had been well-known to histologists for years but only at the end of the last century was their role as sensory receptors recognized. They signal the degree of stretch operating in the muscle.

That these sensory receptors are themselves innervated by fine centrifugal fibers that control the messages entering the central nervous system has become known through the work initiated by Leksell in Sweden [2] and confirmed and expanded by the work of
Hunt and Kuffler [3] in the United States. By fractionating down to behavior of a single receptor and to stimulation of a single nerve fiber, these workers have shown that the number of discharges sent up to the spinal cord from the stretched muscle, at different degrees of tension, is greatly influenced by efferent stimulation sent down the fine efferent fiber. It is as though the activity of these fine efferent fibers were acting as an “amplifier” of the muscle spindles’ message, for these slowly conducting fibers of small diameter have no ability to make the muscle contract, and therefore, although efferent, they are not motor in function. They serve only as modulators of the incoming impulses. When we realize that these efferent fibers that specifically serve the spindle receptors of the muscle can be excited by brainstem stimulation [4] (with facilitation persisting long after stimulation ceases), and also by cerebellar stimulation [5], we begin to see how far into the nervous system this centrifugal control of incoming messages can be followed. Not only can facilitation be produced in this way, but there are locations in both brainstem and cerebellum that on stimulation inhibit the incoming impulses from the muscle spindles.

This downstream control from the brainstem over the sensory receptors is a different order of phenomenon from the well-known descending influence of the reticular formation on the motor nerve impulses in the fibers of large diameter that are causal for muscle contraction [6]. The latter are controls, not on input, but on output. There is little doubt, however, that in the brain itself these controls over output and input are very closely integrated, especially in the cerebellum.

The sense receptors for information from the muscle spindles are not the only sense organs whose input is under centrifugal control. Let us look at the eye. Quite apart from the gross control exercised over input by the pupillary reflex, evidence for a controlling feedback from the retina through the reticular formation in the brainstem and back to the retina has been brought forward by Granit [7]. His experimental procedure was to place microelectrodes in the cat’s retina and record, from single cells, the number of unit responses to a standardized flash. Having done this he proceeded to stimulate the reticular core of the midbrain with a tetanizing current. He was able to demonstrate a slowly developing effect consisting of an increase in the rate of retinal unit discharges that persisted for some time after stimulation ceased. Even in the absence of a test flash, reticular stimulation increased the rate of unit discharge that is continuously present in retinal neurones even in the absence of light.

Both inhibitory and facilitatory influences on single retinal neurones have been elicited by Granit by stimulation at stations along this feed-back route to the retina (for example, in the superior colliculus and from fiber tracts just above it). Dodt [8] by stimulating the optic nerve, has convincingly differentiated retinal response to the
centrifugal neurones from the antidromic effect back-firing to the retina in its afferent fibers. The latter stimulus travelling back to the eye in the large sensory fibers of the optic nerve in a direction opposite to that of normal conduction, evokes a retinal cell spike almost immediately. In contrast, the retinal spike, evoked after central conduction in the finest fibers of the optic nerve has synaptically fired the returning efferent neurone, appears after a necessarily long delay.

It is difficult to explain such a result on any basis except a return pathway including neurones within the brainstem, although the anatomical identification of their cell bodies has not yet been made. Efferent fibers entering the retina have, of course, been known since Cajal's [9] demonstration of them in the dog, and anatomical evidence for them is impressive.

At the Laurentian Symposium on Brain Mechanisms [10] that was held in 1953, I presented some of my reasons for postulating an ascending inhibitory system in the brainstem (in addition to the descending one established by Magoun). From electrophysiological data recorded from the visual system, I demonstrated that nembutal anesthesia blocked this ascending inhibitory effect, releasing responses of abnormally high voltage in the nonspecific pathways that reach the visual cortex by synapsis with the dendrites. This effect is seen at a level of nembutal anesthesia too light to affect responses in the specific pathways that synapse onto the cell bodies. This anti-inhibitory effect of nembutal has since been confirmed by Purpura [11]. It is a point that has to be born in mind by neurophysiologists who use this anesthetic.

Some interesting experiments have been reported this year by Hernández-Peón [12] who has found that this ascending inhibitory action can be demonstrated by recording (with implanted electrodes) the responses to flash in the optic nerve, lateral geniculate and visual cortex of the cat. If a series of slowly repeated flashes is continued over a long period the responses decrease in size in the thalamic and cortical locations (but not in the nerve). This developing inhibition can be blocked, and full-sized responses released, by nembutal.

This is a type of control being exercised at a higher level than the receptor, but Hernández-Peón went on to show that stimulation in the brainstem in contrast to the above effect, would inhibit the response to flash in the optic nerve itself as well as at later stations. His work is strong evidence that in this case the inhibition is at the retina and is mediated through centrifugal fibers from the brainstem. A finding of great interest in relation to the functional role of the brainstem reticular formation was that distraction of the animal's "attention" from the light stimulus by strong bombardment of other sense receptors (by sounds and smells) had the same inhibitory effect on optic nerve responses as had been found with brainstem stimulation. Hernández-Peón has demonstrated that in the auditory
system an inhibitory effect can be produced in the fibers from the cochlear nucleus though this is, of course, not the primary neurone of the receptor organ itself, but a central relay en route to higher centers.

This brings us to a consideration of centrifugal control of input from the organ for hearing. Electrophysiological evidence in this case has lagged for some years behind the anatomical, but some recent work by Galambos [13], [14] has demonstrated, with great clarity, centrifugal control in the cat over the responses (to a click in the ear) that can be recorded peripherally at the round window of the ear, a response that is generally accepted as that of the afferent nerve from the peripheral auditory receptor (namely the hair cells of the cochlea). He found that stimulation at a site in the floor of the 4th ventricle in the brin stem suppressed the nerve's response to the sound of a click.

It is interesting that Galambos, working entirely by electrophysiological methods, finds the optimal location for evoking this centrifugal effect to be where fibers, identified by anatomists some years ago, cross the midline of the brainstem on their way to the cochlea of the opposite side. That a centrifugal efferent pathway to the ear existed had been known to anatomists since 1946, through the work of Rasmussen [15], [16], [17], [18], [19]. His work described the passage of these efferent fibers across the midline from cells near the superior olivary nucleus in the brainstem to the auditory nerve on the opposite side, where they lie alongside afferent fibers conducting in a central direction.

Whether these centrifugal fibers do in fact terminate on the receptor cells themselves (as do the centrifugal fibers to the muscle spindles and to the retina) is still not proven, and hence it would be premature to include the auditory system in the category of receptors that have feed-back control right at the first stage of input, although it seems highly likely.

Yet another sense modality has its centrifugal fiber system, as the work of Kerr and Hagbarth [20] on the olfactory system has demonstrated. In this case, efferent fibers enter the olfactory bulb from the anterior commissure and end, not on the primary olfactory neurones themselves, but on interneurones (the granular cells). It seems likely that these granular cells act (under this centrifugal control) as inhibitory cells controlling the input from the sensory cells of the olfactory epithelium.

It is perhaps impossible to overemphasize the impact that the realization of this form of feed-back has had in neurophysiology. It is bound to have a similar effect on psychology, for no longer can the simple stimulus-response type of concept (so useful in behavioral studies of the organism as a whole) be lifted into the nervous system for meaningful study of the correlation between sensory messages and the external stimulus to the receptor organ. The concept needs
a further degree of sophistication before it will help us to understand the nervous system.

The demonstrations of feed-back control at the very points of contact of man with his environment have caused a revolution in the science of sensory physiology, and the impact of sensory physiology on psychological and psychiatric concepts is bound to make itself felt, although experience tells us to expect a delay.

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Studies of Evoked Responses by Flash in Man and Cat*

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In our laboratory we have for some time been making a comparative study of various anesthetic agents and have centered this research around a concept in which depression of activity may be due to a decrease of excitatory transmission, or to an increase in discharge of inhibitory neurons, or, of course, to a combination of both processes. This formulation emphasizes particularly an active inhibitory process consisting of discharges in different neuronal elements from those involved in the excitatory process and operating through different chemical mediators. That these contrasting chemical events might be differentially affected by the various anesthetic agents seemed a reasonable working hypothesis when examined together with the closely allied concept that a differential reactivity of component parts of a neuron (the soma, the axon, the axon hillock, and the various zones of dendrites) may be a factor. This possibility is strongly suggested by the work of Eccles and his group, and by that of Grundfest and Purpura.

Fractionating the sensorily evoked primary response at the cortex into its contributing parts, as identified outstandingly by Bishop and, with some modifications, by other workers, brings out some of the different actions of such anesthetics as chloroform, chloralose, tribromethanol, and pentobarbital (see Figure 1). This presentation is, however, not concerned with the primary evoked potential but with events that come later, and hence, because of its implications for the subject matter of this symposium, mention will be made only of the fact that it is the slow surface-negative wave of the primary response that is outstandingly affected by these agents. In other words, the most marked effect is on that component of the potential complex the origin of which, according to mounting evidence, is a response of the dendrites to activation reaching

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151

EFFECT OF ANAESTHETIC AGENT ON WAVEFORM OF PRIMARY
RESPONSE TO FLASH

(AVERAGED RESPONSES)

Figure 1. Responses evoked at the surface of the lateral gyrus in a single cat
with implanted electrodes. Above: unrestrained and unanaesthetized. Below:
anaesthetized by four different agents. Note in the record without anesthesia
the surface negative peaks at 26 and 42 msec. after flash and development of a
long-lasting surface-positive wave followed by surface negativity. Note also the
changes in these components with the various narcotic agents.
The pen deflections are at intervals of 1 msec., increasing in length from left
to right, the first of the continuous series is coincident with the flash. (The
first and last three pen deflections that stand apart are for calibration of the
instrument.) The envelope of the pen deflections gives the average wave form
of about 50 responses. For discussion of technique see text.

Concerning the late events evoked by flash in man and cat, we have
used an electronic averaging device in an attempt to obtain clearer infor-
mation about these potentials, especially in light anesthesia and in
control experiments without anesthesia, where the background EEG may
be of such high amplitude as to hide the evoked potential. This is a prob-
lem of signal-to-noise ratio, “signal” in our case being the specific re-
ponse to the stimulus, and “noise” being the continuous EEG ac-
tivity.

In order to perform this type of analysis of our data, the EEG is
recorded on 7-channel frequency-modulated magnetic tape; one channel
is reserved for recording a pulse signaled by a photocell every time a
flash occurs. The method for averaging the evoked responses is one in
which the brain potentials are cross-correlated with this pulse. The ap-
paratus was designed and constructed by Dr. John Barlow, who has
collaborated in the research I am about to describe, as have the other
members of the team in my laboratory, Miss Ruth Carpenter, Miss Lillian
Tozian, and Mr. Melvin Meister.
The averaging circuit is part of a correlator system for EEG which
has been developed by Professor W. A. Rosenblith, Mr. R. M. Brown and Dr. John Barlow at the Research Laboratory of Electronics at the Massachusetts Institute of Technology.* The method utilizes the magnetic delay drum, integrator, and automatic recycling device of the correlator, but a gating and storage circuit is used instead of the multiplier of that instrument. Both these techniques have been described elsewhere. Details of their construction will therefore not be repeated here, and only a brief indication of the instrumentation follows.

The signal from the photocell recorded on the magnetic tape every time a flash occurs is transformed into a brief square pulse of selected gating width that can sample both negative and positive deflections in the EEG. The gating pulses sample the EEG for the amplitude present at a selected interval (set by a magnetic delay drum) after each of the total number of flashes used, the instantaneous amplitude found after each flash being stored on condensers and led serially into an integrator. The output of the integrator records graphically on an Esterline-Angus ink-writer, giving a pen deflection proportional to the averaged amplitude (at that interval) of all the responses. Amplitudes at another selected interval after the flash are then similarly sampled, stored, integrated, and recorded as another pen deflection on the ink-writer, and so on, for as many steps as may be needed to obtain the whole envelope of the wave form. An automatic recycler rewinds the magnetic tape for each successive step; the intervals between steps are also automatically set by a magnetic drum. The object is not only a report of the amplitude found at each step, but also that these values should eventually be written out in a serial form that reproduces the original wave form. It is therefore necessary that each sample be stored at the value found, so that the next sample starts from that level and not from some meaningless baseline. For example, in the first position of the gate, the cross-correlation of the sample of the evoked response may register positivity. The next sample on cross-correlation may reveal an increase of positivity. If wave form is to be preserved, the positivity found by the second position of the gate must be added to that of the previous one; i.e., the previously occurring voltage must be stored in such a form that it can function as the point of departure for the next sample. This addition is performed by the integrator.

The intervals between samplings may be as short as 0.05 msec., and such intervals would be needed for fine analysis of, for example, the fast spikes on the surface-positive wave of the primary evoked response, or for exact measurements of latency; but for the later slower responses, steps of 1 msec. have been generally used. An advantage of this system is

* The work of this laboratory is supported in part by the Air Force (Office of Scientific Research, Air Research and Development Command), the Army (Signal Corps), and the Navy (Office of Naval Research).
that the stimulus does not have to be periodic in order for the response to be analyzed.

Since this method gives a statistical report of a long sample of record, in other words, the waveform and latency characteristics averaged for many evoked responses, fluctuating variables are minimized. Figure 2 illustrates in a simulated experiment the clarification obtained by averaging a number of mock responses of constant amplitude, amid an unrelated fluctuating background. The averaging process not only emphasizes those potentials the latency of whose phase changes is constant in respect to the flash, but, of course, as shown in the figure, it also minimizes all unrelated competing potentials that serve to mask the fine detail in the original unanalyzed EEG tracing. When applied to the analysis of evoked potentials in man it has enabled us, among other things, to isolate and examine the “sensory afterdischarge” described many years ago in rabbits by Bartley and Bishop.9 (See Figure 3.)

That this rhythmicity is not a function of the flash rate is evidenced by the fact that it is equally prominent when the flash is delivered arrhythmically and randomly. I shall not spend more time on this since my colleague Dr. Barlow presented a detailed paper on these potentials at

\[ \text{SINGLE "RESPONSE"} \quad \rightarrow \quad \text{AVERAGE OF 180 "RESPONSES"} \]

100 CPS SINE WAVE

100 CPS SINE WAVE

100 CPS SINE WAVE IN BACKGROUND ACTIVITY

BACKGROUND ACTIVITY ALONE

Figure 2. Simulated experiment to illustrate the detection of a signal in noise by electronic averaging.
AVERAGED RESPONSES TO RHYTHMIC AND TO RANDOM FLASHING

MIDLINE PARIETO-OCcipital RECORDING

RHYTHMIC FLASHING 0.7/SEC

RANDOM FLASHING

Figure 3. Averaged response evoked by repeated flash in a normal man. Upper record: rhythmic flashing. Lower record: random flashing. Note sensory afterdischarge.

the annual meeting of the American Society of Electroencephalography in 1956.

It is interesting that although the sensory afterdischarge was first described in animals, it has a far more prominently rhythmic character in man. In none of our cats, either anesthetized or unanesthetized, have we found such marked and prolonged periodicity as seen here. This is paralleled by the contrast in alpha rhythms, where again in the cat the periodic component is insignificant compared with that of man. These phenomena, the sensory afterdischarge and the alpha rhythm, involve the same neuronal mechanisms, and it may be that experimentation on the cat may not serve to elucidate all the problems of the EEG in normal man.

As regards the flash-evoked response in man, all electroencephalographers are familiar with the main occipital potential that has a latency of about 90 msec. from the flash, and that appears to be an association area response. Other workers, notably Monnier and Dieterle and Cobb and Dawson, have detected in some individuals earlier potentials that in all likelihood are the analogue in man of the primary evoked response of the specific receiving cortex in animals. These authors have emphasized how elusive these are in man with the skull intact; and indeed in some individuals the potentials of the hidden striate cortex appear inaccessible to surface electrodes. Experience with our averaging technique for searching for these potentials has led us to the same conclusion, although there can be no doubt about the existence of these earlier potentials (see Figure 4).

The more easily recordable late response has been presumed by many writers to be the parallel in man of the Forbes secondary discharge in the cat, although there is some uncertainty as to whether the secondary discharge, originally described in the somatosensory system on stimulation of a peripheral nerve, can in fact be elicited by flash. Part of our research
has been concerned with this exact issue, but before describing the experiments I must refer to yet another response evoked by flash in the unanesthetized animal. This is the response in the so-called association cortex of the suprasylvian gyrus of the unanesthetized cat that has a latency of 8 to 10 msec. longer than that of the primary. This response is vulnerable to barbiturate anesthesia and is enhanced by chloralose. Buser and Borenstein have made special studies of this response in the visual system and conclude that it is not totally dependent on an antecedent primary response, and that it apparently has in addition an independent pathway to the cortex.

Returning to the problem of the secondary discharge in the visual system, it seems fitting that I should speak of this in Detroit, Dr. Derbyshire’s city, since the first paper to be published on this potential was that by Derbyshire et al. In this paper the authors described in the cat the cortical response to electrical stimulation of the sciatic nerve that has a long latency (40 to 80 msec.). They interpreted this as an effect of deep anesthesia since they found it at deep levels of avertin and pentobarbital narcosis. Forbes and Morison followed up this work, again restricting their observations to responses evoked by sciatic stimulation, but they expressed the opinion that the secondary response bore some relation to
the slow waves found by Bishop and O'Leary on stimulation of the optic nerve. They suggested that these waves might be the sign of a centrifugal discharge. In the same laboratory a few years later, Morison et al. from ablation and stimulation experiments reached the conclusion that the secondary discharge traveled upward through the subthalamus and the rostral pole of the amygdala, close to the temporal horn of the ventricle.

There is much less available information about the late response to flash, and because of its appearance and reaction to barbiturates, it has often been tacitly assumed that this is the analogue in the visual system of the Forbes secondary discharge (Figure 5). Some authors have assumed that the late response to flash is due to the arrival at the cortex of the impulses relayed in the brain stem reticular formation, but as I have reported elsewhere, this view is untenable for several reasons, outstanding among which is the enhancement of this response by barbiturates in contrast to the blocking of the reticular formation responses as demonstrated by French et al.

The long-latency response to flash has been one of the phenomena we have been investigating in the course of our wider study of the action of various anesthetics, including barbiturates, tribromethanol, chloralose, chloroform, and ether, using unrestrained unanesthetized cats with implanted electrodes for controls. We feel that this gives us a more
Physiologic control animal than the curarized or *encéphale isolé* preparation, and in fact we find differences in response between these freely moving animals and those that have been curarized. Not only are all excitatory and inhibitory synapses in a more physiologic state, but centrifugal control from sensory receptors is also presumably intact. I shall have time to report only on the results obtained by single flash. These flashes have a 10 μsec duration of an intensity supramaximal for the retinal cells.

The electrodes used in the animals with chronic implantation are enameled stainless steel wires 1/100 inch in diameter, inserted in pairs side by side, but with recording points 1 mm. to 2.5 mm. apart in the vertical direction. A Horsley-Clarke stereotaxic instrument is used for guiding these electrodes to their locations. These cats survive for long periods, but eventually when they are sacrificed their brains are perfused through the carotids and later removed and cut. The same type of electrode has also been used when recordings have been made across the cortex from surface to white matter, although for purely surface recording in the chronically prepared animals we use blunted stainless steel dural leads inserted through nylon plugs. For the brain stem recordings, a grid of electrodes was used giving ten recording points in two horizontal layers of five, at inter-electrode distances of 2 mm. in the anteroposterior direction and 2.5-mm. inter-electrode distances in the vertical plane.

Both monopolar and bipolar recordings were always made. Two references were used and were checked against each other and sometimes also against a third grounded electrode. The most usual locations for the reference leads were on the back of the neck and on the dura low down near the rhinal sulcus. The frontal sinus cannot be used for a reference with flash since it records the electroretinogram. All responses were recorded simultaneously on an ink-writing electroencephalograph and on a 7-channel frequency-modulated magnetic tape for later correlation analysis. Samples of all responses were photographed from a cathode ray oscilloscope to detect responses whose latencies might fluctuate, thus causing them to be lost in the averaging process.

Figure 6 shows a typical averaged response from an animal under a moderate degree of pentobarbital anesthesia. The envelope of the pen deflections gives the average wave form as sampled at 1-msec. intervals. In this and all subsequent records to be shown relative negativity is recorded in an upward direction. The vertical curved lines on the graph paper are 20 msec. apart. The onset of the late response is at 77 msec. after the flash and the peak of maximum surface positivity is seen to be 94 msec. after the flash. The groups of three pen deflections at the beginning and end of each record to be shown are calibrations of the instrument. The delay steps in this system of analysis are adjustable and
Figure 6. Averaged response to approximately 50 flashes recorded from the lateral gyrus of a cat under moderate pentobarbital anesthesia. The pen deflections are at intervals of 1 msec., increasing in length from left to right, and the first of the continuous series is coincident with the flash. The positive peak of the second response is at the 94th pen deflection and its onset is 77 msec. from the flash.

can be made as short as 1/20 msec. A finer resolution than used here would of course be necessary in a study of the primary evoked response, and a faster tape speed (to increase frequency response) if the individual spike components were to be isolated and if more exact values for latency were needed. Since the emphasis in this communication is on late events, only steps of 1 msec. are illustrated, in order to present in the figures a sufficient length of the correlograms (i.e., 150 to 200 msec.).

In the somatosensory system, as noted above, Morison et al.16-18 established that the secondary discharge did not pass through the thalamic nucleus specific for that sense modality. It therefore seemed of interest in the present work to determine whether a secondary response to flash could be detected in the lateral geniculate nucleus in an animal under pentobarbital anesthesia.

Figure 7 illustrates some averaged responses that are typical for the whole series. In addition to the primary response at the cortex there is a late response reaching its positive peak at approximately 90 msec. after the flash. The optic tract shows the bimodal response described by many authors. Some trace of this is also seen in the lateral geniculate, but there is no trace of a late response corresponding to that from the lateral gyrus. The long lasting surface positivity that develops in the geniculate, after the negative wave, is unrelated in time to the late response at the cortex. (This positivity reaches its peak at about 120 msec. in most of our cats under pentobarbital anesthesia.)

Although sample recordings of this kind from electrode sites within a nucleus cannot positively rule out the possibility that some portion of it is traversed by the impulses responsible for the secondary responses, this
Reticular Formation of the Brain

Figure 7. Averaged responses to flash from three stations in the visual pathway of a cat, recorded simultaneously under moderate pentobarbital anesthesia. Reference lead on the back of the neck. Pen deflections at 1 msec. intervals. Flash coincident with first of the continuous series of pen deflections. (The heavy lines on the chart paper are 20 msec. apart.)

Figure 8. Averaged responses to flash recorded from the cortex just posterior to the primary visual area, from the visual area, and from 2 mm. above the geniculate nucleus in the region traversed by the geniculocortical radiations. Cat was under pentobarbital anesthesia.

result (i.e., absence of late responses in the lateral geniculate) is representative of our experiments in which recordings have been made in this nucleus within the Horsley-Clarke coordinates F5 to F9, L8 to L12, and at depths from H1 to H5 above the horizontal zero.

The response does, however, appear to travel in the region traversed by the geniculocortical radiations to the lateral gyrus. In Figure 8 are
Studies of Evoked Responses by Flash in Man and Cat

shown the responses obtained from two points on the lateral gyrus, 1 cm. apart in an anteroposterior direction (reference lead on the back of the neck). The lowest strip is the averaged response of a simultaneous recording at frontal plane 8, 2 mm. above the upper border of the geniculate, which shows some trace of an event simultaneous with the late response recorded from the surface 12 mm. above. This distance is too great for the deflection to be assignable to a field effect. No trace was found of this potential at this depth at frontal plane 5. I suppose the possibility must be considered that this electrode location may pick up from the wing of the reticular nucleus.

We have also recorded from the caudal diencephalon, and in the center median we have found evidence for more than a single response even in pentobarbital anesthesia.

Figure 9 is from a cat recorded with a grid of electrodes, beginning at the left in the collicular region of the brain stem; it shows the change in response as the location is moved rostrally from frontal plane zero on the left to plane 8 on the right, and as recording points are lowered toward the center median in the most rostral plane. The double response from the center median was highly localized and could not be detected at F6, only 1 mm. caudal to this nucleus. All these recordings were made 3 mm. from the midline. The double response in the center median is rather difficult to see in these small photographs but shows more clearly in Figure 10, from another cat. We are reluctant to kill our animals that have implanted electrodes, so that the only justifications we have now for putting this name to our recording location are the Horsley-Clarke coordinates used and the fact that these locations on stimulation gave us a recruiting response at the cortex, as is shown in this figure. Incidentally, in uncurarized, unanesthetized animals recruiting responses can be clearly obtained. In this figure the peaks in the recording from the center median occur 24 and 47 msec. after the flash; those at the cortex recorded simultaneously occur at 33 and 87 msec. (the first, of course, having traveled by the specific route). The double response suggests that impulses from the single flash have reached this nucleus by more than one pathway, and their wavelike form suggests that they have passed through multiple relays. A double response, the earlier of which had a more spikelike form, was found in the brain stem of monkeys by French et al., on electrical stimulation of the optic nerve.

We have also recorded from the subthalamic region, since it was here that Dempsey and Morison traced the Forbes response to sciatic stimulation. The results are in striking contrast to the collicular responses (Figure 11). In the subthalamus there is a double response suggestive of the arrival of impulses by two different pathways, differing in conduction rate or in number of synapses. Simultaneously in the geniculate there is
RESPONSES TO FLASH IN THE
BRAIN STEM
(NEMBUTAL ANAESTHESIA)

Figure 9. Averaged responses to flash in the superior colliculus (S.P.), dorsal to the red nucleus (N.R.) and in the center median (C.M.). Cat was under light pentobarbital anesthesia. The H and F numbers refer to the Horsley-Clarke coordinates of the recording sites.

Figure 10. Left: averaged responses to flash at the surface of the lateral gyrus and in the center median. Right: Recruiting responses obtained from the recording point in the center median (used as localizing evidence for electrode placement).
In our comparative studies of anesthetics we have also been interested in the different effects that these agents have on the responses to flash that can be picked up in the colliculi and in the pretectal regions dorsal to the central core of the brain stem. Ingvar and Hunter have mapped the responses in unanesthetized curarized cats, so that I shall refer only to our results in anesthesia.
Averaged responses evoked in the superior colliculus by flash under nembutal anesthesia are shown in Figure 12. The difference in latency between the colliculus and the primary cortical response can be clearly seen, and the two events appear independent, sharing only their initiation. At this level of anesthesia there was only a poorly represented secondary discharge at the cortex. As was seen in Figure 9, these collicular responses are comparatively resistant to barbiturate anesthesia.

With avertin (tribromethanol), the responses in this region of the brain stem are not apparently impaired. Figure 13 shows, on the left, the gross change in the EEG resulting from the increased depth of anesthesia, whereas the evoked responses photographed at these two levels show little change. The upper records are at the spindling stage that moderate doses of this anesthetic induces, and it is interesting that the mechanism responsible for tripping off the spindling is more vulnerable to the anesthesia than are the collicular and pretectal responses. These latter
Studies of Evoked Responses by Flash in Man and Cat

Figure 13. Averaged responses to flash recorded in the collicular regions of the brain stem at two levels of tribromethanol anesthesia: spindling stage (upper four records) and deep stage of suppressed background activity (lower four records). The H and F numbers refer to the Horsley-Clarke coordinates of the recording sites.

Responses may perhaps be regarded as primary specific responses of this region, where many fibers from the retina, the superior colliculus, and the preetectal portion of the brain stem are represented.

These findings having been reached, it was clear that several experimental procedures would have to be undertaken in order to define more clearly the nature of the delayed responses at the cortex. One of these is the placing of lesions to find the sites whose destruction would abolish the responses. In this work we are experimenting with the use of ultrasound in an attempt to produce lesions in deep structures without disturbing the more superficial ones. In this research we are indebted to Dr. H. T. Ballantine and Dr. T. F. Huetter, in whose laboratory the ultrasound technique is being developed. The results will form the subject of another report. One example only may be given as an illustration (Figure 14). In this animal a small lesion placed in the region of the radiations in one hemisphere, just above their emergence from the geniculate, abolished both the primary and the late response.

From the results reported above it is clear that the late discharge in the visual system, although having many features in common with the Forbes response to somatosensory stimulation, has many important differences. The late response does not specifically need barbiturate anesthesia for its appearance, although at a certain stage of narcosis it is augmented. It seems likely that other anesthetic agents have this same
Figure 14. Effect on response to flash of ultra-sound irradiation of the geniculo-cortical radiations. Recordings are from the lateral gyri.

effect. As discussed in previous publications \(^{19, 23}\) this preliminary augmentation has the characteristics of an anti-inhibitory phenomenon, as though the first action of barbiturates, at light levels, were to remove an ascending inhibitory influence before the depressive effect on excitatory synapses develops.

One of the most outstanding differences is that the secondary response to flash is not diffusely distributed over the cortex. We have failed to find it in the ectosylvian gyrus, the anterior lateral gyrus forward of the visual area, or the sigmoid gyrus. It is only poorly represented in the posterior lateral gyrus. We have found a late response at low amplitude in the posterior suprasylvian gyrus. Deepening narcosis undoubtedly increases the cortical area from which both the primary and the late responses can be recorded, and for a valid comparison with the original workers' findings in the somatosensory system, larger doses of anesthetic should perhaps be used. At the light levels of barbiturate narcosis at which the present observations were made, the late response might be thought to represent the first wave of the slow cortical afterdischarge. If the latter proves to be the case, it would appear that this potential has a counterpart 12 mm. below the cortical surface, even if the brain stem and diencephalic responses prove to be unrelated. Several workers have suggested that the sensory afterdischarge involves a thalamocortical reverberating circuit. We find no evidence for reverberation to the specific thalamic nucleus. In none of the cats have we found the late response in an area that does not also give a primary one. There seem to be no grounds for regarding this as essentially a response of the association areas. As this work progresses it appears less and less likely that this particular response is carried to the cortex by a truly diffuse system of corticopetal projection.

In summary, such conclusions as can be made at this stage of our work would be that the secondary discharge evoked by flash does not have a diffuse representation at the cortex and that it has no counterpart in the lateral geniculate. Its pathway does, however, appear to share part of the region traversed by the geniculocortical radiations. The amplitude of responses to flash in the collicular and more rostral dorsal levels
of the brain stem is not as vulnerable to barbiturate or avertin anesthesia as are those of the more mesial brain stem, and indeed the collicular responses may be regarded as primary evoked potentials for this region. Latencies, duration, and recovery are, however, profoundly affected by barbiturates — less so by avertin — and hence, as is well known, the effect of the former anesthetic is more striking with repetitive than with single stimuli. The double response at the cortex has more the appearance of the blocking of a usually active inhibitory system than of action in an excitatory one. We have felt that the averaging technique has proved useful in detecting responses, especially in unrestrained animals, and in light levels of anesthesia where competing potentials predominate. The double responses detected in the center median and subthalamus suggest that impulses evoked by the flash reach these centers by more than one pathway, but these regions form such a crossroads for afferent inflows from the optic nerve as well as cortifugal return \(^{24-28}\) that their interpretation must await the results of the ablation experiments.

REFERENCES


THE APPLICATION OF AUTOCORRELATION ANALYSIS
TO ELECTROENCEPHALOGRAPHY

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The electrical activity of the brain, recorded from electrodes placed on the scalp, appears as a series of continuously fluctuating potentials, mostly of low frequencies, i.e. below 35 c.p.s. Such voltage-time graphs are commonly known as electroencephalograms, or EEG's, and may be recorded from multiple locations on the scalp as an inked trace by means of amplifiers especially designed for the purpose.

Fig. 1 (Plate 16) shows the EEG of a normal human subject, recorded from 8 sets of electrode pairs on the scalp. The characteristics of the EEG are dependent on a number of factors; the particular region of the brain underlying the electrodes, and the state of consciousness, to mention only two. These fluctuating potentials represent, in the main, the activity of cells in the outer layer of the brain (the cortex). Visual inspection of inked records such as those shown here has resulted in a great amount of descriptive knowledge about the characteristics of the EEG in both normal subjects and in patients with brain disease.

As an adjunct to visual inspection of inked records, several types of summary analysis have been developed. One of these is frequency...
Another method of analysis, which has been applied to electroencephalography in recent years is that of autocorrelation and crosscorrelation (1). This method of investigation, which has among its roots the work on generalized harmonic analysis by Wiener (2), and which is based on a consideration of randomly varying processes, gives an average statistic of the time series under consideration.

The correlation function for time series is defined as

$$\phi(\tau) = \lim_{T \to \infty} \frac{1}{T} \int_{0}^{T} f(t)g(t - \tau) \, dt$$

in which $f(t)$ and $g(t)$ are two stationary time series (phenomena whose statistical properties are independent of the particular period of observation $T$); $T$ is the duration of the interval of observation in time; $\tau$ is the delay, or shift in time, of $g(t)$ with respect to $f(t)$ during the computation process; and $\lim T \to \infty$ indicates that the computation becomes increasingly accurate as the interval of observation $T$ becomes infinitely large.

Thus the correlation function $\phi(\tau)$ is defined as the limiting value of the time average of the product of a function multiplied by itself (or, by another function) displaced in time. If $f(t)$ and $g(t)$ are the same function, we have the autocorrelation function of $f(t)$; if $f(t)$ and $g(t)$ are different functions, we have the crosscorrelation function of $f(t)$ and $g(t)$. It is important to note, in this strict definition, that $f(t)$ is a stationary function in time, i.e. its statistical properties are independent of the particular interval of observation.

Certain additional properties of the correlation function bear mentioning. Waveform information, in the process of autocorrelation, is not preserved, except for certain special cases, i.e. sinusoidal waveforms, although by crosscorrelation of a repetitive signal with a synchronously occurring repetitive brief pulse (the Dirac delta function), the average waveform of a signal is extracted (3). Another property of the correlation function is its relationship to the power density spectrum; these two functions are, in fact, Fourier cosine transforms of each other (4). One may be easier to compute than the other, depending on the particular problem; at times both may be desirable. In this last instance, the procedure is often to obtain the correlation function, and from it the power density spectrum by Fourier transformation. The power density analysis, and a considerable amount of data has been collected by this method.

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spectrum, of course, is the square of the frequency spectrum as ordinarily obtained by tuned filters.

Returning to electroencephalography, we have been interested in the application of correlation techniques to the fluctuating potentials of the brain since the early experiments of Brazier and Casby (5). By visual inspection, some EEG ink traces appear to be very nearly periodic, others almost devoid of periodicity, and yet others appear to have characteristics between these two extremes. It was of interest, then, to obtain autocorrelation of these different types of EEG’s in order to gain some idea of their average statistical structure. For obtaining such correlation functions, a small-scale computer was built at the Research Laboratory of Electronics, M.I.T., (6). The input for the correlator is in the form of frequency-modulated magnetic tape recordings of EEG’s.

In Fig. 2 (Plate 16), some results obtained with the correlator for known signals are given. In the top section is shown the autocorrelation of a 100-c.p.s. sine wave, appearing as the envelope of the successive pen excursions, each excursion representing the value of the correlation function for the corresponding shift in time of the sine wave with respect to itself, beginning with zero shift. The delay between successive peaks of maximum positive correlation is 10 msec, which corresponds to the period of the 100-c.p.s. sine wave.

In the lower section of the figure is shown the autocorrelation of noise after passage through a lowpass RC filter with a cutoff frequency of 50 c.p.s. The exponential nature of the autocorrelation function is the result of this frequency cutoff of the noise. If the noise were wideband, rather than filtered, the autocorrelation function would have a peak at zero delay and would vanish elsewhere.

A typical result obtained from a tape-recorded EEG is shown in Fig. 3 (Plate 17). In the upper part of the figure is shown a brief portion of the original ink tracing from this subject, recorded from bipolar parieto-occipital scalp electrodes. In the lower section, on the left, is the autocorrelation of this EEG, and on the right is the power density spectrum, obtained from the autocorrelation function by Fourier transformation. The delay between the successive peaks in the autocorrelation function in this example is 100 msec, which corresponds to the peak in the power spectrum at 10 c.p.s. The smaller additional component shown in the power spectrum at about 8 per second corresponds to the slight irregularity in the decrement of the initial part of the autocorrelation function.
Autocorrelations and inked records are shown in Fig. 4 (Plate 17) for the three different types of normal EEG's discussed above. In the top example in the figure, a strongly rhythmic autocorrelation is obtained; in the lower one, almost no periodic activity is evident; an intermediate example is shown in the middle. To date, too few of the third type of EEG have been recorded to shed any light on the question of whether or not there is in these cases an underlying but severely attenuated rhythm at about 10 per second, the so-called alpha rhythm.

We have found that a sample of EEG a few minutes in length appears to be representative; i.e. the EEG may be considered to be quasi-stationary over this period of time for the purpose of obtaining an autocorrelation function. There will be variation from autocorrelation to autocorrelation for samples that are appreciably shorter than about one minute, as illustrated in Fig. 5 (Plate 18). The autocorrelation of a one-minute sample of EEG is shown on the left in this figure, and on the right, the autocorrelations of 8 subsections of this same EEG, each section being 7.5 sec long. The variation among the several subsections is evident from the figure, particularly in the initial portions of these autocorrelations.

Fig. 6 (Plate 18), in contrast, shows the autocorrelations obtained from the EEG's of the same subject recorded four months apart. The remarkable similarity between the two results indicates a reasonably stable character of the EEG of this individual, as reflected in the autocorrelation function, if a sufficiently long sample of the EEG is used.

Only brief mention will be made of the changes that may occur in disease of the brain. Fig. 7 (Plate 19) shows the autocorrelations obtained from comparable recording points on the right and left sides of the head of a patient with a brain tumor (verified at operation). The quite striking difference that is seen between the sides of the head would not be seen in a normal subject.

It should be emphasized that the results presented in this paper were obtained with one method of analysis; another method, of course, would be the visual one of the electroencephalographer in making his report from the original EEG ink tracing. It is evident that there is no single ideal method unless the purpose of analysis is sharply defined.

SUMMARY

(a) Autocorrelation analysis, a method of investigation of random signals developed in communications engineering, can be applied to the
study of brain potentials. For obtaining such correlation functions, a small-scale automatic computer has been designed for the processing of EEG potentials recorded on magnetic tape.

(b) The autocorrelation function yields information not readily available by visual inspection of the inked trace, about the statistical characteristics of the EEG, averaged over a period of time, particularly about the inherent rhythmicity of the EEG.

(c) This method of analysis represents only one way of handling these data, and can be used as convenient displays in the study of the EEG both in normal human subjects, and in patients with disease of the brain.

REFERENCES

Fig. 1. EEG of a normal adult (awake).

Fig. 2. Autocorrelation functions of known signals.
PLATE 16

100 CPS SINE WAVE

NOISE
(RC LOW-PASS FILTERED, WITH CUTOFF AT 50 CPS)
Fig. 3. EEG, autocorrelation function, and power density spectrum for a normal human subject.

Fig. 4. Autocorrelations of one-minute samples of the EEG's of three human subjects recorded from bipolar electrodes (right parietal to right occipital) of the scalp.
Plate 17

Autocorrelation Function

Power Density Spectrum

E.E.G.

Frequency—Cycles per Second

Normalized Amplitude

Delay (sec)

0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9

20 μV

1 Second

1 Second
Fig. 5. Autocorrelation functions of a one-minute sample of EEG, and of its eight component parts (7 1/2 seconds each).

Fig. 6. Autocorrelation functions of the EEG of a normal human subject recorded four months apart. Length of recording, one minute.
Fig. 7. Autocorrelations in a patient with a right-sided tumor.
The electrical activity of the brain may conveniently be classed under three headings: (1) potential shifts evoked by nerve impulses initiated by changes in the organism's internal or external environment; (2) the steady potential difference that is always present between the cortical surface and the white matter below it; and (3) the oscillating potential of the brain commonly called the electroencephalogram. All of these electrical events are interdependent. The changes of potential in category (1) are of the order of a few millivolts in reptiles and lower animals, of microvolts in monkey and man. Those in category (2) are of the order of several millivolts, those in (3) rarely more than 200 microvolts in normal man when recorded through the skull and scalp. It was in the search for potentials of the first category that the electroencephalogram was discovered in the nineteenth century.

GROWTH OF THE CONCEPT OF NERVE ELECTRICITY

The observations of Galvani (49a) that so startled the scientific world in 1791 included among others the finding (which he did not understand at the time) that when a nerve or muscle is injured, a current flows from the outer uninjured surface to the cut one. Galvani's preparation was a pair of frog's legs, intact up to the knees with the sciatic nerves laid bare above, and retaining their connection to a truncated piece of the vertebral column. The complexities of this preparation and Galvani's lack of our present day knowledge of electricity masked the true character of the phenomena he demonstrated.

It was the Italian scientist Matteucci (83), professor of physics at Pisa, who in 1838 established the "muscle current" (as he called it), and Du Bois-Reymond (41), professor of physiology at Berlin, who confirmed it and in addition demonstrated the "nerve current." There was still some uncertainty among physiologists as to how much of this potential difference was intrinsic to nervous tissue (i.e. a resting potential) and how much an artifact due to injury (i.e. a current of injury). Hermann (60), Du Bois-Reymond's pupil, named the latter the demarcation potential and took the extreme view that all the electricity in nerve came from this source. His teacher held out for the existence of intrinsic animal electricity and went on to discover that the steady potential difference between cut surface and the undamaged exterior of a nerve trunk changed if he stimulated the nerve. He called this the "negative variation." This was the first demonstration of the action potential of nerve and it was this finding that led directly to the discovery of the electro-
encephalogram, a discovery made independently at times 15 years apart in two widely separated countries.

DISCOVERY OF THE ELECTROENCEPHALOGRAM

The first discovery was made by Richard Caton (26) working at Liverpool University where he was later to have a chair in Physiology created for him (Fig. 1). He set out to see whether the negative variation in demarcation potential that Du Bois-Reymond had found in nerve could be demonstrated in brain on stimulation of any of its sense receptors. In other words, Caton was looking for the potential swing that is classified as type (1) in the categories listed at the beginning of this essay. However, he not only found what he was looking for, but he also had the acumen to note (and not discard as later workers did) an unexpected finding. This was that when both his electrodes were on uncut cortex (thereby excluding the demarcation currents) there were incessant fluctuations of potential even when he eliminated all experimental stimulation of the animal. He named these the “electric currents of the brain” and reported them to the British Medical Association in 1875, and to the International Medical Congress in Washington in 1887, after paying a visit to the City Hospital in Boston. He visited Russia in 1897. In spite of his discovery appearing in the journals of three countries: England (26), the United States (27) and Russia (28), it remained comparatively unnoticed.

Fifteen years later Adolf Beck, a young instructor in physiology at the University of Jagiellianski in Krakau planned his work for an inaugural thesis with exactly the same concepts in mind that had activated Caton’s researches, namely a search for signs of action potentials in the brain when impulses initiated in sense organs passed through it. Beck was as successful as Caton, though ignorant of his work, and published his thesis in full in the Polish language (5) and in shorter form in German (in 1890) (6).

ELECTRICAL LOCALIZATION OF BRAIN REGIONS

In the latter part of the nineteenth century when these pioneers were publishing their novel findings, neurophysiologists were engrossed with the controversial issue as to whether the various faculties, physical and mental, had specific locations in the brain, and it was therefore the localizing potentialities of the evoked changes in the electrical activity of the brain that were most eagerly adopted, its fluctuating baseline being ignored.

Views of cerebral localization varied from adherence to Gall and Spurzheim (49) who favored specific locations for mental faculties, through those who sought centers for sensory and motor functions (for example, Gocht and Horsley (57)) to those, like Flourens (46), who took a global view of the
three main divisions of the brain. The new electrophysiologic technique gave experimenters another tool, and even the first to use it, Caton, succeeded in demonstrating responses to photic stimulation in both rabbits and monkeys, though he failed with sounds. Beck, who specifically named his thesis "The determination of localization of brain and spinal cord function by means of electrical phenomena" was equally successful with photic stimuli. An independent physiologist, Fleischl von Marxow (44, 45) in Vienna, also working in ignorance of Caton's discoveries, localized the visual responses in animals and attempted olfactory stimulation.

As the twentieth century opened, the ruling concept of the electrical activity of the brain was still related to its response mechanisms, but in studying these, workers in many laboratories—in Poland (7, 33) and in Russia (34, 68, 89, 90)—were observing and learning about the fluctuating baseline potentials of the brain "at rest." To their aid had come the great invention of the vacuum tube and its use in electronic amplifiers, so that Caton's "feeble currents" could now be magnified and studied in detail. The work of these experimenters received recognition in their own countries though some (98) thought the potential changes recorded were all artifacts due to muscle movements. It was only when a German worker, after repeating and confirming Caton's observations on animals showed that what was true for monkey was true for man that the rest of the scientific world began to take notice (Fig. 2).

THE ELECTROENCEPHALOGRAM IN MAN

Hans Berger, a psychiatrist in a hospital in Jena, who later reported having made unpublished studies on the electrical activity of the brain in animals since 1902, while working in secretive seclusion in his laboratory extended his investigation to man in 1924. One of his first subjects was his young son, from whom he was able to record a fine 10 per second rhythm. Praw-dicz-Neminski (89, 90), in Russia, had differentiated in dogs the two types of rhythm now known as $\alpha$ and $\beta$ and Berger found their counterparts in man (8). He applied the same tests that Caton had used for establishing the biologic origin of these rhythms, namely hypoxia and anesthesia, and acknowledged his indebtedness to his predecessor. The outstanding contribution of Berger is not only that he demonstrated for the first time the electroencephalogram of man, but that he established its abnormality in epilepsy. His discoveries are directly responsible for the existence of the hundreds of clinical electroencephalographic laboratories that are now to be found all over the world. Not until 1929 did Berger share his findings with the scientific world. In that year and during several to follow he published a long series of papers that are the classics of electroencephalography. His last paper was published in 1938, and in 1941 he committed suicide.
Berger's concept of the electroencephalogram seems to have been a global one. In many of his first experiments he used two very large electrodes, one on the forehead, one on the occiput (though in some he used needles inserted in the scalp). As a result he was plagued by muscle artifacts and although he detected an abnormality during epileptic seizures he missed the spike potentials of cerebral origin that accompany them. His single fronto-occipital placement of electrodes hid from him the localizing potentialities of the electroencephalogram.

The global concept of the brain's oscillating potentials finally gave way before Adrian and Yamigawa's demonstration (by phase reversal) that the a-rhythm in normal man is localizable to the occipital regions (3), (a finding that Berger was unwilling to accept as correct). Then a whole new field of clinical application was opened up by Grey Walter's discoveries in 1936 (102) that it was not necessary to open the skull to detect from the tissue surrounding a neoplasm abnormally slow potential swings (which he named δ-waves), that the tumor tissue itself is electrically silent, and that Adrian's technique of phase reversal can be used to locate cerebral tumors through the unopened skull.

The year before, another outstanding contribution had been made to clinical electroencephalography. This was the discovery by Gibbs, Davis and Lennox (52) of the three per second wave-and-spike discharge in petit mal epilepsy. This finding and that of Grey Walter's of δ-waves associated with brain tumors remain to this day the two major diagnostic aids of the clinical electroencephalographer.

THE SEARCH FOR THE UNDERLYING PHYSIOLOGY

Meanwhile investigators were puzzling over the nature of the oscillating waves. In the first three decades of this century nerve physiology was dominated by the "all or nothing" law and by the discoveries that were being made in axonology. Progress in this field was accelerated by the development of vacuum tube amplifiers and by the application of the cathode ray oscilloscope to the detection of biologic potentials. It naturally followed that attempts to explain the comparatively slow potential changes of the brain should first be made in terms of envelopes of axon spikes. Axon spikes in the periphery have a duration of less than a millisecond, and very many of them, slightly asynchronous in their discharge, would be needed to give the envelope of one a-wave. Later knowledge showed some spikes (from the discharge of cell bodies) to be of only slightly longer duration (2 to 3 milliseconds), and soon physiologists began to look for electrical events within the brain that had a slower time-course. The structures that suggested themselves were the dendrites. Among the first to recognize this possibility were Gerard, Bremer and Bishop and later they were to be joined by Adrian. But it is only in recent years when recording from microelectrodes in the brain became an established technique that this concept has come to the fore in a more detailed form.

It will be noticed that any concept that considered the axon spike as the building block of the cortical wave implied neuronal activity in the form of a discharge. All the empirical observations of the a-wave in man pointed to its being a phenomenon of the brain at rest (though not asleep), and for many years the major application of the recording of brain potentials was channeled in this direction. In the clinical laboratories the patients were examined in quiet conditions and told to make their "minds a blank." Many painstaking and somewhat unrewarding studies were undertaken in attempts to correlate these recordings of the "engine when idling" with psychologic states and psychiatric conditions, for Berger, himself a psychiatrist, had hoped the brain's rhythms would relate to mental processes (9).

To many, however, electrical activity
meant neuronal activity of some kind and not a mere state of rest. Early in the development of this branch of electrophysiology, Bremer suggested that the oscillating potentials were the sign of “tonus” in the cortex (23), indicators of fluctuation in excitability rather than of discharge. The concept of electroencephalographic potentials being concomitants of the excitability changes of cortical neurones is basic to today’s thinking. In the intervening years, however, the possibility that the α-rhythm might be related to transmission of impulses in the brain has not been entirely abandoned. In the 1940s the ingenious suggestion was made, first by Marshall and Talbot (82), and later independently by Craik (32), by Walter (101) and by Pitts and McCulloch (88) that the α-rhythm might act as a scanning mechanism setting the level of excitability of the visual projection areas for incoming stimuli, and hence it would play a role in the perception of form. Attractive as this hypothesis was, it did not stand up to the experimental testing of MacKay (77) or of Walsh (100).

Throughout most of this period the parameter of the α-rhythm that claimed the most interest was its frequency. In line with the hint derived from Caton that anoxia had a depressing effect on the electrical currents of the brain, numerous studies of cerebral metabolism were initiated in the many countries where interest had now been aroused. The indubitable relationship of any form of neuronal activity, electrical or otherwise, to the metabolism of the neurones concerned made this a fruitful field, and at this time Gibbs (51) proposed a system of chemical oscillators as the underlying mechanism of the EEG. The work of Lennox and the Gibsoss (71) on the oxygen and carbon dioxide content of the blood, that of Davis and Wallace (37) on overbreathing and that of Hoagland (62) on the effect of anoxia and of insulin on the frequency parameter are outstanding among the early work in this area.

Emphasis on the frequency characteristics of the electroencephalogram created a demand for an instrumental method for its determination and this resulted in the design by several centers of instruments for automatic frequency analysis. Two different designs, that of Gibbs and Grass (53), and that of Walter (103) were applied to the quantification of frequency changes resulting from alterations in cerebral metabolism (54, 14), a problem for which they were the suitable tool since no transient or paroxysmal potentials were present to confuse the analysis. Among the newer techniques developed in recent years are the frequency analyser of Storm van Leeuwen and co-workers (95), the toposcopic analysis designed by Walter and Shipton (104), and the application of autocorrelation to the study of the periodic component of the EEG (19).

The susceptibility of the brain’s electrical activity to changes in its metabolism is marked in the second category of potentials listed at the beginning of this essay, namely the transcortical potential difference. The detecting devices of the earliest workers (such as Caton, who used nonpolarizable electrodes) allowed them to see swings in this potential, but the advent of the electronic amplifier brought with it circuits with resistance-capacitance coupling. Such circuits, almost ubiquitous in all commercially distributed equipment for routine clinical electroencephalography prevent slow fluctuations of steady potential from being seen by the electroencephalogram. Directly coupled amplifiers have been available, but only in comparatively recent years has the technical difficulty of drift been overcome. This disadvantage, together with the problems introduced by the necessity for using nonpolarizable electrodes held back the investigation of this aspect of the brain’s electrical activity for many years. The recent design of chopper circuits has, however, now made the study of steady po-
tentials a practical laboratory technique that is proving exceedingly fruitful.

Prominent among the groups studying these steady potentials are the workers at Washington University in St. Louis. In their opening investigations (on man and animals) Goldring and O'Leary (55) concluded that the potential measured in this way is the algebraic resultant of two components of opposite sign tending to balance in a manner consistent with cerebral homeostasis. Certain chemical agents applied to the cortical surface enhance the component contributing to surface positivity (e.g., veratrine or malononitrile), and others augment the one responsible for surface negativity (e.g., strychnine). These slow potentials are influential on the brain's response to peripheral stimuli and the effect of disturbances of this homeostasis is reflected, not only in distortions of the positive or negative phases of primary cortical responses to such stimuli, but in the prolongation of cortical disturbance resulting from a single stimulus. Later work by the same team has taken this technique into the clinical field, where one of its applications is in the detection of changes due to vascular occlusion. Another clinical application has been opened by Cohn (30) with his discovery of the marked shift of this potential during the three per second wave-and-spike paroxysms of the petit mal attack. This finding has been confirmed by Bates (4) and by Walter (105). Apart from the import such findings have for the elucidation of brain dysfunction, it would seem that no hypothesis that attempts to relate memory traces or the interaction of sensory modalities within the brain to neuronal events should ignore these long-persisting electrical changes.

In the last decade a marked change in the standard clinical test has become general. The hypothesis that abnormalities in the brain's structure would be revealed best by studying its electrical activity when "at rest" has been largely replaced by a search for anomalies of brain function when its neurones are "at work." In the majority of clinical laboratories today the response characteristics of the electroencephalogram form an important part of the routine examination. Until after the war the only form of activation generally used was that of overbreathing, a test directly related to the concept of cerebral metabolism being the basic formulator of the brain's rhythms. In 1948 the Walters and the Gastauts published a joint paper (107) on the evocation of seizure discharges in certain epileptics by photic stimulation. It had been known to clinicians that some patients reported that their seizures were provoked by incidentally encountered flickering lights but the technique now became a laboratory procedure. The number of epileptic patients who are photo-sensitive is relatively small (perhaps not more than 6 per cent) but by lowering the convulsive threshold by careful systemic administration of metrazol a differentiation can be made between the normal reaction of photic driving and the abnormal one of paroxysmal discharge (92). Metrazol alone had been used to activate seizure patterns in the EEG since 1938 when Cook and Walter (31) and Strauss and Landis (96) published their initial findings.

That the brain potentials of the normal animal or man can be driven to the frequency of an intermittent light shone in the eyes is among the earliest of observations in this field. In Washington in 1887 Caton (27) reported that he "tried the effect of alternate intervals of light and darkness" and that in those experiments in which he succeeded "the relation between the intervals of light and darkness and the movement of the galvanometer needle was quite beyond question." In more modern times the following of the flash frequency by the brain rhythm was beautifully illustrated by Adrian and Matthews (2) and later demonstrated quantitatively by automatic analysis by Walter and associates (106). The latter technique revealed a persistence of
the α-rhythm coincident with a resonance to the flicker rate that made α-driving a misnomer.

Photic stimulation is not the only form of activation used by the modern electroencephalographer. Another, which may at first glance again seem a misnomer is the induction of sleep. One of the early findings of Berger (10) was that the EEG changed as his subject fell asleep though from his description it would appear that he was observing drowsiness rather than deep slumber. It was in 1935 that descriptions of the EEG in normal man in sleep came from Loomis, Harvey and Hobart (75) and in 1937 from investigators in many countries: from Klaue (69) and from Drohoeck (40) in Germany, from Blake and Gerard (13) in the United States, and from Marinesco, Sager and Kreindler (81) in Roumania. The electrical activity of normal sleeping man consists of slow potential swings and the Davises and their co-workers (35), realizing this, in 1939 used direct coupled amplifiers to record them. Although a focus of slow waves at the vertex was found by the Davises, it was only later (15) that emphasis was laid on the fact that not only frequency but location of maximal activity changed in sleep. In the latter state maximal potential gradients are recorded in the precentral regions in place of the occipital foci of the α-rhythm in the awake subject, and this shift of focus gives the objective demarcation between drowsiness and sleep.

In the course of these investigations of the sleep state considerable information was gathered on the effects on the EEG of soporific drugs and this was added to the accumulating material on the action of anesthetics and of anticonvulsant drugs (70, 20, 99). The application of "activation" by sleep to clinical electroencephalography derives from the discovery by Fuster and! the Gibbeses (50) that spike potentials from the temporal cortex occur more frequently in patients with temporal lobe epilepsy when they are asleep than when they are awake. A further use of the sleeping state in clinical electroencephalography is based on the Davises' finding in 1939 (36) that stimulation from any sensory modality, but most strikingly that from sound, evokes a characteristic potential change in the precentral region on the human head. This phenomenon, named by the Davises the "K-complex" has been used with success by Fischgold (43) in the elucidation of coma states.

Noticeable in this discussion of the sleep state is the omission of any reference so far to Bremer's classic work. The omission has been purposeful, for an attempt will now be made to lead up to a current hypothesis of the basic mechanisms responsible for EEG potentials. This hypothesis will lean heavily on the ideas and findings of others who will be named, but they should not be held responsible for the speculative synthesis that will be attempted. In any case, the statement of the hypothesis that follows should be regarded as fundamentally statistical in nature, the parameters of which can only be described in terms of probabilities.

Running like a golden thread through the fabric of electroencephalographic knowledge is a characteristic of the electrical activity of cortical cells that provides the unifying factor for the many diverse phenomena that have been empirically established in normal man and in the patient with brain disease.

The clue was noticed by the first man to discover the electrical activity of the brain and has been observed by every worker in electroencephalography since then. The key finding is that changes in states of consciousness are accompanied by alterations in cortical potentials. Caton's observations on the effect of anesthesia (26), Berger's confirmation of them and his notes on sleep (10), his discovery that alpha activity waned when the eyes were opened, Adrian's demonstration (2) that this phenomenon accompanied consciously directed vision rather than mere eye-opening—all of these logic explanation. The first major lead came...
from Bremer whose classic finding is the cornerstone of modern electroencephalographic theory.

In 1935 Bremer (22) observed that a cat whose neuraxis was transected at the intercollicular level, i.e. one whose cerebrum was isolated from its mesencephalic brain stem, remained in an apparently sleeping state that was accompanied by slow waves in the electroencephalogram. Bremer named this preparation the "cerveau isolé" and explained the chronic sleep state as being due to a de-afferentation of the brain, retention of the first two pairs of cranial nerves (the optic and olfactory) being insufficient to keep the animal awake. Bremer went on to show that if the transection were made lower down (at a level of the first cervical vertebra) the animal retained its sleep-waking cycle with the appropriate electroencephalographic concomitants. This preparation in which the whole contents of the cranium retained their interconnections though losing their spinal inflow, Bremer named the "encéphale isolé." His demonstrations made clear the importance of the integrity of the mesencephalic brain stem for the state of vigilance, an observation which tallied with and became explanatory for the symptoms of brain stem disease familiar to the clinician.

Involvement of subcortical neuronal influences in problems of sleep and wakefulness had been emphasized by previous workers, though attention in these studies had been given to more rostral structures in the diencephalic brain stem. For example, Hess (61) had defined in cats a region lateral to the massa intermedia, extending caudally to the habenular-interpeduncular tract and rostrally to the mammillo-thalamic bundle, stimulation of which induced a sleep-like state. In the years immediately following Bremer's publication the first experimental evidence for implication of the hypothalamus came from Ranson and Magoun (91), and 6 years later Murphy and Gellhorn (86) showed that electrical stimulation of the hypothalamus altered the electroencephalographic pattern. The later work of Ingram et al. (63) added further to our knowledge of the relationships between hypothalamic and cortical activity.

That electroencephalographic potentials recorded from the cortical surface were influenced by diencephalic activity was definitively established by the work of Morison and Dempsey (84), published in a series of papers in the early forties. Their work stemmed from that of Forbes and his associates demonstrating that even in deep anesthesia sensory impulses reach the cortex (39). At that time (1936) this seemed a paradoxical finding for it was generally believed that arrival of sensory impulses at the cortex was associated with "awareness" of them. Forbes and Morison (47) went on to show that in addition to the impulses that passed through the thalamus to the cortex from the periphery in both the vigilant and the anesthetic state, there were others traveling by a different route. Thus it was established that the cortex had supply lines from the periphery that bypassed the classical lemniscal tracts with their nuclei in the thalamic nuclei specific to the sensory modality involved. Moreover, Forbes's group showed that impulses traveling up this nonspecific route affected the cortex diffusely and not merely in circumscribed areas devoted to the modality of the sense organ originally stimulated. The existence of multiple afferent systems to the cortex supplies the element of redundancy of information so necessary for the maintenance of stability in a self-organizing system such as the brain.

This was the first hint of the existence of a neuronal system that could influence the cortex in a wider and more general sense than had been previously demonstrated electrophysiologically. The first drive to follow up this lead was focused on the diencephalic structures involved and received most concentrated study from Morison and Dempsey (84, 38). These workers
were able to make clear distinctions between the dual ascending systems from the diencephalic level of the brain stem. In the classical system the responses evoked at the cortex were of short latency, and discretely and unilaterally located. In the nonspecific system the latency of response is markedly longer, bilaterally distributed and has the remarkable characteristic (peculiar to this system) that repetitive stimulation at a rate approximating to that of the brain's own rhythms evokes successive increase in amplitude of response over widespread areas of the cortex. Morison and Dempsey named this phenomenon the recruiting response.

The finding of a bilaterally distributed electrical event in the cortex resulting from stimulation of medial nonspecific nuclei in the thalamus was the basis for Jasper and Droogleever Fortuyn's hypothesis to explain the bilaterally synchronous discharges of petit mal epilepsy familiar to all electroencephalographers. No hypothesis for their mechanism had been suggested until these workers in 1947 recognized the importance of this diffuse thalamic projection system. Jasper and Marsan gave the system this name and went on to map its diencephalic nuclei and to investigate their influence on cortical potentials. Jasper's results led him to suggest a schema in which cell bodies in the intralaminar nuclei and the nucleus reticularis of the diencephalon might have direct projections to the cortex.

In 1949 a discovery was published that has been profoundly influential on the understanding of the electroencephalogram and has opened a line of investigation of the brain in terms of integration and behavior that was previously hidden. This was the demonstration by Moruzzi and Magoun that electrical stimulation of the central core of the mesencephalic brain stem has an arousing reaction outlasting the stimulus (usually both behaviorally and electrophysiologically). A reaction similar to the alerting evoked by peripheral stimulation. The anatomic connections and electrophysiologic properties of the brain-stem had previously received extensive study from Magoun for several years, and had resulted in the demonstration by him of caudally directed facilitatory and inhibitory influences. The new finding, of import for anyone interested in the brain and behavior, was of a cephalically directed control, not only of the electroencephalographic potentials, but of the state of vigilance of the animal.

The electroencephalographic change in the neocortex resulting from stimulation of this ascending activating system in the sleeping animal is a shift from slow waves of high voltage to fast activity of low voltage. This change is immediately reminiscent of the modification in the electroencephalogram that accompanies alert attention to visual stimuli ("a-blocking"), a phenomenon noted by Berger and studied more intensively by Adrian and Matthews (2) and by Jasper and Cruikshank in their early work and by many others since then. The correlation of the shift to this fast type of activity with a change to behavioral alertness is indubitable. No hypotheses concerning "conscientious," "awareness," "attention," or sleep can ignore the impact of this finding.

That the pertinent pathways of this system lie in the mesial brainstem and are not dependent on integrity of the more laterally placed classical sensory tracts has been proven by the ablation and transection experiments of Lindsley and associates. Evidence for this system receiving its sensory inflow through collaterals from the classical sensory paths has been provided by Starzl, Taylor and Magoun (94). Bremer's classic observation that his cerveau isolé preparation cannot be aroused from apparent sleep is now explicable on these grounds, rather than as the result of section of the specific sensory afferents. Bremer was however correct in using the term "deafferentation" because afferent impulses are...
necessary to excite this system if it is to keep the animal in a state of vigilance.

Once the impulses from the periphery have entered the reticular core they lose the information they carry as to sense modality through interaction on the same neurons and take on the function of activating the ascending system so that the cortex may be in an appropriate state of facilitation or inhibition for processing of the impulses received by the specific routes (for there is evidence also for an ascending inhibitory influence) (76, 16). It is the specific impulses travelling in their segregated pathways that convey the message as to which sense organ received the initial stimulus.

Attempts to Reach a Neuronal Analysis

One further area of knowledge needs to be outlined before an attempt at synthesis can be made. This concerns the intimate electrophysiology of the neuronal elements in the cortex whose potentials are being discussed. In the recording of potentials from the unopened skull and scalp of man it is extremely unlikely that the electrodes pick up electrical activity of any neuronal units farther from them than those in the outer cortical mantle. As noted above the activity of these neurones is under control from lower centers but the extracellular current flows of the deeper units do not cause sufficiently steep voltage gradients on the scalp for surface electrodes to detect potential differences. Evidence for this statement comes from personal experience with implanted electrodes in patients with temporal lobe epilepsy (21). Such electrodes in the conscious patient may record seizure discharges of extremely high voltage (500 microvolts and more) in deep structures without any disturbance of the electroencephalogram recorded from the scalp (Fig. 3). This fact, the experience of all who have recorded in this way from epileptic patients, is a sober-

Fig. 3. Seizure discharge in the amygdaloid region of a patient with temporal lobe epilepsy. Note that the seizure discharge does not reach the scalp electrodes. The amygdaloid electrodes were implanted parallel to the interaural line. The numbers on the circle on the left indicate the spatial relationship of the amygdaloid recording points in the parasagittal plane. Interelectrode distance was 3 mm., the central point C being 3 mm. shorter than the others.
ing corrective for anyone in the habit of regarding a normal scalp recording as con-
traindicative of an epileptic condition. Another reason for doubting whether any but
cortical potentials contribute to the electroencephalogram recorded from the
scalp is the impedance of the brain tissue. This is greater than that of saline by a con-
siderable factor and, as Freygang and Landau (48) have shown, white matter
has an even higher impedance than grey. An added complexity is the recent demon-
stration by Brown (24) that intracerebral impedance levels are dynamic rather than
static.

If the oscillating potentials recorded from the scalp originate in cortical neurones they
must be derived from nerve cells whose component units are uniformly oriented,
for were they randomly distributed their potential fields would tend to cancel each
other. One of the outstanding contributions that the physiologist with his microelectrode
has made in recent years is the demonstra-
tion that all parts of a neurone do not have
the same electrical characteristics. Not only
are the time characteristics of the spike dis-
charge greatly different for the cell body,
the axon and the dendrite respectively, but
the recovery rates after a discharge are
vastly different. This means that activity
in any part of a cell or its processes sets
up extracellular current flows between the
rapidly repolarizing areas of membrane and
the more slowly recovering parts. In order
for these current flows to reach a density
that can be recorded at the scalp they
must be closely massed and flowing pre-
dominantly in the same direction. A field
of current flow of density adequate to meet
these requirements, from structures geo-
metrically oriented so that the voltage
gradients they present at the cortex are
sufficiently steep, is found in the radially
oriented apical shafts of the pyramidal cells
reaching up and branching towards the cor-
tical surface. Moreover, these long den-
dritic processes have electrical character-
isties radically different from those of their
cells and axons and thus with their extensive
area of membrane constitute a powerful
source of extracellular current flow.

It should be noted however that on an-
atomical grounds this is a vast oversimplifi-
cation, for the cell structure and layering
of the cortex, especially in regions other
than the visual receiving area, is of a com-
plexity that defies an analysis such as this
which ignores other cellular components
whose orientation is less conspicuous.

As mentioned above, the role of the apical
dendrite as a significant structure in EEG
potentials has been suggested by many
neurophysiologists: Adrian, Bremer, Ger-
ard, O'Leary, Eccles, Chang, Tasaki, and
outstandingly by Bishop. It is to Bishop
(11) that the electrophysiologist owes a
great deal of his knowledge of these struc-
tures and the matrix of the hypotheses as to
the role they play. In recent years the ex-
perimental findings of Grundfest (58) and
Purpura have drawn added attention to
transmission at synapses between axon
endings and dendrites, and for the electro-
cephalographer knowledge of synaptic
potentials is essential, for they have been
postulated as the stuff of which cortical
rhythms are made (for example, by Li and
Jasper (72) and others cited above).

As Bishop and Clare (12) have demon-
strated, normal activity in these dendrites
appears to consist very largely of non-
propagated graded potentials spreading
decrementally from the point at which the
stimulus is received. These nonpropagated
potentials are of long duration and are
not all-or-nothing in character, but reflect
the strength of the stimulus. They have no
refractory period and can therefore sum
with any consequent potentials that are
set up before they die away. This discovery
of graded responses in the central nervous
system brought with it a flood of inter-
pretations of brain mechanisms that had
previously proved difficult to reconcile with
the rigidity imposed by the all-or-nothing
law of neuronal behavior. Conceptual models of activity similar to digital computers with either a “yes” or “no” action gave way to the greater flexibility of analog models in which varying degrees of stimulation evoked graded responses. The lack of a refractory period with the resultant effect that an incoming impulse could sum with the traces of a previous one gave a basis for the nonlinearity of response that is so typical of the biologic system.

No experience finds the organism in the same condition twice. Every event changes the organism in some way so that the relation of input to output is nonlinear. This fact lies at the basis of all learning, all conditioning, all habituation. Explanation of this in neuronal terms was elusive as long as the response mechanisms of the brain were conceived as analogous to those of peripheral nerve where the summation of new with past events was largely excluded by refractoriness.

It has been pointed out is a previous publication (17) that in the experimental animal dendrites can only with difficulty be made to give a spike discharge and this finding was cited in relation to the fact that one of the outstanding characteristics of the normal brain is that it does not give spikes in recordings from the convexity of the cortex. The spike of the epileptic discharge is not merely an excessive form of a normally occurring event, it is a new entity unknown to the normal brain.

The spikes from the epileptic cortex are of far longer duration than those of axon or cell-body discharge, being never less than 15 milliseconds and usually nearer 30 (Fig. 4). This is of the order of the spike potential of the dendrite when it can be induced to fire and the suggestion was therefore made (17) that the typical epileptic spike is an abnormal discharge of apical dendrites of pyramidal cells in some cases fired from the cortical surface—as for example by scar tissue, and in others by triggering from lower centers via the non-specific afferents synapsing onto them in the higher levels of the cortex.

The firing of abnormal dendritic spikes from the surface can be mimicked in the experimental animal by stimulation of the cortical surface as was shown long ago by Adrian (1) and more recently by Bishop and Clare (12; and others (97). The surface negative spike evoked in this way has a duration of about 15 milliseconds and has been shown by the microelectrode recordings of Burns and Grafstein (25) to lose its negativity at a level 0.7 mm. below the pial surface in the cat’s cortex. When excessive, the discharge may spread antidromically down the dendrites to their cell bodies and fire them. Since these cell bodies are the pyramidal cells that carry the efferent discharges from the cortex any mass firing of them spreading to the motor cortex could evoke violent muscular movements (or, in other words, the clinically observable epileptic fit).

What protects the normal brain from...
this disaster? Why does not every discharge of the pyramidal cells resulting from impulses bombarding them from the specific afferents spread up the dendrites and fire them? In another place (18) the suggestion has been made that a feedback of an inhibitory nature plays on the cell body, through returning axon collaterals and small inhibitory interneurones, in such a way as to limit the degree of depolarization that it can develop. There is evidence now from intracellular microelectrode studies of Phillips (87) for the presence of small interneurones in the cortex whose function is solely inhibitory, i.e., their action is to produce a postsynaptic hyperpolarization (and not the depolarization typical of the excitatory state). Such cells are analogous in their function to the inhibitory cells discovered by Renshaw (93) in the spinal cord whose hyperpolarizing characteristics have recently been studied by Eccles et al. (42). The existence of recurrent collaterals from the axons of pyramidal cells has been known ever since the beautiful drawings of Camillo Golgi (56) (Fig. 5).

The inhibitory influence reining in the over-action of cortical efferent discharge may be what saves the normal brain from the convulsive seizure. It is only one of a complex of integrating controls, for the brain stem in addition to its projection routes to the cortex receives a return inflow not only from the cortex but from the cerebellum. The brain stem also has a control system acting centrifugally on the sense receptors themselves. There is now evidence from the work of Hernandez Peón (59) that in the actively alert state accompanying conscious attention selective perception of certain stimuli may be mediated through inhibition of nonpertinent sensory inflow, the inhibitory influence being carried by the centrifugal fibers from the brain stem to the receptor organs.

The hypothetical synthesis now begins to take shape: In the resting but awake brain the typical \( \alpha \)-rhythm is compounded of the massed synaptic potentials of the apical dendrites of pyramidal cells, synchronization resulting from the electrical field of maximal amplitude present in the total activity. In such a postulate the rhythm of this massed activity would be expected to be of lower frequency than that of the fluctuations of its individual units and to be influenced by the degree of depolarization they retain over and above their discharge threshold. The constant influx of stimuli from the external and internal environment of the organism reaches the pyramidal cells through the specific afferents (probably with an intercalated Golgi type-2 cell), and the resultant postsynaptic depolarization moves towards the cortical surface by electrotonic spread in the apical dendrites. The degree of depolarization of the dendritic tree (the substratum of the EEG) is controlled by the arrival via nonspecific afferents of facilitatory and inhibitory impulses from the brain stem modifying the level of excitability. This type of afferent plays onto the dendrites by axodendritic synapsis in the superficial layers of the cortex, adding algebraically to the summating level of polarization. At the same time any excessive development of discharge by the pyramidal cells is checked by the hyperpolarizing action of the small inhibitory cells activated by recurrent collaterals of these same pyramidal cells. The relative time courses of these three events with their different rates of recovery set the rhythm of the waking brain.

In summary then, variations from this homeostatic condition may be conjectured to occur as follows:

1. Sleep or coma: Remove the activating influence of the ascending reticular system and the \( \alpha \)-rhythm is lost; the slow waves of sleep or coma come in its place with their behavioral correlates.

2. Vigilance: Activate the ascending reticular system beyond the homeostatic level of the resting brain and the \( \alpha \) is replaced
by fast activity, while the organism is not only awake but alert.

3. Selective attention: Direct the attention to a fraction only of the sensory inflow and both facilitatory and inhibitory influences come into play in order to highlight the part and mask the surround.

4. Efferent output: Activate the pyramidal cells through their specific afferents to a state of discharge and the α-rhythm will be suppressed not only by simultaneous activation of the nonspecific system but also by the inhibitory feed-back circuit through the recurrent collaterals.

5. Photic driving: Repetitive stimulation in a uniform manner of a given afferent system may cause a persisting facilitation of intercellular transmission extending beyond the pathways used by stray stimuli, the projection system for this being in part the
specific one (as in photic activation of seizures). On a short time-base this could be the mechanism underlying photic driving.

6. Conditioned reflexes: On a longer time-base a somewhat similar facilitation of transmission resulting from repetitive coincidence of two different modalities of stimulus (a degree of coincidence that must exceed chance) may be the substratum of the EEG correlates of some types of conditioned reflex.

7. Barbiturate anesthesia: Barbiturate, after a preliminary short-lasting stage in which it affects the cortex and excites the patient, acts on the core of the lower brain stem blocking its ascending control with resultant impairment of consciousness, loss of α-rhythm and release of spindle bursts from the nonspecific thalamic system. In the patient with temporal lobe epilepsy and involvement of the amygdaloïd-temporal complex, this loss of restraint under sedative doses of barbiturate releases dendritic spiking at the cortex.

8. Cortical spiking in grand mal epilepsy: Disturb the inhibitory feed-back circuit of axon collaterals and the dendrites will spike and, if spread reaches the motor systems, convulsions will follow. Unlike petit mal discharges the mechanism for these involves primarily the cortex and the specific projection nuclei.

9. Petit mal absences: Activity of the reticular system has been proved to block the recruiting action of the nonspecific thalamic system. Withdrawal of this blocking effect during loss of consciousness in petit mal attacks releases abnormal recruiting activity from these centers, driving the association cortex to a bilaterally synchronous discharge. The self-sustaining character of these discharges suggests the interaction of two mutually controlling variables.

10. Brain tumors: Replace the apical dendrites by superficially growing tumor tissue and the α-rhythm will be abolished. According to Ward (108), tumors below the cortex have, superimposed on their δ-waves, the faster potentials of the dendrites that lie between them and the surface. Tumors of the cerebrum, not themselves invading the dendritic layer, but interrupting the afferent paths interfere with all their (testable) response mechanisms.

11. Destructive lesions of the mesencephalic brain stem abolish all α-rhythm and produce a comatose state.

The above synthesis, stated here in oversimplified terms, necessarily lacks precision at this stage. One can only plead (in Adrian’s words) that “It is difficult to resist speculating about the integrative processes of the brain because the whole of human achievement depends on them.” In any case the role of the dendrite as outlined here is highly conjectural and should be regarded as an assumption open to serious question. Only experiment can decide the issue.

The development from the concept of the electroencephalogram as primarily an aid in assessing the normality of the resting “inactive” brain to a dynamic formulation of it as an indicator of the brain in action has, by emphasis on function rather than on structure, suggested a wider application of the EEG to the study of behavior. It should be no surprise if, in addition to the newer applications of the EEG in neurosurgery, it is in the investigation of the physiology of learning, of behavior and of conditioned reflexes that the major contributions of the next few years will lie.

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The historical development of neurophysiology

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CHAPTER CONTENTS

Early Concepts of Nervous Activity
Excitability and Transmission in Nerves
Spinal Cord and Reflex Activity
Physiology of the Brain: Development of Ideas and Growth of Experiment
Short List of Secondary Sources
Biographies

EARLY CONCEPTS OF NERVOUS ACTIVITY

In contrast to medicine, a science demanding synthesis of observations, experimental physiology, with its reliance on analysis and laboratory work, has little significant history before 1600. Leaders in medicine developed and practiced their therapies for many centuries before they felt the need to understand the nature and functions of the body’s parts in any truly physiological sense and, when the urge for this knowledge first arose, it was to come as much from the philosophers as from the healers of the sick.

Neurophysiology (a term not to come into use until centuries later) had as a legacy from the ancients only their speculative inferences and their primitive neuroanatomy. Aristotle had confounded nerves with tendons and ligaments, had thought the brain bloodless and the heart supreme, not only as a source of the nerves but as the seat of the soul. Herophilus and Erasistratus had recognized the brain as the center of the nervous system and the nerves as concerned both with sensation and movement. However, preliminary to all disciplines was the development of the scientific method and in this Aristotle was a forerunner. If Aristotle is to be evaluated as a scientist, it must be admitted that he was almost always wrong in every inference he made from his vast collections of natural history and numerous dissections; yet in spite of the stultifying effect of the immoderate worship given him by generations to follow, he stands out as a pioneer in the background of every scientific discipline. He owes this position to his invention of a formal logic, and although his system lacked what the modern scientist uses most, namely hypothesis and induction, his was a first step towards the introduction of logic as a tool for the scientist. Unfortunately Aristotle did not use his logic for this purpose himself. As Francis Bacon put it, Aristotle “did not consult experience in order to make right propositions and axioms, but when he had settled his system to his will, he twisted experience round, and made her bend to his system.”

In the second century A.D., Galen’s experimental work added little to establish the functions of the animal structures he dissected, though the hypotheses he suggested were put forward so authoritatively that they remained unchallenged for nearly 1500 years. To the intervening centuries, dominated as they were by the Christian church, the teleology implicit in Galen’s approach was attractive. Early Western acquaintance with his writings depended entirely upon Latin translations of Arabic. It was only after the fall of the Byzantine Empire and the expulsion of the Greek monks from the area of Turkish conquest that the Greek language began to be read at
all generally by scholars in Western Europe (1, 2).

In the sixteenth century Thomas Linacre (3), physician to Henry VIII, who had taught Greek to Eras­

mus at Oxford, translated some of Galen’s works into Latin directly from the Greek. The copies he gave to

Henry VIII and to Cardinal Wolsey can be seen in the British Museum. Erasmus, commenting on Lin­

acre’s translations, said, “I present you with the works of Galen, by the help of Linacre, speaking better

Latin than ever they spoke Greek.”

Galen’s emphasis, in spite of his dissection of ani­

mals, was not so much on the structures he found as

on the contents of the cavities within them. Function,

according to his doctrine, was mediated by humors

which were responsible for all sensation, movement,
desires and thought, and hence pathology was

founded on humoral disturbance. The role of the

organs of the body was to manufacture and process

these humors. His teaching about the nervous system

was that the blood, manufactured in the liver and

carrying in it natural spirits, flowed to the heart where

a change took place converting them into vital spirits.

These travelled to the rete mirabile (the terminal

branches of the carotid arteries at the base of the

brain) where they were changed into animal spirits, 2

a subtle fluid which then flowed out to the body

through hollow nerves. Some of these ideas Galen

developed from those of his predecessors (such as

Alemacon, Herophilos, Erisistratos), some were

inspired by his dissection of animals, but all were

hypothetical, none had any experimental proof or

1. GALEN (130-200 A.D.). Opera Omnia (in aedibus Ald et

Andrea Asulian) (in Greek). Venice, 1525. 5 vol.

2. GALEN. Opera Omnia (in Greek). Basle, 1538.

3. GALEN. De Facultatibus naturalibus, Latin translation by

Thomas Linacre. London: Pynson, 1523; English translation


“Nor lesse Worthy of Commendation are the Cravings. . .

The usage of the term ‘animal spirits’ throughout the centuries carries the connotation of the Latin

anima meaning soul and has no reference to the modern meaning of the word ‘animal.’

No other was to appear until the beginning of the eighteenth
century when Johann Gottfried von Berger (1659-1736)
published his textbook entitled Physiologia Medica sive natura

humana. Wittenberg: Kreusig, 1701.

‘Nor lesse Worthy of Commendation are the Cravings . . .

those eleven pieces of Anatomic made for Andrea Vessalius
design’d by Calcare the Fleming, an Excellent painter, and

which were afterwards engraved in Copper by Valverdi in

little.’ Evelyn, John. Sculptura: or the History, and Art of Chalcog­

raphy. London, 1662. The reference is to the plagiarism of the

Spaniard, Juan Valverde. Vivae Imagines Partium Corporis

Humani. Antwerp: Plantin, 1566. (His artist was Becerra.)

even partial support, yet some of them were to last

well into the nineteenth century.

The sixteenth century gave to physiology its first
textbook. 3 This was the contribution of Jean Fernel,
physician and scholar, who in 1542 published his

De Naturali Parte Medicinae (4). This was so well

received that it saw many editions. In the ninth of

these Fernel changed the title to Medicina (5) and

named the first section of the revised book Physio­

logia. According to Sherrington (6) this was the first

use of the term ‘physiology.’ There is, however, a

manuscript in the Danish Royal Library entitled

Physiologus that deals with animals and monsters.

This copy is an Icelandic version of an apparently

much-copied treatise; it is a kind of bestiary. For some

time after Fernel’s revival of it, the term ‘physiology’

was still used by most writers to mean natural

philosophy. An example of this usage is to be found in

the full title of Gilbert’s book on the magnet published in

1600. Although still grounded in a classification

derived from the four elements of the ancients, Fernel’s

physiology nevertheless shows dawning recognition

of some of the automatic movements which we now

know to be reflexly initiated for, although only the

voluntary muscles were known to him, he realized that

sometimes they moved independently of the will.

Before the seventeenth century opened, a technical

achievement in another field laid a foundation on

which physiology was to spread. Lagging about 50

years after the invention of printing came the develop­

ment of copper plate engraving and accurate repro­

ductions of anatomists’ drawings became more

widely distributed. Supreme, however, among the

woodcuts contemporary with the early engravings

were those made from the drawings of Jan Stephen of

Calcar for the anatomical studies of Vesalius (7-9).

These, published in 1543, were to draw the praise of

John Evelyn in his treatise on chalcography. 4 After
centuries in which human dissection could only be done relatively furtively, a more liberal view had grown up in Italy and among a number of contemporary anatomists, Vesalius is pre-eminent. In themselves, however, with the exception of an experiment showing that the nerve sheath is not vital for conduction, his studies made no contribution to the dynamics of function. Although an opponent of Galen and an exposé of his anatomical errors, Vesalius had no more satisfactory concept of nervous activity to offer than that of animal spirits flowing from the brain down pipe-like nerves to the muscles. Yet for the study of the nervous system, as for other branches of physiology, the publication of De Humanis Corporis Fabrica is the outstanding contribution of the sixteenth century, the earlier chalk drawings of Leonardo Da Vinci (1452–1519) not being widely known to his contemporaries. The major contributions of Vesalius were in anatomy and in the demonstration that Galen was capable of error (though he himself was not without error).

At the opening of the seventeenth century the important event for all science was the appearance (in 1600) of William Gilbert’s classic book De Magnete (10, 11). The significance of this work was not only as a landmark for the future of the physical sciences and of electrophysiology through its dawning recognition of a difference between electricity and magnetism; it was the first book to advocate empirical methods and in this way heralded the scientific ferment of the eighteenth century. If one overlooks the last two chapters of De Magnete, the book is revolutionary in its experimental approach. It stood out alone in an age when scholasticism was concerned with classification on qualitative lines without measurement and without validation. Authoritative statements of the ancients were the guides, and induction from experiment was virtually unknown. Gilbert’s book makes a plea for “trustworthy experiments and demonstrated arguments” to replace “the probable guesses and opinions of the ordinary professors of philosophy.”

Gilbert was physician to Queen Elizabeth (whom he only just survived) and a sketch identified as a portrait of him appears in the contemporary drawing (now in the British Museum) made by William Camden, the Court Herald, of her funeral procession in 1603. A contemporary oil portrait of him painted in 1591 has been lost and remains to us only in engravings. Gilbert was born and lived part of his life in his father’s house in Colchester in East Anglia; a portion of this house still stands and, at the time of writing, is being restored. This flowering of the scientific method came during the golden age of Elizabethan England; among Gilbert’s contemporaries were Shakespeare, Walter Raleigh, Philip Sydney, John Donne, Christopher Marlow and Francis Bacon.

Francis Bacon has a place in the history of all sciences, for he took scientific method a step farther, to observation he added induction and to inference he added verification. Scientists before him were content with performing an experiment in order to make an observation; from this observation a series of propositions would follow, each being derived from its predecessor, not by experiment but by logic. (Bacon somewhat unjustly criticizes Gilbert for proceeding in this way.) Bacon’s contribution to scientific method was to urge, in addition, the rigorous application of a special kind of inductive reasoning proceeding from the accumulation of a number of particular facts to the demonstration of their interrelation and hence to a general conclusion. This was indeed a new instrument, a Novum Organum (12). By its application he overthrew reliance on authority of the ancients and opened the way for planned experiment. Although he had no place in his method for the working hypothesis, and his forms of induction and deduction are scarcely those of the modern methodology, they were of considerable influence in its development. The intelligent lines of Bacon’s face can be seen in his portraits. John Aubrey (13) tells us that he “had a delicate, lively hazel eye” and that “Dr. Harvey told me it was like the eye of a viper.”

The first major work in physiology exemplifying


The spelling of Gilbert’s name follows the form seen on his portrait and memorial tablet; his name on his book is spelled Gilbert.
Bacon's methodology was not on the nervous system but on the circulation of the blood. Harvey's magnificent treatise De Motu Cordis (14) was a model for workers in all branches of physiology to follow. This small book (it has only 72 pages) was the first major treatment of a physiological subject in dynamic rather than static terms. By experiment Harvey disproved the Galenist doctrine that the motion of the blood in the arterial and venous systems was a tidal ebb and flow, independent except for some leakage through 'pores' in the interventricular septum. By further designed experiments Harvey proved his own hypothesis "that the blood in the animal body is impelled in a circle, and is in a state of ceaseless motion." Harvey had advanced this hypothesis in 1616 but, as a forerunner of modern scientific method, had proceeded to verify it before publishing his book. But even this triumph of the empirical method did not unseat in Harvey's thinking the belief in a soul located in the blood ("anima ipsa esse sanguis") (15). Harvey was Galenist enough to accept the rete mirabile as the destination of the blood within the cranium, although doubt as to its existence in man had already been raised by Berengario da Carpi (16, 17) a hundred years before. Harvey (18) had his own views of nervous function. "I believe," he said, "that in the nerves there is no progression of spirits, but irradiation; and that the actions from which sensation and

motion result are brought about as light is in air, perhaps as the flux and reflux of the sea."

That nerves might play a role in the working of the heart as a mechanical pump was first suggested by Borelli the Neapolitan, professor of mathematics at Pisa and later at Florence, who applied the reasoning of his discipline to physiology and evolved mechanical models for various bodily functions. His concept of the innervation of muscle was an initiation by the nervous fluid ("succus nervos") of a fermentation in the muscle swelling it into contraction, for there were still many years to go before a dynamic concept of muscle was to emerge in spite of Harvey’s demonstrations on the heart. Peripheral muscles were still regarded as passive structures rather like balloons to be inflated by nervous fluid or gaseous spirits reaching them through canals in the nerves. Borelli, by an ingenious experiment in which he submerged a struggling animal in water and then slit its muscles, demonstrated that the spirits could not be gaseous since no bubbles appeared in spite of the violent contractions. It was this experiment that led him to the suggestion of a liquid medium from the nerve, mixing in the muscle to cause a contraction by explosive fermentation ("ebullitio et displosio") (19).

Giovanni Alphonso Borelli was a member of the group of experimental scientists banded together in the Accademia del Cimento under the patronage of the science-loving Medici brothers in Florence. This small scientific society, successor to the Lincei, existed for only a decade but was typical of the independent groups centered on laboratory experiment that were to spring up in independence of the universities where the scholars had still not looked up from their books. Few as they were (there were only nine members) these laboratory scientists of the Accademia were to have a far-reaching though delayed influence on European thought, for in the final year of the academy’s existence they published their proceedings (20). Founded entirely on empirical methodology, this was a truly scientific text. It was, however, written in Italian although soon translated into English, and it did not reach the scientific world at large until Petrus van Musschenbroek of Leyden made a Latin translation (21). It was this book that, for example, influenced Stephen Hales so greatly in his experimental work. The volume included only one series on animal experimentation, but almost all the rest deals with the physics which are basic to the work a physiologist does in his laboratory.

To his contemporary, Descartes, Borelli owed his application of mathematics to muscular action. This pungent philosopher, who rarely did an experiment, wrote a text that was to influence all experimenters, The Discourse on Method (22). It is not experimental method that he discusses, but his own method of thought, his theory of knowledge. Scientists had just begun to look around them to observe nature and to let the statements about her by the ancients lie in the books when they had to meet a new and brilliant challenge; mathematics was the tool they were to use. Mathematics would not only elucidate the laboratory experiment but would provide the basis for an all-embracing theory of science.

This great man bred in the gentle landscape of Touraine was to devote his life to a search for the truth, seeking for himself a quiet environment for free thinking. This he found for 25 years in the


"Méthode de bien conduire sa raison, pour trouver la vérité dans les sciences."

"Cum nil dignum apud homines scientia sua invenisset, eremum ut Democritus alique veri Philosophi elegit sibi justa Egmundum in Hollandia, sibique solitarius in villula per 25 annos remanit, admirandaque multa meditatione sua detexit" (Borel, p. 9).
Descartes (24, 25), having become convinced that in mathematics lay the tool for a unified theory of all science, had now to explain its role in physiology. It followed logically that the animal body and all its workings was a machine, the operation of this machine being directed from a control tower. In the brain with its bilateral development, the singly represented pineal body was chosen by Descartes to play this master role and (in man) it was given the added responsibility of housing the soul. In the concept of the body as a machine, energized not by an immaterial anima but by the external world impinging on it, lies a germ of the idea of reflex activity.

To coming generations of neurophysiologists Descartes bequeathed the notion that impressions from the external world were conveyed by material animal spirits to the ventricles and there directed by the pineal gland into those outgoing tubular nerves that could carry them to the part of the body the subsequent action of which would be the appropriate one. In animals this was presumed to be a purely mechanical action, but in man the soul, resident in the pineal, could have some say in the direction taken by this

village of Egmond in liberal Holland, though even here he could not entirely escape being hounded by bigots. The mistake he made that the world regrets was to leave a milieu so congenial to his philosophic nature for the cold of Sweden and the exacting demands of Queen Christina. There, within a year, he died. His striking face with the intelligent eyes and quizzical eyebrow has been preserved for us in the fine portrait by Franz Hals that hangs in the Louvre.

A great man has many ‘lives’ written about him but those set down by his contemporaries usually have a special flavor. In the case of Descartes, the short account of his life and his philosophy written by Borel (23) (the microscopist) in 1669 gives one the feeling of bridging the centuries. Borel gives a list of the manuscripts found in Stockholm at Descartes’s death in 1650, including the early treatise he wrote on music when he was only 22. Several of his letters were found, some of which Borel reproduces. The letters date from 1632 and give an intimate glimpse of the struggle Descartes had to face in overcoming resistance to his theories among some of his contemporaries.


*It is an error to suppose the soul supplies the body with its heat and its movements.* — Passions de l’Âme, Article 5.
central relay. Descartes recognized, however, that perhaps some of these actions lay outside the control of the will, citing as examples involuntary blinking and the withdrawal of the hand on burning.

To neurophysiologists Descartes bequeathed another seed—what was later to be known as the reciprocal innervation of antagonist muscles. In order to ensure that while animal spirits were flowing into one set of muscles the opposing set should relax, he argued that the latter must have their supply of spirits blocked and he postulated that this must be effected by valves. Whether or not he was influenced in his thinking by Harvey’s explanation of the valves of the veins is not known, although he was certainly aware of, and had commented on, Harvey’s discoveries. Descartes was a member of what a subsequent irreverent generation was to call ‘the balloonists.’ Apparently unaware of Borelli’s experiments, he thought the animal spirits to be “like a wind or a very subtle flame” and that “when they flow into a muscle they cause it to become stiff and swollen, just as air in a balloon makes it hard and stretches the substance in which it is contained.”

A young contemporary of Descartes, though less directly influenced by him than was Borelli, was William Croone who was working on muscle action. He too thought that the nervous ‘juice’ must interact in some way with the muscle (26). The “spiritous liquid” flowed in, mixed with “the nourishing juice of the muscle,” and then the muscle “swell’d like a Bladder blown up.” Later (27) Croone was to modify this to a number of small bladders for each muscle fiber. Just as Borelli had been a founding member of a scientific society, so was Croone. He was one of the original group who in England formed the Royal Society, a society which unlike the Cimento has continued to flourish and in which to this day eminent scientists not only discuss but demonstrate their experiments before the members. The Royal Society has several distinguished lectureships, among which is the Croonian Lecture founded by the widow of William Croone.

The Royal Society of London received its charter in 1662, being founded for the promotion of ‘Natural Knowledge,’ and it numbered among the founding members many whose contributions are fundamental to physiology. The moving spirit was Robert Boyle, the ‘father of chemistry’ (whose first published work was, however, on Seraphick Love). Famous for his law (28) of gaseous pressures, he made his most directly physiological experiments on the respiration of animals. It was still many years before physiologists were to elucidate the effects of anoxia on the nervous system, and another hundred years were to pass before Priestley’s and Lavoisier’s work on oxygen, but Boyle, by using an ingenious compression chamber, demonstrated that air is essential for life. Almost unnoticed at the time, but since then perhaps overpraised, were the observations of John Mayow (29) on the chemistry of respiration. His publication preceded (although his work was contemporary with) the somewhat similar experiments of the Accademia del Cimento.

In the early seventeenth century emphasis on the search for a chemical foundation for living phenomena characterized for the most part work in Holland and England in contrast to the physical and mathematical approach of the Italians and the French. The two contrasting schools of thought were long to be known by the clumsy names of the iatrochemical and iatromechanical schools. Iatrochemistry, on the rather shaky foundations given to it by van Helmont (1577–1644) and by Sylvius (de La Boé) (1614–1672), provided the approach to the study of the nervous system of Thomas Willis, Sedleian Professor of Natural Philosophy at Oxford (30). Willis, whose clinical achievements outshone his scientific acumen, is recognized in neurology for his description of the circle of Willis and his dissection of the spinal accessory nerve. (Galen had identified only seven pairs of cranial nerves.) Willis was a close colleague at Oxford of Richard Lower, the Cornishman, champion of the theory that spirits flowing into the heart from

its nerves were what caused it to beat (31). Lower's more spectacular achievement was the apparent transfusion of blood, first in dog and then in man (32, 33). We are surprised today that the man survived as long as he did, for the blood donor was a sheep.

Thomas Willis had added to the prevalent Galenic ideas of nervous function the concept that the soul had two parts which he likened to a flame in the vital fluid of the blood and a light in the nervous juice. When they met in the muscle, they formed a highly explosive mixture which inflated the muscle. Yet even before the seventeenth century had run out, a voice went to see him in his old age. There is a poignancy known to Europe, had been gloriously opened by

The students of the nervous system had the hardest fight against dogma for in their province lay the structures most suspect as being the guardians of man's soul. But ranked behind them and influential on them were some of the greatest philosophers of their time. Prominent among these was Locke (36), the father of empiricism. Born in the West of England and trained as a physician, this man with his colorless personality and his clumsy prose was to channel the efforts of the next several generations of workers on the nervous system into a search for the physiology of the mind. For his Essay on Humane Understanding he received immediate recognition and monetary reward, obtaining for it more than was paid to John Milton for Paradise Lost.

Straddling like a colossus the division between the seventeenth and eighteenth centuries is Newton, friend and correspondent of Locke, though to scientists it is perhaps a bit disappointing to find that the subject of their correspondence was the interpretation of the New Testament (biblical history was a life-long interest of Newton). Newton's insight into the movement and forces of nature led him to make some tentative suggestions about the working of the nervous system, and these were noted by the physiologists of the time. There is scarcely a single neurophysiologist of the eighteenth century who does not explicitly attempt to align his findings with these conjectures of Newton.

In the General Scholium (37) which he added to the second edition of the Principia (26 years after its first publication), Newton included a speculation. This was the idea of an all-pervading elastic aether "exceedingly more rare and subtle than the air," which he again suggested in the form of a question in the series of Queries added to the second English edition of his Opticks (38). Applying this suggestion to the nervous system, he said, "I suppose that the Capillaments of the Nerves are each of them solid and uniform, that the vibrating Motion of the Aetherial Medium may be propagated along them from one End to the other uniformly, and without interruption. . . ." It is easy to understand how eagerly such a statement would be received by those who accepted the idea of a nervous principle running down the nerves but were worried that they knew of no fluid sufficiently swift and invisible. Newton's rather sketchy suggestion was therefore eagerly embraced by many of his contemporaries, one of whom, Bryan Robinson,
Regius Professor of Physic at the University of Dublin, even went so far as to claim that "Sir Isaac Newton discovered the Causes of Muscular Motion and Secretion" (39).

At the opening of the eighteenth century the science of the nervous system had reached different levels in the various countries of Europe. In Germany in the first half of the century the Thirty Years War had brought science almost to a standstill, and in the fields of chemistry and physiology this stagnation developed into a retrogression owing to the emergence of an extremely influential figure, Georg Ernst Stahl. In opposition to both the chemical and mathematical schools, Stahl set back the clock by the reintroduction of an immaterial anima which he held to be the sole activating principle of the body parts (40). The latter were regarded as having no dynamic properties of their own, being essentially passive structures. Since the search for an immaterial agent lies outside the scope of science, Stahl's doctrines, promulgated with arrogance and dogmatism, virtually extinguished experimental inquiry among his followers. Yet even writers sympathetic to his viewpoint granted that in attempting to follow his arguments one became "involved in a labyrinth of metaphysical subtlety" (41).

The metaphysical approach of Stahl later came under criticism from Vicq d'Azyr (42) who suggested that the invention of an imaginary soul to resolve those phenomena that could not yet be explained by the laws of physics and chemistry was merely a cloak for ignorance. van Helmont did not escape the same criticism.

In opposition to humoral or vitalistic concepts of nervous and muscular activity was a prominent champion of a 'solidist' theory, Giorgio Baglivi. This young man, whom Pope Innocent XII had appointed to be professor of the theory of medicine and anatomy at Rome, put emphasis on the fibers of the muscles and the nerves, and so foreshadowed the importance that was to be given in the eighteenth century to the intrinsic structural properties of these tissues. He developed a theory (43) of an oscillatory movement of nerve fibers in order to account for both efferent and afferent activity and envisaged the dura mater as the source of these movements and the recipient of the returning oscillation.

The leading medical center in Europe at this time was the University of Leiden. The empirical approach was urged by the physicist S'Gravesande (44) who advised that "It is Nature herself that should be examined as closely as possible... progress may be slow, but what we find will be certain." Petrus van Musschenbroek (45), who had come to the Chair of Physics at Leiden from Utrecht in 1740, had in a discourse on scientific method emphasized that physics should stand apart from metaphysics, that experimental analysis should antecede synthesis, that in the collection of evidence the exception should not be ignored, and that argument by analogy was fraught with danger. Yet it was essentially by analogy that the early eighteenth century viewed the func-

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45. van Musschenbroek, Petrus (1692-1761). *Discours à l'Organisation de l'Expérience.* 1750. (His swansong as Rector at the University of Utrecht.)
tions of the nervous system; the brain was analogous to the heart and the nerves analogous to the arteries. In the one case the content was blood; in the other, nervous fluid. Some writers even spoke of "the systole of the brain . . . whereby the animal Juices are forcibly driven into Fibres of the Nerves" (46).

van Musschenbroek had been a pupil of Hermann Boerhaave who came to the Chair of Medicine in Leiden in 1701. Boerhaave, essentially a chemist and a clinician, had an almost legendary fame as a teacher, which must, one feels, have been due to his personality, for he was not an experimenter and his doctrines were not at all progressive. He added little if anything new to the existing body of physiological knowledge. In his lectures (47, 48) on the nervous system he taught that "The Ventricles of the Brain have also many Uses or Advantages in Life, such as the perpetual Exhalation of a thin Vapour, or moist Dew." Himself a chemist, he made no experiments in physiology and was content to teach that "Tho' the nervous Juice or Spirits separated in the Brain are the most subtle and moveable of any Humour throughout the whole Body, yet are they formed like the rest from the same thicker Fluid the Blood, passing thro' many Degrees of Attenuation, till its Parts become small enough to pervade the last Series of Vessels in the Cortex, and then it becomes the subtle Fluid of the Brain and Nerves." His authority for this doctrine which he handed on to his eighteenth century pupils was the works of Galen who had died in 200 A.D. These teachings are difficult to reconcile with the exhortation expressed in his Aphorismi (49) that attention to facts and observations is the best means of promoting medical knowledge.

Yet among his pupils Boerhaave numbered nearly all the prominent students of the nervous system in the eighteenth century: Haller, van Swieten, Monro, Cullen, de Haen, Pringle. His pre-eminence lay in the clinical field, and there can be no doubt that he had the greatest gift of a teacher, that of lighting the fire of enthusiasm in his students. It was two of them, Haller (50) and van Swieten (51), who were responsible for the wider publication of his lectures, for on his own initiative he published little.

van Swieten, who as a Catholic had little chance of advancement at the University of Leiden, went to Austria under the patronage of Maria Theresa and there founded the 'Old Vienna School,' patterning it on the medical clinic at Leiden. He was an advocate of a spare diet and active exertion and quoted in support of his views "the case of a rich priest, who had


FIG. 6. Albrecht von Haller, the greatest physiologist of the eighteenth century, and de La Mettrie whose treatise *L'homme machine*, addressed to Haller, caused a controversy that highlighted the question as to whether the soul lay in the province of the physiologist. The portrait of Haller is from the frontispiece of his *Elementa Physiologiae* and is an engraving by Tardieu; that of de La Mettrie is from an engraving in the Bibliothèque Nationale (reproduced here with permission), the original painting being a pastel by Maurice Quentin La Tour.

enjoyed a fat living and long been a martyr to gout, chancing to be carried into slavery by a Barbary corsair, and kept for two years to hard labour and spare diet in the galleys lost his gout and his obesity together..." His master, Boerhaave, a martyr to gout, had died 34 years before, corpulence hastening his end.

We have a contemporary description (52) of Boerhaave's habits and also of his looks. "He had a large head, short neck, florid complexion, light brown hair (for he did not wear a wig), and open countenance, and resembled Socrates in the flatness of his nose..." We are told that he rose at four in the morning, but in the cold Dutch winters he allowed himself an extra hour in bed before settling to work in his unheated study. His chief relaxation was music and he played several instruments of which his favorite was the lute.

It is at about this period—the middle of the eighteenth century—that experimental work on the nervous system began to be channeled into three main divisions: a) the elucidation of peripheral nerve physiology and its differentiation from that of muscle, b) the recognition of the function of the spinal cord together with the development of ideas about reflex action, and c) the growth of knowledge about the brain as a neural structure unencumbered by dogma concerning the soul.

**EXCITABILITY AND TRANSMISSION IN NERVES**

In the field of physiology Boerhaave's most prominent pupil was Albrecht von Haller. Haller, a Swiss, was born in Berne and studied at Tübingen but was drawn to Leiden by the magnet of Boerhaave's teaching. After taking his medical degree he returned to Switzerland where he divided his time between medicine, poetry and botany. In 1736 George II of England, Elector of Hanover, appointed him to the chair of the mixed sciences Anatomy, Surgery and Botany at Göttingen, a newly-founded university. It was here that Haller spent the experimental phase of his life as a scientist.

Unlike his master Boerhaave, Haller was a great laboratory worker as well as a phenomenal scholar.

and was the author of the most famous of the eighteenth century textbooks of physiology, the *Elementa Physiologiae* (53). Although these volumes came into print after Haller’s retirement to Berne, he had while teaching at Göttingen brought out his *Primae Lineae Physiologiae* (54) for, as he proceeded with his anatomical and experimental studies, his master’s texts became less and less useful to him. In the preface to his own work he remarks that, since the time of Boerhaave, anatomy had developed so greatly as to become almost a new science. Haller had himself brought out an anatomy book (55) with fine engravings, and anatomy was one of the four subjects on which he compiled bibliographies (56–59) that are a great source of information for the medical historian. They contain tens of thousands of references.

For neurophysiologists Haller’s most interesting work is his development of the concept of irritability. An earlier student of Boerhaave’s at Leiden was Johannes de Gorter who later became physician to the Empress Elizabeth of Russia. He had in 1737 published a volume (60) in which he brought out of obscurity the idea of the intrinsic irritability of tissues that had been postulated by Francis Glisson in the previous century. It is not clear whether de Gorter owed any of his ideas to Glisson. He mentions him only once (in *De Motu vitale*, paragraph 58, p. 40) and this only in reference to the capsula hepatis. In any

57. von Haller, A. *Bibliotheca Chirurgica.* Basle: Schweighauser, 1774; Berne: E. Haller, 1775.
60. de Gorter, Johannes (1689–1762). *Exercitationes medicæ quatuor.* I: *De motu vitale,* 1734; II: *Somno et vigilia;* III: *De fame,* IV: *De Sitt.* Amsterdam, 1737.
case his concept of intrinsic irritability differed from that of Glisson in being part of a dynamic scheme in which movements of muscles and nerves acted mechanically on each other (61). Glisson (62) had been among the few scientists of the seventeenth century to test experimentally the Galenist doctrine that muscular contraction was due to an inflow of nervous fluid inflating the muscle. He had demonstrated by immersion of a man’s arm in water that the level did not rise on contraction. Swammerdam,10 in Holland, reached the same conclusion from experiments on frogs (fig. 8). From such experiments, Glisson had gone on to develop a concept of intrinsic irritability varying in kind for the different nervous functions. As Regius Professor of Physic at Cambridge, Glisson was to a certain extent bound by the statutes governing these professorships to teach the doctrines of Hippocrates and of Galen, and this may have limited him in the development of this new idea of irritability.

In Haller’s hands the idea blossomed into a concept that was to dominate physiology for over a century. His theory differed from Glisson’s in that he omitted the intermediate element of psychic perception between the irritation and the contraction. The first expression of his theory of the relationship of contractility to irritability is found in 1739 in his commentaries on Boerhaave’s lectures and a fuller development in his Elementa Physiologiae, but it is in his

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61. DE GORTER, J. Exercitationes Medicae Quinta V: De actione sive effusione parcellarum. Amsterdam, 1748.

10 No known portrait of Swammerdam exists. In the nineteenth century a publisher took one of the heads from Rembrandt’s Anatomy Lesson and put out a lithograph which he labelled with Swammerdam’s name. This was a stroke of imagination rather than fact.

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**FIG. 8.** Swammerdam’s experiments including the one by which he proved that muscles were not swollen by an influx of nervous fluid when they contracted. Fig. V is of an experiment to show the change in shape of a muscle when stimulated by pinching its nerve. Fig. VI illustrates the pulling together of the pins holding the tendons when the muscle contracts. Fig. VIII is the crucial one in which a drop of water is imprisoned in the narrow tube projecting from the vessel enclosing the muscle. Swammerdam found that when he stimulated the nerve by pulling it down by a wire, the muscle contracted but the drop of water did not move. He concluded that the volume of the muscle did not expand on contraction. It is the fact that the wire was made of silver (filium argenteum) and the loop of copper (filium aeneum) that has credited Swammerdam with the use of bimetallic electricity as a stimulus to nerve. Some authors however interpret the action in this experiment as the mechanical pull on the nerve. Some originals of Swammerdam’s plates can be seen at the National Museum of the History of Science in Leiden. (From Biblia Naturre. Amsterdam, 1738).
Götingen lectures (63) given in 1752 (and published the following year) that the concept is most fully developed and supported by experimentation. Haller's own definitions for the dual properties of irritability and sensibility were as follows: "I call that part of the human body irritable, which becomes shorter on being touched; very irritable if it contracts upon slight touch, and the contrary if by a violent touch it contracts but little. I call that a sensible part of the human body, which, on being touched transmits the impression of it to the soul; and in brutes, in whom the existence of a soul is not so clear, I call those parts sensible, the Irritation of which occasions evident signs of pain and disquiet in the animal."

One sees immediately the bogey of the early physiologists raising its head—the necessity, on invoking the soul, for differentiating processes in man from those in animals. Haller describes his technique for determining sensibility as follows: "I took living animals of different kind, and different ages, and after laying bare that part which I wanted to examine, I waited till the animal ceased to struggle or complain, after which I irritated the part, by blowing, heat, spirit of wine, the scalpel, lapis infinalis, oil of vinegar, and bitter antimony. I examined attentively, whether upon touching, cutting, burning, or lacerating the part, the animal seemed disquieted, made a noise, struggled, or pulled back the wounded limb, if the part was convulsed, or if nothing of all this happened."

Haller recognized that nerves are "the source of all sensibility," but applied his dichotomy of irritability and sensibility to various types of nerves, noting that all nerves are not irritable according to his definition (with its insistence on resultant contraction). He thus approached the differentiation of motor and sensory nerves. Still incorporated in his hypothesis was the 1600-year-old concept of a nervous fluid within the nerves. It might be thought that once the microscope had been invented, the question of whether or not the nerves were hollow pipes might have been quickly settled. Indeed in 1674 Leeuwenhoek (64), with the limited magnification of his simple micro-


64. van Leeuwenhoek, Antonj (1632-1723). Phil. Trans. 9: 178, 1674.


among the muscular Fibres we may with good reason conclude, how short this Force is of producing so great an Effect, as that of muscular Motion, which wonderful and hitherto inexplicable Mystery of Nature, must therefore be owing to some more vigorous and active Energy, whose Force is regulated by the Nerves; but whether it be confined in Canals within the Nerves, or acts along their surfaces like electrical Powers, is not easy to determine."

At the end of the century came Galvani. His famous *Commentary*, published first in 1791, appeared at a time of intense interest in electricity. The demonstration by Stephen Gray (67) in England that the human body could be electrified had been taken up and popularized by the Abbé Nollet (68) at the French Court and by Hausen (69), the Professor of Mathematics in Leipzig. Each had copied Gray's experiment in which he suspended a boy by ropes from the ceiling, bringing a flint-glass tube that had been charged by friction close to his feet and watching the attraction of a leaf-brass electroscope to his nose (see fig. 10).

Electroscopes of this primitive type were the only instruments then available for the detection of electricity, the most sensitive one being that developed by the curate of a rural parish in Derbyshire (70). This delicate instrument with its gold leaves was identified by his name as Bennet's electrometer, though it was scarcely a metrical device. Sources of electricity were still the frictional machines, first globes of sulphur, glass or porcelain, and later revolving discs. It was

not until the development of the Leyden jar by Petrus van Musschenbroek, Professor of Physics in Leiden, that physiologists gained a much more stable and powerful source of electricity.

van Musschenbroek, striving to conserve electricity in a conductor and to delay the loss of its charge in air, attempted to use water as the conductor, insulating it from air in a nonconducting glass jar. However, when he charged the water through a wire leading from an electrical machine, he found the electricity dissipated as quickly as ever. His assistant, Andreas Cuneus, while holding a jar containing charged water, accidentally touched the inserted wire with his other hand and got a frightening shock. With one hand he had formed one ‘plate,’ the charged water being the other, and the glass jar the intervening dielectric. A condenser was born. On touching the wire with his other hand he had shorted this condenser through his body giving himself such a jolt that he thought “his end had come” (71). van Musschenbroek wrote to Réamur describing a similar experience. Storage of electricity had now become possible and in fact had been achieved independently by almost the same means (an electrified nail dipping into a vial containing liquid) by von Kleist (72) of

Kamin in Pomerania, yet another of the indefatigable company of eighteenth century clergymen to whom science owes so much.

Both the electroscope and the Leyden jar were used by Galvani in the experiments he had begun not later than 1780. He was also familiar with the fact that some animal forms, notably the marine torpedo and the electric eel, had intrinsic electricity. Scientific studies of this type of animal electricity had begun with the work of John Walsh (73) in 1733 and have continued to this day. In those days the production of a spark was considered a sine qua non for full acceptance of the electrical nature of a phenomenon; this was lacking for the fish until after Galvani’s time when Matteucci developed a technique for demonstrating it (see fig. 12). For many years before Galvani’s day, as demonstrated for example by Swammerdam and by the French anatomist Joseph Guichard Duverney,11 it had been known that the limbs of a frog could be convulsed by mechanical irritation, and electricity applied directly to the muscle already had been used by many physicians (and quacks) to animate paralytics.

The three chief observations that stand out from the many experiments reported by Galvani in his original Commentarius (74) were a) that a frog’s nerve muscle preparation, although at a distance from a sparking electrostatic machine, would twitch when touched by an observer (in the light of later knowledge this was called induction at a distance, with stimulation occurring by the ‘returning stroke’ at the moment of sparking); b) that atmospheric electricity could be used to stimulate frogs’ legs if a long wire were erected (the principle of the lightning conductor); and c) that frogs’ legs twitched when hung by brass hooks to an iron railing even in the absence of a thunderstorm. This last, the most important discovery in his first set of experiments, was due to the current that flows between dissimilar metals when connected in a circuit, though Galvani did not understand this at the time and attempted to explain all his results as the presence of intrinsic animal electricity.

The Commentarius was reprinted three times, twice in 1791 and again in the turbulent year 1792 (the year that France seized Savoy); then it reached scientists outside Italy. Through the great controversy stirred up by Volta which continued after Galvani’s death in 1798 (Galvani’s less prudent nephew Aldini championing his cause), two extremely important areas of knowledge developed from the original observations. One was the recognition and elucidation of the electrical properties of muscle and nerve which were to lead directly to the discovery (by du Bois-Reymond in the next century) of the action potential of nerve, and the other was the development (by Volta) of bimetallic electricity into the electric battery, one of the major technological steps in the history of science. Volta had striven to explain all the frog experiments by bimetallic currents, insisting that to produce electricity three substances were always necessary, two heterogeneous metals and a third conducting material

11 This, one of the early public demonstrations of the stimulation of muscle through irritation of its nerve, was made before the Académie Royale de Sciences in Paris in 1700, and is reported for that year as follows: ‘M. Du Verney showed a frog just dead, which in taking the nerves of the belly of this animal which go to the thighs and legs, and irritating them a little with a scalpel, trembled and suffered a sort of convulsion. Afterwards he cut these nerves in the belly, and holding them a little stretched with his hand, he made them do so again by the same motion of the scalpel. If the frog has been longer dead this would not have happened, in all probability there yet remained some liquor in these nerves, the undulation of which caused the trembling of the parts where they corresponded, and consequently the nerves are only pipes, the effect whereof depends upon the liquor which they contain.’ History and Memoirs of the Roy. Acad. Sci. Paris. Translated and abridged by John Martyn and Ephraim Chambers. London: Knapton, 1742. p. 187.
to complete the circuit. If this third material were a frog's muscle, it would by virtue of its irritability react to the flow of bimetallic electricity, but its role (according to Volta) was solely that of an electroscope (75). When Aldini (76) demonstrated by dipping ends of nerve and muscle in mercury that the same effect could be obtained with a single metal, Volta replied that the surface in contact with the air suffered a change that made it heterogeneous with the depth. This tortuous argument was disproved by von Humboldt (77).

Before Galvani's death an anonymous (78) tract was published, almost certainly with his collaboration, in which an experiment was described on the twitching of muscles in the absence of any metals or external source of electricity. A contraction was demonstrated when the cut end of a frog's spine fell over onto its muscle or when one limb was drawn up to touch the exposed sciatic nerve (see fig. 12). In this case the source of electricity was what we now recognize as the current of injury. Even after this demonstration (79) Volta tried to explain the current flow as the result of heterogeneity of tissues (muscle and nerve).

The design of Humboldt's experiments and the clarity of his reasoning are a pleasure to study in the welter of acrimonious controversy that greeted Galvani's findings. Without bias towards either protagonist Humboldt repeated their experiments, examined their interpretations, designed new experiments to test their hypotheses and came to the conclusion that Galvani uncovered two genuine phenomena (bimetallic electricity and intrinsic animal electricity) and that these were not mutually exclusive. Humboldt demonstrated that both great scientists erred in their interpretations of their experiments; however, from these were to grow the science of electrophysiology on the one hand and, on the other, the brilliant development of the electric battery. Not only does Humboldt expose the erroneous parts of Galvani's and of Volta's interpretations but also
those of the writers who rushed in so precipitately to take up arms for one or the other protagonist—Faff (80), Fowler (81), Valli (82), Schmuck (83), each received his rebuke. He tells us that he thought some of the problems out while sitting at the foot of Mt. Bernard reading de Saussures’ *Voyages dans les Alpes* (84). Humboldt was a great traveller (especially at a period when he was an inspector of mines) but did not let this interfere with his experiments, for he took his apparatus along with him, even on horseback.

The pursuit of research in animal electricity was carried on in many countries, the most valuable contributions coming first from the Italian scientists. Their task was made easier for them by Oersted’s discovery of electromagnetism and its development by Nobili into a useful form of galvanometer. Oddly enough Oersted’s researches (85, 86) that led to his important experimental demonstration of the relationship between electricity and magnetism were motivated by a metaphysical belief in the universality of nature, a faith inspired by his adherence to Naturphilosophie. This romantic doctrine with its façade of facts was very powerful in Germany from about 1810 to 1840 and was derived from Kant’s rejection of empiricism and his philosophy of universal laws known a priori by intuition. Oersted’s own a priori belief was so strong that he did not hesitate to make his first experimental test of it in the classroom during a lecture to advanced students at the University of Copenhagen.

The experiment worked; when current flowed in a single loop of bent wire, a magnet below it moved. This great discovery led to the development of instruments with multiple windings and to moving coil galvanometers. The contribution of Nobili, Professor of Physics

84. de SAUSSURES, H. B. *Voyages dans les Alpes*. Neuchatel, 1796.

and Natural History at Florence, was the astatic galvanometer (87) in which two coils of wire wound in opposite directions cancelled the effect of the earth’s own magnetism.

It was Matteucci, the Professor of Physics at Pisa, who laid the groundwork of muscle electrophysiology that was to be developed so exhaustively by du Bois-Reymond. Carlo Matteucci (88) was one of the prominent figures in the Risorgimento. A great liberal and a great patriot, he attempted to coordinate the efforts of all European liberals when the 1848 revolution broke out. When Italy was united in 1859, he was made a Senator. He was one of the early Ministers for Public Instruction in Italy. His contributions have never received adequate recognition, mainly owing to the acrimonious attacks made on his work by du Bois-Reymond who came near to diminishing his own stature by his sour polemics. Matteucci had raised the question as to where in the nerve-muscle


FIG. 14. Matteucci and two of his experimental procedures. The portrait is reproduced from the old yellowing photograph in the Schola Normale Superiore in Pisa (by courtesy of Dr. G. Moruzzi). Above on the right is Matteucci’s illustration of his rheoscopic frog, and below is his experiment demonstrating that the discharge of a marine torpedo can make a spark cross a gap.
preparation the electricity lay and had thought that muscle alone could produce it. The preparation used by Matteucci was a frog’s leg complete below the knee with only the isolated nerve above it. Galvani’s frogs retained a piece of the vertebral column with the insertion of the nerve into its portion of the spinal cord. Matteucci’s contributions in brief were a) the galvanometric detection of a current flow between the cut surface of a muscle and its undamaged surface, demonstrated in both animal and man (89, 90); b) the multiplication of current by serial arrangement of cut muscles so that the transverse section of each touched the longitudinal section of the next; c) the decrease in this current during tetanus caused by strychnine (90) (the germ of the discovery of the action current); and d) the ability of a frog’s muscle contraction to generate enough electricity to stimulate the nerve of another nerve-muscle preparation when laid across it (the rhesoscopic frog) (91, 92). Matteucci was inconsistent in his interpretation of this finding and showed his characteristic vacillation between an explanation in terms of electricity and one based on nervous force. He named the effect the ‘secondary contraction.’ Matteucci (93) also noted such important laboratory phenomena as the difference in stimulating effect of ‘make’ and ‘break’ shocks, and the polarizing effects of prolonged flow of current on electrodes. He noted that polarization could occur inside the muscle and thus laid the ground for all the work that was to follow on polarization and electrotonus.

du Bois-Reymond, of French name and Swiss descent, lived all of his working life in Berlin. He was a pupil of the greatest physiologist of the time, Johannes Müller. Müller, professor first at Bonn and then at Berlin, was a gifted teacher who could count among his pupils von Helmholtz, von Brücke and Sechenov. His Handbuch der Physiologie (94) was the great textbook of the nineteenth century, and the journal he founded, Müller’s Archives für Anatomie und Physiologie, as a successor to Reil’s first physiological journal, was the main outlet for the stream of research that was coming from the German schools at that time. His own interests lay mostly in sensory physiology where his name is always associated with the ‘Law of Specific Nerve Energies,’ although this concept in fragmentary form had certainly occurred to others before him, including notably Charles Bell (95) and John Hunter. By this law Müller formulated the findings that wherever along its course a sensory nerve was stimulated, the resultant sensation was that appropriate to the sense organ it served. On the issue of electricity in nerve, Müller took the position that it was indeed an artificial excitant but had no part in natural excitation. He reached this conclusion largely from an experiment in which he mashed the nerve and demon-


...while each organ of sense is provided with a capacity of receiving certain changes to be played upon it, as it were, yet each is utterly incapable of receiving the impression destined for another organ of sensation.” Quoted from Bell, Charles (1774-1842). Idea of a new anatomy of the brain, submitted for the observation of his friends. Privately printed. 1811.

“...it is more probable that every nerve so affected as to communicate sensation, in whatever part of the nerve the impression is made, always gives the same sensation as if affected at the common seat of the sensation of that particular nerve...” Quoted in The Works of John Hunter edited by J. F. Palmer. London: Longmans, 1835. 4 vol.
strated that, although electricity passed through the damaged zone, mechanical stimulation of the nerve above the injury provoked no twitch.

During the era of intense concentration on electrophysiology in the Italian and German schools, laboratories in other countries were developing a different approach. Among these was that of Claude Bernard (95), pupil of Magendie. Claude Bernard made use of curare as a blocking agent, interpreted by him as a nerve poison that spared the muscle. He found that in a curarized preparation the muscle would not twitch if he stimulated it directly and hence concluded that normally transmission could not be electrical either. In these experiments he used the ingenious little stimulator built from a Voltaic pile of alternate copper and zinc plates that is shown in figure 16. He did not recognize that his failure to evoke a contraction by direct stimulation of the muscle was due to his ‘pile’ giving too feeble a current.

Müller was the last of the great physiologists to retain a trace of vitalism in his thinking. This he probably owed to his exposure as a student at Bonn to Naturphilosophie and the influence of its leader, Schelling (96). Although more extensively indoctrinated in this sterile philosophy than Oersted had been, Müller was later able to free himself more easily from its stultifying effects, and he eagerly encouraged the physical and chemical approaches to biological experiment. Not a trace of vitalism is found in his pupils.

Towards the half-century a marked swing away from the metaphysics of Naturphilosophie characterized neurophysiology. du Bois-Reymond considered himself (and with some right) to be the champion of this movement which strove to explain all physiology on chemical and physical grounds. And in fact, as we have seen, it was the physicists of the period who were contributing most of the new experiments and concepts of muscle and peripheral nerve action. Before this, neurophysiologists had reached a stage in their work in which progress was hampered by lack of sufficiently sensitive instruments. The physicists came to their help and indeed were themselves intrigued by the types of physical phenomena that biological preparations provided.

In 1841 du Bois-Reymond received from his master a copy of Matteucci’s book Essai sur les Phénomènes Électriques des Animaux (97), together with the suggestion that he repeat and extend Matteucci’s experiments. By November of that year he had already completed a preliminary note (98), but his major work, the Tierische Elektricität (99), did not appear until 1848. The first part of this long and detailed book, unlike its later sections, shows little originality in scientific ideas, the author with a chip on his shoulder being carried along in the wake of Matteucci of whose publications he was outspokenly critical. However, where du Bois-Reymond shines, and what makes his book a classic, is his skill in instrumentation, far surpassing that of Matteucci, so that he was able to extend and improve on these earlier observations. Moreover, not being hampered (as Matteucci was) by residual traces of a belief in


FIG. 16. Claude Bernard at the age of 53, and the ingenious stimulators he used in his electrophysiological studies of nerve. They were miniature voltaic piles built up of alternate discs of copper and zinc. Just before use they were moistened with vinegar. Such devices were made obsolete by the du Bois-Reymond induction coil and it is rather surprising to find Bernard still advocating them in his day. Although adequate for nerve stimulation, they gave too feeble a current to stimulate a muscle directly; from this Bernard concluded that the nervous effect on muscle could not be electrical.
‘nerve force,’ he brought clearer inductive reasoning to the interpretation of his observations.

du Bois-Reymond confirmed Matteucci’s demonstration that not only nerve-muscle preparations but muscles themselves could produce electricity and, with some acerbity, claimed priority for naming this the ‘muscular current’ (Muskelstrom). Both Matteucci and du Bois-Reymond distinguished muscular current from the ‘frog current’ (la correnta propria della rana), so named by Nobili to describe the current flow between the feet of the prepared frog and any other part of the animal. Neither Nobili nor Matteucci, nor even du Bois-Reymond at this time, recognized that the so-called frog current was an injury current consequent to their having transsected their frogs. Nobili had thought it was a thermo-electric effect due to differential cooling times of nerve and muscle.

du Bois-Reymond, using faradic stimulation, also confirmed Matteucci’s finding that the muscle current was reduced during tetanic stimulation and named this the negative variation. It is what is now called the action current of muscle, du Bois-Reymond went on to demonstrate the same negative variation in nerve during activity and thus discovered the action current of nerve which Matteucci had failed to find with his less sensitive instruments. du Bois-Reymond made the following claim, "If I do not greatly deceive myself, I have succeeded in realizing in full actuality (albeit under a slightly different aspect) the hundred years’ dream of physicists and physiologists, to wit, the identity of the nervous principle with electricity." His great contemporary Carl Ludwig (101) was unwilling to accept this for, thinking still in terms of the nerve as a telegraph wire, he held (among other objections) that its resistance was too great and its insulation too poor for it to be a good conductor.

Pflüger (102) tried to overcome some of these difficulties by his ‘liberation hypothesis.’ In this he stated that nervous transmission was “not a simple advancing undulation in which the sum of the living forces is not increased” but a situation in which “new tension forces are set free by the living forces of the stimulus and become in turn living forces with each onward step.” In spite of the obscurity of the terminology (this is Morgan’s translation), one can detect a foreshadowing of the ideas held by today’s physiologists.

du Bois-Reymond elaborated a theory that all undamaged muscle had a resting potential between the middle (positive) and the tendons (negative) and that during activity this decreased, thus giving the ‘negative variation.’ He was still not clear on the role of injury currents for he thought injury merely intensified the resting potentials. On this point he entered into acrimonious dispute with his pupil Hermann who was equally stubborn in insisting that there were no resting potentials in the absence of injury and that all current flow in muscle and nerve was due to damage (103). Hermann therefore introduced the term ‘demarcation currents’ to describe them. Later experimentation has shown both men to have been partially right and partially wrong.

du Bois-Reymond’s conception of regularly oriented ‘electromotive particles’ arranged along the surface of muscle and of nerve was the forerunner of the schemata of polarization that were to be developed more fully and more accurately by his pupil Bernstein (104) and that lie at the core of modern theory. The critical issue as to whether the negative variation in nerve potential was identical with the excitatory process (i.e. the nerve impulse) was taken up by Bernstein who set out, at du Bois-Reymond’s suggestion, to compare their velocities. von Helmholtz, one of the same brilliant group schooled in Müller’s famous laboratory, had in a triumph over primitive apparatus succeeded in measuring the velocity of

the excitatory processes (105) in the frog. In his success he had proved his old teacher wrong. In 1844 Müller had said, "The time in which a sensation passes from the exterior of the brain and spinal cord and thence back to the muscle so as to produce a contraction, is infinitely small and immeasurable." von Helmholtz's technique was as follows: the moment of nerve stimulation, by the break shock of an induction coil, was signalled by the closing of the primary circuit. The resultant muscle contraction lifted a contact in the same circuit, thus breaking it. The break signalled the arrival of the nerve impulse in the muscle. By timing this interval, with stimulation at measured distances along the nerve, von Helmholtz was able to calculate its conduction velocity. This simplified description masks the extreme ingenuity of the original experiment. In technique von Helmholtz had come a long way from Haller's attempt to discover the velocity of nervous action. Haller had read parts of The Aeneid aloud, timing himself, counting the syllables and calculating the length of the nervous paths used in reading and speaking. In some way that is not entirely clear, he arrived at a figure of 50 m per sec.

The conduction rate found by Bernstein (approximately 29 m per sec.) tallied sufficiently well with von Helmholtz's final results, 27 to 30 m per sec., for him to be satisfied with the inferred identity of the impulse and the negative variation. Bernstein's experiments, using for stimulation a rheotome devised by himself with a galvanometer for detection of response, enabled him to plot the time course of what we now call the nerve's action potential and to determine its latency, rise-time and decay. One of the pregnant observations he made was that the negative variation caused a deflection of his galvanometer that sometimes crossed the base line, thus exceeding the value for the resting nerve potential. In today's terminology, he found the overshoot of the action potential beyond the resting potential level. Bernstein (106) became widely known for his theory that the membrane of the inactive fiber of nerve or muscle was normally polarized, having positive ions on the outside and negative ions on the inside, and that the action potential was a self-propagating depolarization of this membrane. This was based on his assumption that the membrane is selectively permeable to potassium ions. His explanation of injury currents was that they were the result of a break in the membrane.

In the later nineteenth century, after a long hiatus, physiology in England was again coming into its own. At the half-century, which saw such brilliance in the German schools, there was virtually no physiological work in progress in England. There were no physiological laboratories and there was no systematic physiological research. A dual chair in anatomy and physiology had been created in 1836 at University College, London, and had been given to the anatomist William Sharpey. Such teaching as he gave in physiology was from books and his pupils saw no experiments, yet from among them came the leader of one of the more famous English schools of physiology, Michael Foster (1836-1907), founder of the Cambridge School. Though not himself a neurophysiologist, Foster could count among his pupils some to become later among the most brilliant in the field, Sherrington (1857-1952), Gaskell (1847-1914), Langley (1852-1925) and, as descendents from the last, Keith Lucas and in turn Adrian.

This, the late nineteenth century, was an age of great progress in the development of instrumentation and, with their improved tools, physiologists were able to make more accurate observations of stimulus strength, response characteristics and time relationships than had their predecessors. In 1871 Bowditch (107) demonstrated that heart muscle did not respond with graded contractions to graded stimuli. He assumed that the global response he observed was due to a leakage of excitation throughout the fiber population of cardiac muscle. It was in fact the experimental evidence for what was later to be called the 'all-or-nothing law.' Bowditch, an American, did these experiments in Ludwig's laboratory in Leipzig where he worked on the problem with Krönkecker, the teacher of Harvey Cushing. On his return to Harvard, Bowditch founded the first laboratory for physiological research in the United States.

Forgotten by Bowditch, or unread, were the writings of Fontana in the eighteenth century in which, in discussing heart muscle, he said, "... the irritability of the fibre can be activated by a small cause, and by a feeble impression: but once activated, it has a power proportional to its own forces, which can be

much greater than those of the exciting cause..."¹⁴ Fontana (108) went on to a recognition of the refractory period (a term introduced by Marey) in heart muscle which he explained as an exhaustion of irritability resulting from the contraction.

That skeletal muscle might share this property was also foreshadowed by Fontana but did not receive experimental proof until the work of Fick (109), another pupil of Ludwig's, although the finding was not further developed until the ingenious experiments of Keith Lucas (110) at the beginning of this century. In the meantime, an all-or-nothing property in nerve had been detected by Gotch (111), the predecessor of Sherrington in the Chair of Physiology in Liverpool, a finding that was to reach definitive form in the hands of Keith Lucas' pupil, Adrian (112, 113). That the law applied to sensory as well as to motor nerves was established by Adrian & Forbes (114) in 1922 (in a paper whose title replaced the term 'all-or-none' by the more grammatical one 'all-or-nothing'). This line of work led on to investigations of the refractory period of peripheral nerve and the accurate plotting of the time course of after potentials. The invention of the vacuum tube amplifier and the cathode ray oscilloscope opened the modern era of electrophysiology, and with them the foundations of today's techniques were laid by Gasser & Erlanger (115).

One branch of peripheral nerve physiology remains to be outlined. This is the subject of neuromuscular transmission. Its history is short for, before the latter half of the nineteenth century, continuity between nerve and muscle was assumed, the neuron theory had not been formulated and neuroneural synapsis had not been conceived. The 1700-year-old hypothesis of a nervous fluid implied humoral transmission in structures having continuity and only at mid-nineteenth century, when this was finally abandoned, did the possibility of junctional tissues become a live one.

In 1862 Willy Kühne (116, 117), pupil of von Brücke and later professor of physiology in Heidelberg, published a memoir on the end organs of motor nerves. Noting the histological differences between muscle and its innervating nerve, he suggested that action currents of the nerve by invasion of the muscle caused it to contract. That there was a delay at the neuromuscular junction was noted in du Bois-Reymond's laboratory and the master himself considered the possibility of a chemical influence (the agents he mentioned were ammonia and lactic acid which Leibig had demonstrated in muscle in 1847); he went to great pains, however, to sketch electrical fields in support of what was called the 'modified discharge hypothesis' (as shown in fig. 17).

The controversy surrounding the mode of transmission at the motor end plate was carried into the modern era and, at a time not yet history, essential agreement was reached that transmission at the neuromuscular junction is chemical in nature. The major contribution that settled the issue came from pharmacological experimentation of today's scientists, stemming from the pioneer work of Elliott (118), Dale (119) and Loewi (120) in the early part of the century. Elliott, while a student at Cambridge, noticed that smooth muscle responded to adrenin even when deprived of its sympathetic nerves and this led him

to suggest that adrenin "might then be the chemical stimulant liberated on each occasion when the impulse arrives at the periphery." Langley (121), who was at that time professor of physiology at Cambridge, recognizing that in some smooth muscle the action both of sympathetic nerve stimulation and of adrenin was to produce contraction whereas in others the result was a relaxation, postulated the existence of two kinds of receptor substance—excitatory and inhibitory. That adrenin mimicked sympathetic action was then accepted.

The possibility of a chemical mediator for the vagal action on the heart was explored experimentally in several centers. Bottazzi (122), Martin (123) and Howell (124) thought the agent must be potassium, Dixon (125) that it was muscarine, an alkaloid closely related in structure to the cholines. These substances had been shown to be active in several puzzling ways. In 1906 Hunt & Taveau (126) had demonstrated the extremely potent effect of acetylcholine on arterial pressure, and by 1914 the work of Dale (127) was already pointing so strongly to acetylcholine being the drug involved in parasympathetic action, that he described it as 'parasympathomimetic.' Direct experimental proof was lacking that a chemical substance excreted as a result of nerve stimulation would in fact activate a tissue in a similar way, although the hypotheses both for epinephrine in the sympathetic and acetylcholine in the parasympathetic system seemed highly plausible.

The direct proof came from the brilliant researches of Otto Loewi (128) in which he demonstrated that the fluid bathing a frog's heart which had been stimulated through its vagus had an inhibitory action on the beat of another heart. He named the agent 'Vagusstoffe.' From this classic observation, one of the landmarks of physiology, experimentation spread out to the examination of other tissues, other nerves, and other mediators and inhibitors, and forms one of the wide fields of today's research. With the recognition of neuroneural synapses the problem of transmission was carried from the peripheral neuromuscular system into the central nervous system.

SPINAL CORD AND REFLEX ACTIVITY

The functions of the spinal cord long remained an enigma to the early physiologists. For as long as the belief persisted that every nerve in the body required its own canal leading directly from the brain in order to insure its supply of animal spirits, the spinal cord appeared to be merely a bundle of nerve fibers grouped together. In other words, it was a prolongation of the peripheral nervous system channeling into the brain.
The relationship of the spinal cord to peripheral nerves and to the rest of the central nervous system could hardly be understood until the structure of the neuron had been learned. The period that saw the great development of knowledge of cell structure came with the high-power microscopes of the nineteenth century. Before then descriptions of the finer elements necessarily lacked exactness, though in 1783 Fontana had given a good account of the axis cylinder, and there seems little reason to doubt that the bodies Alexander Monro (129) saw in the spinal cord in 1783 were the anterior born cells. Nerve cells were certainly seen by Dutrochet (130) in 1824 though we do not find a very exact description of them before 1833, when Ehrenberg (131, 132) published his findings on the spinal ganglia of the frog.

The visualization of axis cylinders on the one hand, and of cell bodies on the other, still did not help the physiologist very much in his search for understanding of nervous connections. It was from the botanists that the next lead came. The cell theory had a long history among plant physiologists and its emphasis on the role of the nucleus and the cellular matrix appealed to microscopists who could see similar structures in animal tissues. In 1837 Purkinje (133), working at home for lack of a laboratory at the University of Breslau where he was professor, realized the significance of the observations on plant tissues and suggested that the cell theory might justifiably be extended from botany to zoology. Two years later Schwann (134) marshalled the facts and crystallized the idea in his classic monograph.

For an understanding of function, knowledge of the cell bodies was not enough. The nerve tracts were of primary importance, and during this same period histologists were finding that the medullated axon was not the only kind of fiber. In 1838, in a little book that was one of the last scientific texts to be published in Latin, Remak (135) revealed the existence of non-medullated nerves. His work is illustrated by many delicate drawings of cells from various parts of the nervous system, mostly taken from ox and man. But by 1865 physiologists knew that in addition to medullated and nonmedullated nerves there were other fibrous processes which Dieter's (136) work (published posthumously) showed to be dendrites. In the same monograph there is a description of the glia. The cell theory did not explain how all these fibrous structures related to the cell body, and a student's thesis was one of the early publications to take this step. In 1842 von Helmholtz (137), in the earliest of the many brilliant contributions he made to physiology, established the connection between peripheral nerve and ganglia in invertebrates using the crab. von Helmholtz was 21 years old when he wrote this inaugural thesis.

The next major advance came in 1850 from Waller (138) with his demonstration that axons degenerate when cut off from their cell bodies and his conclusion that the latter were their source of nutriment. The development by Marchi & Algeri (139) of the osmic acid stain for degenerating myelin sheaths gave the physiologist a technique for tracing the nerve tracts.

The definitive study of the relationship of the medullated axon to the nerve cell followed in 1889 and was the work of von Kölliker (140), professor of anatomy in Wurzburg. From this wealth of accumulated knowledge, a generalized concept of neuron behavior became possible and in 1891 a clear formulation was achieved by Waldeyer-Hartz (141). The neuron theory was established. In reviewing these basic steps that had to be taken before any unravelling of central nervous system pathways could proceed with certainty, one is struck by the fact that so many of the contributors (Schwann, Remak, von Helmholtz, Kölliker) were pupils of Johannes Müller.

Another of the early stumbling blocks to an understanding of the spinal cord was the differentiation of motor and sensory function. It was early suspected that the ganglia of the spinal roots were in some way involved in this question. Galen had thought that the ganglia of the spinal roots were in some way involved in this question. Galen had thought that the presence of a ganglion indicated that the nerve was powerfully motor in action and here the matter rested for some centuries. In 1783 Alexander Monro (129) noted that the spinal ganglia were formed on the posterior roots and that their coalescence with the anterior roots occurred peripherally to these swellings. But like Galen he thought that they were concerned with 'muscular' nerves and defended them as such against the suggestion by James Johnstone (142) that their action was to cut off sensation. This rather bizarre concept had received some consideration in the mid-eighteenth century.

The presence of ganglia suggested to several minds a specialization of function in the nerves on which they were formed. Both Prochaska (143) and Soemmering (144) had drawn attention to the

142. JOHNSTONE, JAMES (1730–1802). Essay on the use of the ganglions of the nerves. Phil. Trans. 54: 177, 1765.
semblance between the ganglia of the fifth cranial nerves and those of the posterior roots, and Bichat (145), the brilliant French pathologist who died so young, had gone so far as to associate all ganglia with the nervous processes of involuntary, unconscious 'organic' life.

The differentiation between the ganglia found in the sympathetic nervous system and those on the roots of the central nervous system was to come later. Charles Bell made the distinction but admitted he did not know what role was played by the sympathetic nerves or by their ganglia (146). His many studies on the fifth and seventh cranial nerves (146–148), illustrated by his own beautiful drawings, are classics, and his demonstrations of the function in the nerves of the face are perpetuated in the name Bell's palsy. Bichat, on dissecting out some nerve roots gave a sensory service for the skin. An Edinburgh anatomist, Alexander Walker (149), suspected that they might serve separate roles but unfortunately picked the posterior root as the motor and the anterior root as sensory.

In 1811 a small pamphlet was privately printed, entitled Idea of a new anatomy of the brain submitted for the observation of his friends. The author was Charles Bell (150). This pamphlet had no general distribution, no more than 100 copies being printed. (Only three are known to exist today, one of which is in the National Library of Medicine in Washington; in England, copies can be seen at the British Museum and at the Royal Society.) Bell stated that the purpose of this pamphlet was to assure his friends that in his dissections of the brain he was investigating its structure and not searching for the seat of the soul. In this work he stated his opinion that nerves owe their differences in properties to their being connected to different parts of the brain. He said that, holding this opinion, he wondered whether the double roots of the spinal nerves might indicate that "nerves of different endowments were in the same cord, and held together by the same sheath." To test this idea experimentally, he cut "across the posterior fasciculus" and noted that there were no convulsive movements of the muscles of the back; but that on touching the anterior fasciculus with the point of a knife, the muscles of the back were immediately convulsed. From this experiment he concluded at that time, "The spinal nerves being double, and having their roots in the spinal marrow, of which a portion comes from the cerebrum and a portion from the cerebellum, they convey the attributes of both grand divisions of the brain to every part, and therefore the distribution of such nerves is simple, one nerve supplying its distinct part."

It may be noted that there is in this pamphlet no suggestion that the posterior columns or roots might be sensory in function. Bell considered the cerebellum to be concerned with involuntary and unconscious functions ("the secret operation of the bodily frame" and "the operation of the viscera") whereas he recognized the cerebrum "as the grand organ by which the mind is united with the body. Into it all the nerves from the external organs of the senses enter; and from it all the nerves which are agents of the will pass out."

147. Bell, C. On the nerves, giving an account of some experiments on their structure and functions, which lead to a new arrangement of the system. Phil. Trans. 111: 396, 1821.
148. Bell, C. Of the nerves which associate the muscles of the chest in the actions of breathing, speaking, and expression. Being a continuation of the paper on the structure and functions of the nerves. Phil. Trans. 112: 284, 1822.
In essence, therefore, Bell regarded the cerebellum, posterior columns and posterior spinal roots as concerned with unconscious impressions and involuntary movements; the cerebrum, anterior columns and anterior roots as conveying conscious sensation and willed movements.

On July 22, 1822, François Magendie, member of the Academy of Sciences of Paris (and later to be professor at the Collège de France), read a paper (151) to the Academy as a result of which the following entry was made: "M. Magendie reports the discovery he has recently made, that if the posterior roots of the spinal nerves are cut, only the sensation of those nerves is abolished, and if the anterior roots are cut, only the movements they cause are lost." This report was followed by a fuller account (152, 153) in the journal that Magendie himself had founded. The experiments, made on puppies which survived the surgical procedures, gave Magendie the confidence to state "that the anterior and posterior roots of the nerves which arise from the spinal marrow, have different functions, that the posterior appear more particularly destined to sensibility, whilst the anterior seem more especially allied to motion."

In spite of his not having suggested a function of conscious sensation for the posterior roots in either the privately printed pamphlet or published papers (147) on the fifth and seventh cranial nerves, Bell with a questionable lack of scruple claimed full priority and engaged in a wrangle that invaded the scientific journals for many years. This carried the unpleasant flavor of evidence twisted by hindsight. Bell's 'republications' in 1824 (154) of his earlier writings contained subtle changes in wording that deceived his supporters into believing his claims to be better founded than they were. Among those hoodwinked were Flourens and, at first, Magendie's pupil, Claude Bernard. Posterity gives each some credit by serving the nomenclature of the Bell-Magendie Law. In spite of his claims, Bell made no move to get experimental proof of the function of the posterior roots and as late as 1832 (155) was stressing that their sensory nature was only inferred. He said in his lectures to the Royal College of Physicians, "... as we have proved the anterior column to be the origin of the motor nerves, we may infer the posterior roots are those which render the entire nerve a nerve of sensation." In 1844 Johannes Müller (156) confirmed the law experimentally, something Bell had never done, but the conclusion seems inescapable that the concept in its complete form as well as its experimental proof was first contributed by Magendie.

Magendie, whose youth coincided with the French Revolution, came from surgery into physiology where his urge towards experimentation could give him greater satisfaction. So strongly empiricist was he that he rarely made generalizations from his observations by

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18 For a detailed comparison of the texts see Flint, A. Considérations historiques sur les propriétés des racines des nerfs rachidiens. J. de l'anat. et de physiol. 5: 520, 1688.
in the laboratory which were many and varied. His work on the spinal roots led him to follow the differentiation of function into the spinal tracts where he found that pressure on the posterior columns, but not on the anterior, caused signs of pain. One other aspect of Magendie's work on the spinal cord should be mentioned, his rediscovery of the cerebrospinal fluid (157). Sixty years earlier this had been seen and described by Cotugno (158), at that time a young physician in the Hospital for Incurables in Naples, but his monograph had stirred no general interest though it helped to win him the chair of anatomy at the university. Magendie described the foramen known by his name, but oddly revived a valve-like role for the pineal as controller of this opening. He thought the fluid was secreted by the arachnoid membrane, and it was many years later that its origin in the choroid plexuses was discovered. A later pamphlet by Magendie (159) on the cerebrospinal fluid has some fine illustrations by H. Jacob.

Once the differentiation of function between the anterior and posterior roots had been accepted, the finer points as to which regions were innervated by their fibers began to occupy the physiologists. The question as to whether all the fibers of an anterior root served the same or many muscles was paralleled by its corollary as to whether one muscle received fibers from one or many roots. That the last arrangement is the correct one was first clearly shown by Eckhardt (160) in frogs and by Peyer (161) in rabbits. Both were working in Carl Ludwig's laboratory. The definitive demonstrations came later from Sherrington's (162) careful analyses, mostly in the monkey, from which he concluded that "the position of the nerve-cells sending motor fibres to any one skeletal muscle is a scattered one, extending throughout the whole length of the spinal segments innervating that muscle."

Tracing of the fibers of the sensory roots was intrinsically more difficult: Türck's (163) studies in Vienna had indicated the complexity of sensory innervation in the dog, and Herringham (164) had found the segmental relationship with the vertebrae; but again it was Sherrington (165) who, using the reflex as criterion of the existence of afferent fibers, unravelled the phenomena of overlapping of segmental cutaneous innervation. Until the time of Sherrington it had been thought that the motor fibers to a given muscle were derived from the same spinal segment that received the sensory inflow from the skin surrounding it. This was particularly the view of Krause (166). Sherrington's mapping of myotomes and dermatomes showed this rule to be erroneous.

Sherrington's development of a comprehensive theory of reflex action could scarcely have been envisaged before the sensory endings in muscle had been discovered. This advance was mainly the work of Ruffini (167, 168) who in 1892 identified as sensory organs muscle spindles, tendon organs and Pacinian (169) corpuscles. These structures had been seen and described by others, but their function had not been appreciated. The need for an apparatus for muscle sense had been felt by Charles Bell (170) in order to convey "a sense of the condition of the muscles to the brain," and he postulated "a circle of nerves," saying that "every muscle has two nerves, of different properties supplied to it." That sensations are aroused by

movements of the limbs is an observation that goes back at least to Descartes’ posthumous treatise (171), but that the act of volition in itself could also be ‘felt’ was an idea espoused by some, including, rather surprisingly, von Helmholtz. But a peripheral rather than a central mechanism had more adherents for, like Bichat, they thought that muscles must be sensitive.

Infiltrating the early work on spinal cord physiology is the gradual development of the idea of the reflex. The eventual emergence of a concept of reflex activity grew out of centuries of attempts to explain animal movements, motion receiving more attention than sensation for it was considered to be the sign of life. Galen had regarded movements as three in kind: natural (such as the pulse), governed by the heart; voluntary, governed by the soul (located in the brain); and unconscious movements of voluntary muscles (such as in respiration). Involuntary muscle was unknown even in the days of Fernel (172) and Descartes (173), both of whom emphasized a distinction between movements dictated by reason and those due to the appetites. The ideas of Fernel and of Descartes have both long been regarded as forerunners of the concept of reflex activity. The claims for Fernel rest on his observation of automatic movements, some of which we now know to be reflexly initiated; but the peripheral origin or the stimulus that caused them was not recognized by him. An ardent supporter of Descartes as the originator was du Bois-Reymond (174) who stressed this claim in his eulogy of Müller, written at the time of the latter’s death.

The first suggestion that perhaps the spinal cord could be a center for communication between nerves was made by Thomas Willis (175) who came very close to picturing the reflex. He thought that all voluntary movements came from the cerebrum, all involuntary from the cerebellum and that they were ruled by a soul that resided both in the blood and in the nervous fluid. For Willis the medulla was an appendix of the brain which he likened to a musical organ (30) taking air into its bellows (i.e. animal spirits from the brain) in order to blow them out into the appropriate organ pipes (the nerves). Elsewhere (176) Willis showed his interest in the organ as a musical instrument and gave some description of it.

Where Willis came close to describing reflex action was in stating that sense impressions carried by the animal spirits to the sensorium commune (which he put in the corpus striatum) went on to higher levels of the cerebrum where they were perceived and formed into memories. Some, however, were reflected back towards the muscles (‘species alia reflexa’). Although the resultant movement was automatic and although one might be unaware of the sensory stimulus, Willis held that one was conscious of the resultant muscular effect. The example he gives is irritation of the stomach causing vomiting, and it is noticeable that Willis’s discussion of ‘reflexes’ comes in his chapter on knowledge and recognition.

Willis used ‘motus reflexus’ and the verb ‘refluere’ in making this proposition and the terms were used again by Baglivi (177) who refers to him. Their usage of ‘reflexus’ reads as though it were closer to the modern term than Descartes’ ‘esprits réfléchis’. Across the centuries the changing nuances of word meanings make it impossible to catch the exact connotation intended by an author, but Descartes’ interest in the reflection of light rays suggests that this may have been the analogy he had in mind.

A mechanism for the mediation of involuntary movements was not the only one for which physiologists were searching. The early workers were much exercised by what they termed ‘the sympathy of parts’ for they recognized an integration of body mechanisms that eluded nervous influence flowing only from the brain. Some suggested an interaction taking place peripherally in a plexus, an anastomosis of the sensory and motor nerve endings. Winslow (178),

176. Ibid., chapt. 6.
177. BAGLIVI, GIORGIO (1668-1707). De fibris motoriae. 1700, book 1, chapt. 5.

12 In discussing the sensation of outward movement of an eyeball the external rectus of which is paralyzed, he says, “We feel, then what impulse of the will, and how strong a one, we apply to turn the eye to a given position.” von Helmholtz, H. Handbuch der physiologischen Optik. Leipzig: Voss, 1887, parts translated into English by William James in his Principles of Psychology.
13 Descartes used this term only once, in Passions de l’Âme.
working in Paris and later in Copenhagen, thought he had found the clue in the ganglia of the sympathetic chain. These he envisaged as small brains in which intercommunication between nerves could take place, effecting sympathy between various visceral organs. "These ganglions ... may be looked upon," he said, "as so many origins or germina dispersed through this great pair of nerves, and consequently as so many little brains." This ingenious but erroneous theory has left its name on the structures, the sympathetic ganglia. Winslow illustrated his text with the fine plates of Eustachius that had lain for so long unnoticed in the Vatican Library. These plates do not however show the 'small brains.'

In following the early ideas about 'sympathy between the parts' it must be remembered that, although so much emphasis was laid on the humors by early physiologists, endocrines were unknown and consequently their influence could not be invoked. There were, however, all down the centuries, some who held that the blood was the great integrator. In the eighteenth century, for example, John Hunter (175) was teaching that the blood was the agent of sympathy. He was drawn to this view from his work on inflammation and fevers arising from gunshot wounds in the soldiers he cared for as an army surgeon in the Seven Years' War with France.

Only slowly did the concept of reflex activity gain ground. Hunter's contemporary and fellow Scot, Robert Whytt, was accumulating observations and making experiments that are fundamental to modern physiology, although his descriptions of them are also often cloaked by his terminology. In the first place (180), he recognized the involuntary nature of pupillary contraction and dilation and demonstrated the dependence of this action on the integrity of the corpora quadrigemina, thus anticipating the work of Herbert Mayo (181) in the next century. He went on to the study of involuntary movements of voluntary muscle systems in decapitated animals. The movements of animals after their heads had been severed was common knowledge to every housewife who had ever killed a chicken and had attracted the attention of scientists since Leonardo's day. Even in the seventeenth century Boyle (182) had recognized the implications of these phenomena, realizing that "these may be of great concernment in reference to the common doctrine of the necessity of unceasing influence from the brain, being so requisite to sense and motion." Boyle's curiosity about the brain and its workings was interwoven with his great interest in theology, although his views on the latter did not please the theologians. Dean Swift was even moved to parody them in a satire called A Prior Meditation upon a Broom-stick in the Style of the Honourable Mr. Boyle.

Glisson (62) had also distinguished between 'willed' movements and those of decapitated animals. He thought the latter analogous to a class of movements depending on a lower form of perception not reaching the mind. One might become aware of them (perceptio sensitiva') but they were not ruled by the mind as were voluntary movements (perceptio perceptionis').

Whytt's experiments (183) carried the argument farther for he showed that this type of involuntary motion could not be explained as due to the innate irritability of muscle tissue (Haller's vis insita), for preservation of the spinal marrow was essential for it. He was, however, not the first to discover that the spinal cord was essential for this type of movement. He had been anticipated by the Reverend Stephen Hales, whose many and brilliant physiological experiments make one wonder how much time he gave to his parishioners in Teddington. Whytt gives full credit to Hales, for he says, "The late reverend and learned Dr. Hales informed me that having many years since tied a ligature about the neck of a frog to prevent any effusion of blood, he cut off its head ... the frog also at this time moved its body when stimulated, but that on thrusting a needle down the spinal marrow, the animal was strongly convulsed and immediately after became motionless." Alexander Stuart (184) repeated


19 Samuel Taylor Coleridge's comment on some of John Hunter's writings is perhaps a little harsh: "The light which occasionally flashes upon us seems at other times, to struggle through an unfriendly medium, and even sometimes to suffer a temporary occultation." Coleridge, S. T. Hints towards the Formation of a more Comprehensive Theory of Life. Philadelphia: Lea & Blanchard, 1848.

183. WHYTT, R. Observations on the Nature, Causes and Cure of those Disorders which are commonly called Nervous, Hypochondria, or Hysteria, to which are prefixed some remarks on the sympathy of the nerves. Edinburgh: Balfour, 1765.
184. STUART, A. Three lectures on muscular motion, read before the Royal Society in the year MDCXXXVIII. London: Woodward, 1739.
and confirmed this experiment and described it in a lecture to the Royal Society in 1738.

Whytt in his experiments on the frog came very close to defining the segmental reflex. He also noted spinal shock, for he remarked that a decapitated frog could not be made to move immediately after transection although if one waited about 15 min. it would react to stimuli. But perhaps the most striking of his observations is the one in which he anticipated Sherrington in regard to the stretch reflex. "Whatever stretches the fibres of any muscle so far as to extend them beyond their usual length, excites them into contraction about in the same manner as if they had been irritated by any sharp instrument, or acrid liquor" (183, p. 9).

With the publication of Whytt’s work physiologists were divided between regarding the movements of spinal animals as a lingering in the cord of powers originally derived from the brain, and the view that the spinal marrow itself was capable of sensation and movement. Whytt inclined to the latter view in his explanation of the writhings of decapitated and eviscerated snakes. "We are naturally led to conclude," he said, "that they are still in some sense alive, and endowed with feeling, i.e. animated by a sentient principle."

Before the end of the century, Whytt’s publications had been followed by those of Unzer (185), of Halle and of his pupil Prochaska (186) who was a practising ophthalmologist in Prague. Both these men contributed more in systematization and formulation at the conceptual level than in the addition of new experimental facts. In England, the Sydenham Society gave both their books to the same translator, Thomas Laycock (the teacher of Hughlings Jackson), and through him the word reflexion became the accepted term. Unzer postulated several sites where reflexion of impressions might take place—in the brain, in the ganglia, in bifurcations of nerves and in plexuses. Only if they reached the brain would these impressions be consciously perceived. Unzer in discussing automatic movements protected himself against the attacks encountered by some of his predecessors by saying that “the animal machines are mysteriously and inscrutably endowed by the Creator.”

Prochaska, with one foot in the past, believed in a sensorium commune where automatic reflexion took place and thought this might be in the medulla or the cord but did not agree with Unzer that reflexion might be at the level of the ganglia. He reverted to


was to regard it as a caudal extension of the brain. Legallois should be remembered for being the first to recognize clearly that the respiratory center lay in the medulla oblongata.

This was the setting of the stage for the man who lifted the whole subject of reflex activity into the framework of modern neurophysiology and into clinical science. Marshall Hall, an Englishman educated in the great school at Edinburgh where he was a pupil of the third Monro, was a successful practising physician who set up a laboratory in his own house (in Malet Street where the present buildings of London University stand). Here he worked on his animals, mostly frogs and reptiles, collating his observations (188) with those he made on patients (189). His acumen enabled him to perceive several details that had escaped his predecessors. For example, the writhings of the decapitated snake that had led Whytt to a postulate of lingering 'life' within the cord were recognized by Hall as motor responses to the renewed sensory stimuli set up by each movement.

Like Unzer, Hall in his work on the machine-like movements of decapitated animals protected himself from onslaught by stating them to be 'all beautiful and demonstrative of the wisdom of Him who fashioneth all things after his own Will.' Hall, again like Unzer, realized that the sensory impression that set off a reflex need not be consciously perceived, although he was consistently remiss in acknowledging the contributions of his predecessors. He also ignored the work of his contemporaries, for nowhere does he refer to the great blossoming of knowledge of nerve physiology that was taking place at this time and which has been reviewed in an earlier section of this essay. He seems also to have been unaware of the contractility of involuntary muscle although Baglivi (190) over a hundred years before he had made the distinction between smooth and striated muscle. Hall had many detractors who vigorously accused him of plagiarism, both from Müller and from Prochaska. The first challenge was easier to meet than the second, for Hall's earliest communication (191) antedated Müller's publication (192) on decapitated animals by one year. In the published report of this first paper,
which Hall gave to the Zoological Society of London in November 1832, there is, however, no full description of the reflex arc nor does he use these terms. The emphasis is on "a function of the nervous system ... distinct from sensation and voluntary or instinctive motion," being a "property which attaches itself to any part of an animal, the corresponding portion of the brain and spinal marrow of which is entire."

The attack was pursued by others with great bitterness and its leaders engaged in such unworthy acts as checking on library slips to prove that Hall had borrowed Prochaska's book. (The slips however postdated Hall's original publications.) To the modern worker the battle seems puerile and undignified and one regrets that its protagonists did not spend the time on experiment instead of polemics. Of the men for whom priority was being claimed, Prochaska was dead and it is noticeable that Müller, a truly great man, after making generous acknowledgement to Hall in his Handbuch stood aloof from these bickerings.

In essence Marshall Hall's major contributions to neurophysiology were, first (192), that sensory impressions coming into the medulla spinalis had far reaching effects in the nervous system in addition to the segmental effector response, secondly the recognition that although reflex activity took place at a spinal level it could be influenced by the will and thirdly, the relationship of this fact to the exaggeration of reflex response on removal of the brain (193). These are not the only areas in which he anticipated Sherrington. He gave a preliminary glimpse of the stepping reflex, "In the actions of walking in man, I imagine the reflex function to play a very considerable part, although there are, doubtless facts which demonstrate that the contact of the sole with the ground is not unattended by a certain influence upon the action of certain muscles."

Marshall Hall introduced the word 'arc' to describe the reflex pathway. Many of his other terms have, happily, not been retained by physiologists, for he was a great lover of neologisms, as his definition of the arc shows: "the existence in Anatomy and Physiology, of a continuous Diastaltic Nervous Arc including an Exotic Nerve, the Spinal Centre and Exotic Nerve in essential relation and connection with each other—and of a series of such Arcs . . ." (194). (One recognizes here that Queen Victoria had a rival among her subjects in the use of italics.)

One further contribution of Hall's at the conceptual level should be noted. Implicit, if not explicit, in the theories of the earlier physiologists was the notion that in voluntary movement volition directed a nervous influence towards the individually appropriate muscles. Hall pointed out that the will was more teleological and less specific in its action and not "directed to any muscle or set of muscles, but to an aim, object and purpose of their contraction" (195). Hall's contributions were not evaluated as highly by his contemporaries as they have been by later physiologists, though he himself had no doubts as to how they should be ranked; he stated that they were the greatest advance in medical science since William Harvey.

The impact of the work of the physiologists on the concepts of the psychologists was very great and so disturbing that their literature was filled with controversy for many years. Long before the concept of reflex activity was carried into the brain by Sechenov to explain its higher functions, the psychologists were in distress over the implication for 'sensation,' for 'consciousness' and for 'volition,' of the developing knowledge of spinal reflexes. The most conspicuous controversy was that waged between Eduard Pflüger (196), von Helmholtz's successor at the Physiological

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192. HALL, M. On the reflex function of the medulla oblongata and medulla spinalis. Phil. Trans. 129: 635, 1833.

193. HALL, M. On the true spinal nerves, and on the excitatory system of the nerves. Lectures given before the Royal Society, privately printed, 1837.


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18 Such as, for example, George, J. D. Contribution to the history of the nervous system. Lond. med. Gaz. 22: 40, 93, 1837-1838.

19 A full account of the controversy (though scarcely an unbiased one) can be found in Longet, F. A. Traité d'Anatomie de Physiologie du Système Nerveux de l'Homme et des Animaux Vertébrés. Paris, 1842. 2 vol.

20 "But the operation of the reflex function is by no means confined to parts corresponding to distinct portions of the medulla. The irritation of a given part may, on the contrary, induce contraction in a part very remote." Phil. Trans. 123: 635, 1833.

21 The true spinal system is susceptible of modification by volition . . ." Memoirs on the Nervous System. London, 1837, part 2, p. 73. (This part of the observation was anticipated by Wivitt.)
Institute at Bonn, and Rudolph Lütze (197), professor of Philosophy at Göttingen. Back and forth the battle raged, swinging from physiology into metaphysics and back again into experiment. The arguments all centered around the problems of whether a spinal animal was sentient and conscious, and whether its movements were purposeful. Was such an animal intelligent? Did it have memory? Pfüger espoused the idea of consciousness in the cord, Lütze denied it; both were dogmatic but to neither can we look for advancement of knowledge of the central nervous system in this context.

In the nineteenth century, while Marshall Hall was still alive, the nature of inhibition became of major interest to physiologists and before the end of the century was to have its role in reflex activity demonstrated by Sherrington. Although the possibility of inhibition had been suggested by several workers, the actual phenomenon had first been observed (and rejected as an error of experiment) by Volkmann (198) in 1838 in relation to the action of the vagus on the heart. It was again observed, and this time accepted, by the Weber brothers (199) in 1845. The elder brother, Ernst, held the joint chair of anatomy and physiology at Leipzig until Carl Ludwig came in 1866 to take over the latter section and set up his famous institute. The technique of the classic experiment that established the existence of vagal inhibition was the stimulation by a voltaic pile of both vagi of the frog. Later the Webers found that unilateral stimulation had the same effect and they confirmed the result by stimulating the vagus of a cat with an induction current. They reported this discovery, one of the landmarks of nerve physiology, at the Congress of Italian Scientists held in Naples in 1845 (which accounts for their publication being in Latin rather than in German). This type of inhibition, like that which was eventually evoked to explain Bernard’s (200) observation of the influence of the chorda tympani on the submaxillary blood vessels, seemed simple to later physiologists faced with the complexities of inhibition in the central nervous system. These had to await exploration by Sherrington.

An enduring interest of Sherrington and one exhaustively explored by him in the laboratory was reciprocal innervation of antagonist muscles, and many of his publications were on this subject. The attempt of Descartes (25) in the seventeenth century to reach an explanation based on channeling of vital spirits had no immediate successor. In the early part of the nineteenth century Charles Bell (201) had postulated the existence of peripheral inhibition by insisting on the need for nerves which had the opposite of an excitatory effect on muscle. “The nerves,” he said, “have been considered so generally as instruments for stimulating the muscles, without thought of their acting in the opposite capacity, that some additional illustration may be necessary.” He went on to describe an experiment in which contraction of a flexor muscle coincided with imposed relaxation of its opponent extensor.

The possibility of a peripherally exerted inhibition of muscle contractility attracted many people at about this time. One of the earliest was a Dr. West (202) of Alford in Lincolnshire (who had heard Bell’s lectures at the Royal College of Surgeons). West’s suggestion was that contraction was an inherent property of muscle and that the action of the nerve supplying it was not to evoke, but to ‘restrain’ or ‘rein’ this innate tendency to contract. He explained a voluntary contraction as a withdrawal of this nervous restraint “so as to allow the peculiar property of muscular fibre to shew itself.” The publication of West’s hypothesis provoked some expostulation, one anonymous correspondent saying this was “certainly one of the clumsiest contrivances that nature was ever accused of.” The mechanism of rigor mortis was not understood at this time and West felt that his theory offered a possible explanation. The idea was also present in the arguments of many others; for example those of Engel (203), of Stannius (204) and of Dugès.
Q ui l'dricana u òciàu lac l J a m ttii.'Figura Mufculi fsctmdum autographum Dos Cartes delineata.

FIG. 23. Left: Descartes' sketch of reciprocal muscles of the eye (De Homine, the Latin translation by Schuyl). Center: a redrawing showing closure of valves on relaxation, opening on contraction to allow animal spirits to flow in and swell the muscle (L'Homme, the French edition of 1677). Right: Sherrington's diagram of the connections and actions of two cells of a dorsal root ganglion. The plus sign indicates that at the central synapses the afferent impulses excite the ipsilateral flexor muscle and the contralateral extensor, while inhibiting the ipsilateral extensor and the contralateral flexor muscle. (From Sherrington, C. S. The Integrative Action of the Nervous System, 2nd ed. Cambridge: Cambridge, 1947.)

In 1868 Hering (206) and Breuer (207) found in the respiratory system a parallel to Bell's experiment whereby distention of the lung acting through the pulmonary branch of the vagus inhibited inspiration while exciting expiration, the well-known Hering-Breuer reflex. And in 1883 Kronecker (208) working on the swallowing reflex in Ludwig's laboratory with his American pupil, Meltzer, demonstrated the inhibitory action of the superior laryngeal nerve on inspiratory muscles during contraction of expiratory ones. The reflex nature of swallowing had been recog-

ized by Marshall Hall (195) in 1823 and the direct afferent nerve for it had been identified by Magendie (209) to be the glossopharyngeal, but the reciprocal effect had not been noted by them.

It is the fact that there are no inhibitory nerves to vertebrate skeletal muscle that drew the whole subject of reflex inhibition into the central nervous system. With the realization that reflex inhibition had its site in the central nervous system, attention was turned to the connection between the incoming sensory element of the arc and the motor component, to the junction between them, in other words, to the synapse (Sherrington's word). That there might be an interaction of a synaptic kind between neurons in the periphery had occurred to several workers, one among whom was Sigmund Freud (210). His work on fresh-water crabs and his illustrative sketches of how he conceived of intercommunication between the axons of their ganglia came close to what is now termed an ephapse, although he pictured transverse crossings that suggest a uniting of fibers rather than a contiguity.

Recognition of the synapse could come only after the neuron theory had replaced the reticular theory. According to the latter, strongly championed by von Gerlach (211), nerve cells were connected with each other by a diffuse fibrillary network forming an anastomosis. This hypothesis received support from Golgi (212), although it was his silver staining technique in the hands of Ramón y Cajal (213) that finally disproved it, for Ramón y Cajal established that both axons and dendrites had free endings. Together they shared the Nobel prize in 1906, Golgi devoting his address to an attack on the neuron theory that his fellow prize winner had done so much to uphold. In modern times, the synapse (an abstraction) is having to be remodelled in the light of what the electron microscope is revealing.

The nature of central inhibition, a still incompletely resolved issue, has evoked many hypotheses. Among them, those depending on mutual interference of impulses at the effector component of the reflex arc form one class. An example is the schema suggested by Rosenthal (214) in 1862 to explain the effect of efferent vagus fibers on the respiratory center. He proposed that an efferent system excited into action by one nerve could have the pulsating rhythm of its nervous supply disturbed by inflow from another nerve, the result being a redistribution of previously grouped impulses into more frequent but less powerful (and hence inadequate) discharges. Lack of evidence for a pulse-like time-rhythm in nerve trunks led to the rejection of this hypothesis by Wundt, Sherrington and others.

In the 1870's and 1880's attempts to explain inhibition on metabolic effects depending directly on the cell's response to stimulation being an assimilation of chemical nutrients were espoused by Gaskell (215).


(for the vagus) and Hering (216) (for black-white sensations of the visual sense), by Verworn (217) (in his Biogenhypothesen). The hypothesis did not survive for long. As Forbes (218) said in his critique, "To assume that increase of anabolism necessarily implies decrease of catabolism, is to suppose that increasing a man's salary ensures decrease of his expenditure." A theory of immobilization of ion transfer during inhibition was proposed by Macdonald (219) in 1905, at a time when the release of potassium from injured nerves was receiving considerable attention.

With the discovery of the refractory period in nerve [by Gotch and Burch (220) in 1889] there was some tendency to regard block of conduction due to excitatory impulses arriving during refractoriness caused by preceding excitation to be the mechanism of inhibition. This is now recognized as a misuse of the term, and in fact Sherrington's demonstration that after discharge persisting after cessation of excitation could be cut short by inhibitory nerve action was an early salutary corrective.

In the course of researches on the inexhaustibility of nerve, a subject which engaged the early electrophysiologists, Wedensky (221) found that a rapid series of strong stimuli would fail to produce more than a single twitch if the transmission from nerve to muscle were blocked either by fatigue at the end plate or by artificially impairing a section of the nerve by narcosis. If however the frequency or the strength of the tetanus were then reduced, the muscle went immediately into tetanic contraction. Wedensky concluded that the nerve was inexhaustible and that the phenomenon was one of inhibition. This may, however, be regarded as a special usage of the term since the effect he observed was merely a characteristic of the relative refractory period of nerve and its time course as related to strength of stimulus (222).

It was Sherrington's insistence on a central site for the inhibitory mechanisms of skeletal muscle that emphasized the reflex nature of inhibition. The contributions of Sherrington and his school are the basis of modern ideas of the reflex at the spinal level. A great number of findings (229-227) made by Sherrington and brought together into a unifying explanatory scheme included the following major observations: that postural tonus of a muscle is dependent not only on efferent nerves but on afferent nerves from that muscle itself, the stimulus to the latter being from stretch receptors [the myotatic reflex (223)]; that decerebrate rigidity (224) is an exaggerated muscle tonus in the antigravity muscles—a reflex standing ['an harmonious congerie of stretch-reflexes' (225)]; that the afferent nerve from a given muscle can elicit a contraction in that muscle itself (226), without involvement of the opposing muscles of the joint,26 that the main stimulus for the stepping reflex (227) does not come from contact of the foot with ground, as might be expected,28 that stimulation causing flexion in one


26 From a series of 14 articles by Sherrington on reciprocal innervation stretching over the years from 1893 to 1909 (and developed in many other of his writings), the following excerpt may be quoted as one of his crucial experiments: "All the nerves of the limb being severed, except those of the vasti and sartorius, the animal is inverted and the knee then gently but fully extended by raising the foot, the thigh being held vertical. The foot is then released, the anticus falls, and in doing so is seen to be suddenly checked by exciting a contraction of the extensor of the knee. This contraction is different from a knee-jerk, for it only slowly passes off." Sherrington, C. S. Proc. Roy. Soc., London, ser. B 76: 283, 1905.
28 "... in the intact animal (cat, dog), severance of all the nerve trunks directly distributed to all four of the feet up to and above the wrists and ankles impairs walking so little as to make it highly unlikely that the loss of receptivity of the feet destroys any large factor in the reflex basis of these acts" (235).
limb frequently evokes an extensor movement in the contralateral homologous limb [the crossed-extensor reflex (229)]; that this reflex can also be centrally inhibited; and that after prolonged inhibitory stimulation there is, on withdrawal of the stimulus, an increase of contraction ['reflex rebound' (230)]. These are only a few of the reflex phenomena that received elucidation through Sherrington's work.

Out of a vast number of laboratory experiments grew his unifying hypothesis of reflex excitation and reflex inhibition, and hence of an interdependence of reflex arcs resulting in an integrative action of the nervous system. Sherrington's classic book bearing this title was published (231) when he was Professor of Physiology at Liverpool University and was based on lectures he gave at Yale University. The concepts of 'the final common path,' of 'synaptic connections,' of 'central inhibition,' of 'central excitation' and of 'reciprocal innervation' are incorporated in modern physiology which recognizes its debt to Sherrington.

The nineteenth century which had opened with only one method for tracing fiber tracts—that of dissecting them out as Bichat had done—gave to physiologists two great new tools, the histological method of Wallerian degeneration and the technique of electrical recordings. In the hands of Victor Horsley and his associates, Gotch, Beever, Schäfer and others, electrophysiology of spinal-cord systems made great advances which can be followed in the series of papers published in the Philosophical Transactions between 1886 and 1891. An overall view of what could be achieved by this new method is given in the Croonian Lecture of Gotch and Horsley in 1891 (232).

Towards the end of the century these techniques were being applied, not only by Horsley, but by many of his contemporaries to the study of the physiology of the brain.

PHYSIOLOGY OF THE BRAIN: DEVELOPMENT OF IDEAS AND GROWTH OF EXPERIMENT

At the mid-eighteenth century, scientists seeking knowledge of the brain could look back on a history of their field that revealed a gradual evolution of anatomical knowledge about its structure but only conjecture about its physiology.

Among the early Greeks the teachings of Plato had placed man's rational faculties where we would put

them now, in the head; the passions he put in the
spinal marrow relating them to the heart, and the
lower appetites were given a place in the cord below
the diaphragm where they could play upon the liver.
For Plato these were the divisions of man's tripalite
soul.

Under the influence of Galen the spinal nervous
system lost this position of importance, for according
to his doctrine other organs of the body, the liver
and the heart, were the primary sites for manufacture
and transmutation of the spirits. From the Islamic physi-
cians came the emphasis on three ventricles with
different functions, an anterior ventricle being the
receiver of all incoming spirits, a 'sensus communis,'
whereas a posterior ventricle formed the reservoir for
the outflow of animal spirits to all muscles through
their nerves. In a middle ventricle was to be found
man's reason. Similar ideas about triple cavities in
the brain and their allotted functions were generally
accepted throughout the unenlightened middle ages
until finally an anatomist, no less a man than Leo-
nardo da Vinci (233), mapped the true shape of the
ventricles by pouring into them melted wax to form
a cast.

Throughout the sixteenth and seventeenth cen-
turies, the structure of the brain was being unfolded
by the anatomists but still without a parallel investi-
gation of function. It was the cranial nerves that
yielded first and Galen's seven pairs26 (accepted on
his authority for 1400 years) swelled to nine in the
seventeenth century. In 1660 Schneider (234) iden-
tified the olfactory pair and 2 years later Willis (235)
dissected the accessory nerve that bears his name.
Today's recognition of 12 pairs of cranial nerves dates
from the eighteenth century and the work of von
Soemmering (236), whose books are illustrated by
engravings rivalled only by those of Charles Bell.
von Soemmering wrote copiously on anatomy, illus-
trating some of his work by his own hand and some
by the drawings of his pupil Koeck.

The role played by each pair of cranial nerves was
still in some degree obscure, for some nerves appeared
to have more than one function, and Whytt (237)
was one of the early workers to observe how complex
their action might be. He found that the optic nerve


236. SORMMERING, SAMUEL THOMAS (1755-1830). De basi en-
cephali et originibus nervorum cranio egredientum. Gottingen:
Vandenhoeck, 1778.
237. Whytt, Robert (1714-1766). An essay on the vital and
other involuntary motions of animals. Edinburgh: Hamilton,
Balfour and Neill, 1751.

26 According to Galen's numbering, the seven pairs of cranial nerves were: 1) optic; 2) oculomotor and abducens taken together; 3) and 4) were both parts of what is now called the trigeminal; 5) facial together with the auditory; 6) the glossopharyngeal, vagus and accessory nerves; 7) the hypoglossal.
tive anatomy and noted that “the filaments or little strings” of the organ of smell were “more remarkable in hunting Hounds than in any other Animal whatever.”

The nerves that had both sensory and motor branches proved the most difficult. Magendie (238) at first thought the fifth nerve was sensory and nutrient to the face, and the seventh nerve entirely motor, since cutting it caused facial paralysis without relieving neuralgia. In 1820 Charles Bell (147), dissecting the nerves of the face, noticed that the fibers of the seventh nerve went to muscle whereas those of the fifth entered the skin. He suspected they served different functions, and being himself an anatomist rather than an experimentalist, asked his brother-in-law, John Shaw, to make a study of the effect of sections of these nerves. Using an unusual experimental animal, the donkey, Shaw was able to demonstrate paralysis in the one case, loss of reaction to touch in the other; neither he nor Bell whose fine drawings illustrate his findings recognized the mixed nature of these nerves. After this beginning several workers added their contributions to the further clarification of the cranial nerves, prominent among these being Mayo (239) (who taught the course in anatomy and physiology at King’s College, London).

It was only in the eighteenth century that doubt was first thrown on the assumption that the sympathetic trunk (or ‘intercostal’ nerve, as it was then called) was an appendage of the brain. This grew from the transection experiments of Pourfour du Petit (240) and his observations on contraction of the pupil. For centuries anatomists had shown this nerve as stemming from the brain. Vesalius (7), in his drawings of the human nervous system, put it in one trunk with the vagus. (In the dog, though not in man, the two nerves lie in the same sheath in the neck region.) Eustachius (241) separated the two, but like many after him, including Willis, he depicted an intracranial origin. These drawings of the anatomists must have been designed to be consistent with Galen.

FIG. 27. Thomas Willis and the illustration of the base of the brain taken from his book De cerebri anatome. The circle of Willis, named for him, had been depicted by several anatomists before him. Willis was fortunate in having Christopher Wren as his illustrator.

was not solely concerned with vision but that it carried the stimulus that led to the contractile response of the iris to light. In the post-mortem examination on a child with fixed pupils he found a lesion blocking the inflow from the optic nerves to the thalamus and inferred that this impairment of sensory inflow was responsible for the motor deficit that had been the clinical sign. This was indeed the recognition of a reflex arc, and the pupillary reflex was for many years known by his name.

As noted above, Willis had dissected the spinal accessory nerve to its junction with the cord but he believed it to convey voluntary control. Lacking a scientific acumen equal to his skill as a disector, and influenced by Galen, he thought this nerve anastomosed with the vagus (the ‘wandering’ nerve). Schneider, on the other hand, had no doubts as to the action of the olfactory nerves for it was his work on the nasal mucosa and olfactory processes that led to his identification of them. Willis also was aware of their function for he called them the ‘smelling’ nerves. He noted that within the skull they had ‘mammillary processes’ and said, “As to the Fibres and Filaments or little strings stretching out from the more soft nerves through the holes of the Sieve-like Bone into the caverns of the Nose, these are found in all Creatures who have the mammillary Processes: so it is not to be doubted, but that these Processes, with this appendix and its medullary origine is the Organ of Smell.” Willis called in his knowledge of compara-

238. Magendie, F. J. physiol. expér. et path. 4: 176, 302, 1824.

27 The quotations are from Pordage’s translation (1684) of Willis, T. Cerebri anatome: cui accessit nervorum descriprio et usu. London: Flesher, 1664.
A marked advance in understanding the physiology, not only of the cranial nerves but of the brain itself, came when techniques were developed for ablating and stimulating parts of the central nervous system without the animal succumbing to the procedures. The surgery in the early attempts was frequently so drastic that results were rarely specific. For example, the experimental results of Willis that confirmed his belief in the cerebellum as a vital center were probably due to his animal's having succumbed to injuries near the fourth ventricle. Other early experimenters such as Duverney (246) with his pigeons, Chirac (247) and Perrault (248) with their dogs had to be satisfied with very brief durations of survival.

At the opening of the nineteenth century interest in localization of cerebral function had been widely stirred by the lectures of Franz Gall (249) in Vienna. Unfortunately Gall's reputation as a phrenologist has overshadowed his more important work on the fiber tracts of the white matter of the brain, work which clarified the previously contradictory ideas as to the anatomy of the commissures and of the pyramidal decussation. But, while his contemporaries were concerning themselves with sites for sensory and motor functions, Gall was proposing localization of mental faculties and he may be regarded as a pioneer in emphasizing the importance of the grey matter for intellectual processes. It was when, together with his pupil, Spurzheim (250), he proceeded to assign separate 'organs' in the brain to the different mental faculties and to relate these to bumps on the skull that he began to be challenged. All the same, in spite


Fig. 28: Above; Gall and Spurzheim's map of a skull with certain areas marked for correspondence with different mental acuities. Below, for comparison; Gall's skull on the left, that of Spurzheim on the right. Although Gall's own ideas were channeled into phrenology, they were influential in directing interest to the study of cerebral localization. (The skull of Gall is in the Musée de l'Homme in Paris and is reproduced here by the kindness of Dr. Ardvège; that of Spurzheim is in the Warren Museum at the Harvard Medical School, and has been photographed by permission of Dr. P. I. Yakovlev.)
of its bizarre concepts, phrenology had a surprisingly wide acceptance for a considerable period even among the medical profession. It was to the psychologists (although that term was not yet in use) that phrenology particularly appealed, for it was the first major consideration of mental characteristics as attributes of brain function.

One of the more prominent men to attack Gall's doctrines was Flourens who made a sweeping rejection of all such ideas, denying the brain any discretely localized action. But Flourens' monograph (254) appeared some years after the deaths of Gall and Spurzheim both of whom had built up comfortable careers out of their speciality. Flourens recognized three major functional regions of the brain (the cerebral hemispheres, the medulla and the cerebellum), but within these entities he envisaged their action as global and their roles as being sensory, vital and motor, respectively. Concerning the cerebral hemispheres he said that animals that survive their removal "lose perception, judgment, memory and will... therefore the cerebral hemispheres are the sole site of perception and all intellectual abilities" (252). He did not hesitate to infer subjective qualities and faculties. In one of the more renowned of his experiments (253) he had kept a pigeon alive after removal of its cerebral hemispheres. The bird was 'blind' and 'deaf' and appeared to be asleep although it stirred when poked. Flourens went so far as to say that the bird lost its volition and "even the faculty of dreaming." He noted that it retained the sense of equilibrium and that its pupils still reacted to light. Others repeating Flourens' experiments were unconvinced, for their decerebrate pigeons could be startled by a loud noise and could avoid obstacles.

Since sudden death followed section of the medulla, Flourens concluded that here lay the essential mechanism for respiration and the maintenance of life. In this conclusion he had of course been anticipated by Legallois. Much of Flourens' fame as an experimentalist derived from his observation that extirpation of the cerebellum (in birds and mammals) caused loss of coordinated movement. Flourens, whose interest lay so deeply in the elucidation of the control of voluntary movement, was himself to suffer paralysis for a long period before his death.

In the 1820's when Flourens was pursuing these experiments, many workers were 'mutilating' animals (to use Gall's phrase) (254), and some jockeying for priority was inevitable. Most of Flourens' observations, particularly those on the cerebellum, had been anticipated by Rolando at Sassari, whose treatise (255) of 1809 (written in the Italian language and printed and illustrated by himself) was therefore republished in French in an abbreviated form in 1824 (256).

Rolando did not succeed in keeping his animals alive. Even his tortoises died after removal of their brains, although Fontana who had been successful with these animals showed him his own technique. Many of Rolando's conclusions (257) were therefore incorrect since he mistook surgical shock for paralysis. Less ruthless extirpations, of the hemispheres only, he found to be compatible with life. Rolando believed the cerebellum to be a kind of 'voltaic pile' and the source of all movement. Flourens thought it merely the regulator. Magendie (258) disagreed, holding cerebellar function to be maintenance of equilibrium.


253. FLLOURENS, P. Arch. gén. de méd. 2: 321, 1823.


255. ROLANDO, LUIGI (1773-1831). Saggio sopra la vera struttura del cervello dell' uomo de' degli animali e sopra le funzioni del sistema nervoso. Sassari, 1809.


He reached this conclusion from studying the disturbance of gait in a duck\(^{25}\) from which he had removed the cerebellum unilaterally. He followed these experiments with bilateral destructions and noticed forced movements. The great contribution towards our modern knowledge of cerebellar mechanisms came from Luciani of Florence whose book *Il Cervelletto* (259) is a classic, as is also his textbook of physiology (260).

Magendie in the observations he made on decerebrate animals (261) anticipated Sherrington by an accurate and detailed description of decerebrate rigidity in rabbits. This was in the days before the discovery of anesthesia and Magendie was severely criticized for his practice of vivisection. But extirpation experiments on animals could give no clue to the cortical representation of speech. This had to come from clinical observation with studies at autopsy. Gall had placed language in the anterior lobes and the first clinical reports seemed to confirm this. In fact, the great surge of work aiming to establish localized centers in the human brain began with the speech center. In his studies of encephalitis Bouillaud (262), a pupil of Magendie and later Professor of Medicine, had reasoned that the anterior lobes of the brain were necessary for speech and went on to observe that other focal lesions of the brain caused localized im-

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**Fig. 30.** Left: Magendie’s technique for sectioning the fifth nerve in the living rabbit. The dissection is to demonstrate the insertion of his instrument. On the rabbit’s right, the probe is seen entering the base of the skull and reaching the trunk of the fifth nerve at H. On the animal’s left, the end of the instrument is seen at E and the sectioned nerve at G. (From: Bernard, C. *Leçons sur la Physiologie et la Pathologie du Système Nerveux.* Paris: Baillière, 1858. Right: pigeon deprived of its cerebral hemispheres in position described by Flourens. (From: Luciani, L. *Human Physiology,* English ed. London: Macmillan, 1915.)
pairment of muscular movement. The cause of cerebral localization was taken up by his son-in-law, Auburtin (263), who predicted that a lesion would be found in the anterior lobes of an aphasie patient who was at that time in the hospital of Bicêtre under the surgeon Pierre Broca. Autopsy confirmed Auburtin’s prediction, pinpointing the lesion in the left anterior lobe. The next aphasie patient on Broca’s service was found at autopsy to have an even more discrete lesion—in what is known to this day as Broca’s area (264). The name of Auburtin has been forgotten, as has Broca’s term ‘aphemia’ for aphasia.

Broca’s speech area (the left third frontal convolution) which he thought to be concerned with articulation was to be challenged by Pierre Marie (265) in the twentieth century, but the new concept of cerebral localization developed like a wave in the later 1800’s—a wave that is only now beginning partially to recede. For the physiologists the impressive experiments were those of Goltz of Strasbourg who, after starting with frogs (266), mastered the technique of keeping warm-blooded animals alive for prolonged periods after drastic extirpations of large portions of their brains (267). Three of his dogs became famous. The first two survived 57 and 92 days respectively, the third being purposely sacrificed at 18 months. Goltz exhibited them at international congresses, killed one of them before an audience and gave their brains to Langley in Foster’s laboratory to dissect (268, 269). Sherrington’s participation in the necropsy of one of these dogs was the subject of his first published paper (in 1884) (270). All who witnessed the remarkable degree of retention of sensibility and


268. LANGLEY, J. N. Report on the parts destroyed on the right side of the brain of the dog operated on by Professor Goltz. J. Physiol. 4: 286, 1889.

269. LANGLEY, J. N. AND A. S. GRUNBAUM. On the degeneration resulting from removal of the cerebral cortex and corpora striata in the dog. J. Physiol. 11: 606, 1890.

mobility by these animals and who later studied the necropsy findings from the Cambridge laboratory were astounded, and there can be no doubt that these experiments gave a great impetus to neurosurgical procedures in animals and in man.

The physiology of the brain was now beginning to unfold and to reveal itself in dynamic terms after centuries of static representation in the two-dimensional pages of the anatomy books. To clinical observation of impairment by disease states, three experimental techniques were added: regional ablation, stimulation (both mechanical and electrical) and eventually the recording of the brain's own electricity.

Mechanical and chemical irritation of the cortical surface had suggested itself to many investigators down the years, some of the attempts reaching the extremes of the bizarre (see, for example, fig 32). Cabanis (271), the celebrated physician and idéologue, had provoked convulsive movements in muscle groups that seemed to vary with the region irritated. Earlier, Haller (272), searching for irritability, had pricked the brain and applied irritating fluids and concluded that the grey matter was insensitive to stimulation and that the white matter was the seat of sensation and the source of movement.

The Italian physiologists had been more successful. The Abbé Fontana (273) and Caldani (274) (Galvani's predecessor in the chair of anatomy at Bologna) had convulsed their frogs by electrical stimulation inside their brains. Rolando (255), following their lead, extended his experiments to pigs, goats, sheep, dogs and also to birds. The influential Magendie however had failed and had proclaimed the cortex electrically inexcitable; an opinion in which he was backed by Flourens (252). In these days before the neuron had been recognized as the unit of the nervous system, before the pyramidal fibers were known to be processes of cortical cells, there was no a priori reason to expect electrical stimulation of the cortical surface to have a peripheral effect, but soon an incontrovertible proof was to be given.

The pioneers were Fritsch & Hitzig (275) (two young privatdocents in Berlin) with their now famous experiments in which they used a galvanic current and from which evolved the idea of a 'motor cortex.'

Ferrier (276–278), a few years later, in a long series of experiments using faradic stimulation in monkeys was able to bring out not merely muscle twitches of an indeterminate kind but also grosser movements. Of course, as we now know, these are imprecise and even athetoid in comparison with movements made by the animal naturally. Benefitting from the parallel development of electrical techniques, Victor Horsley, in a series of papers with Beevor (279, 280) in the next decade, described more closely the motor areas in the monkey cortex. From these experiments there emerged the designation of the precentral gyrus as predominantly motor in function and the postcentral as sensory. Between the two, Beevor & Horsley (281, 282) recognized an area which they called 'the zone of confusion.' An important point that emerged from their use of this technique was that in addition to areas of maximal representation of a given movement, the cortex also has marginal zones that are less specific. In other words, they found no sharp demarcation lines.

With Schaefer (283), Horsley went on to further studies of both motor and sensory function, using ablation as well as electrical excitation. The basic interest was of course in the application of these findings to man, especially in the light of the observations of Hughlings Jackson on the march of symptoms during the epileptic fit (284). Species differences came markedly to light when Beevor & Horsley compared their findings on the bonnet monkey with those in the orangutan. The first pioneers to attempt electrical stimulation of the cortex in man (through holes in the skull) were Bartholow in America in 1874 (285) and Sciamanna 8 years later in Italy (286). These were followed by Keen (287), in his youth an army surgeon in the American Civil War and later professor of surgery at Jefferson Medical College. In 1888, in a patient whose seizures began in the hand, he removed the area the stimulation of which caused movements of the wrist. He used a 'faradic battery,' and with it found areas for hand, elbow, shoulder and face movements. When respiration and circulation became poor, he revived the patient with brandy injected into the forearm. In the same year several other workers applied a similar technique in man but the internal capsule of the bonnet monkey. Phil. Trans. 181: 49, 1890.

282. BEEVOR, C. E. AND V. HORSLEY. A record of the results obtained by electrical excitation of the so-called motor cortex and internal capsule in the orang-utan. Phil. Trans. 181: 129, 1890.


287. KEEN, WILLIAM WILLIAMS (1837–1932). Three successful cases of cerebral surgery including (1) The removal of a large intracranial fibroma; (2) Excision of damaged brain tissue; and (3) Excision of the cerebral centre for the left hand; with remarks on the general technique of such operations. Am. J. M. Sc. 96: 329, 452, 1888.
systematic exploration had to wait for Cushing, Foerster and Penfield in the modern age of neurosurgery, and for the development of clinical neurophysiological investigation.

In the light of clinical observation and the results of electrical stimulation, the concept that the cortical grey matter acted as a whole and that motor function had no representation above the basal ganglia began to crumble. At this same period, the birth of a new technique brought yet another method of approach for the investigator. This was the recording of brain potentials evoked by sensory stimulation and the discovery of the brain's own electrical activity, the dawn of electroencephalography.

In 1875 Richard Caton (288), at the Royal Infirmary School of Medicine in Liverpool, while searching for the cerebral counterpart of du Bois-Reymond's action potential in nerve, not only found it, but noticed that when both of his electrodes lay on the cortical surface there was a continuous waxing and waning of potential. This oscillation of the base line was present in the unstimulated animal and Caton proved it to be unrelated to respiratory or cardiac rhythms. He also proved these fluctuations to be biological in origin by showing them to be vulnerable to anoxia and to anesthesia and to be abolished by death of the animal. In his first work Caton's experimental animal was the rabbit and his detecting instrument was a Thomson's galvanometer. This was in the days before photographic recording of laboratory observations and Caton's first publication of his findings took the form of a demonstration before the British Medical Association (289). Superimposed on these oscillations Caton found potential swings related to sensory stimulation and realized immediately the meaning of this for cerebral localization studies. Caton went on to use monkeys and gave further reports of his results in 1877 and in 1887 (290), the latter at the International Medical Congress held that year in Washington, D. C.

Strangely enough, in spite of the prominent groups before whom Caton gave his demonstrations and the popular medical journal in which he reported them, his work received little attention at the time, even among English-speaking physiologists. Meanwhile in Poland, a young assistant in the physiology department of the University of Jagiellonski in Krakow, 289. Caton, R. Interim report on investigation of the electric currents of the brain. Brit. M. J. 1: Suppl. 62, 1877.
Adolf Beck, not knowing of Caton's work 15 years earlier, was searching initially for the same phenomenon, namely for electrical signs in the brain of impulses reaching it from the periphery. Like Caton before him he succeeded, but he also found the brain wave. His animals were mostly dogs and he published the protocols of all his experiments in the Polish language for a doctoral thesis (291). In order to reach a wider audience he sent a short account to the most widely read journal in Germany, the Centrallabl für Physiologie (292). A spate of claims for priority for finding sensorily evoked potentials followed the German publication of Beck's findings—the first coming from Fleischl von Marxow, Professor of Physiology in Vienna (293), and the next from Gotch and Horsley (294). It is noticeable that it was the electrical response of the brain to sensory stimulation that drew the most interest, for this was a finding that lay directly in the main stream of current thinking about cortical localization of function. The completely novel idea of a continuously fluctuating electrical potential intrinsic to the 'resting' brain was, at that time, of interest only to its two independent discoverers, Caton and Beck.

The somewhat acrimonious wrangle over priority was based in Fleischl von Marxow's case on work done in 1883. This had not been published but only noted down in a sealed letter which he had deposited with the University and which he asked to have opened after reading Beck's report in 1890. He was solely concerned with response potentials and noted "little or no movement of the base line." He was clearly unaware of Caton's reports and demonstrations. Gotch and Horsley's ignorance of their countryman's work is less easily understood. Caton was a prominent figure at Liverpool, the first holder of the Chair of Physiology in which Gotch was to follow him (and later Sherrington).

The dispute in the columns of the Centrallabl over priority for discovery of the electrical currents of the brain was finally stilled by a letter from Caton (295), drawing the attention of the protagonists to his publication of 15 years earlier. By the turn of the century the electrical activity of the brain had reached the textbooks (296). Caton's interests had developed along many lines and he became prominent in several fields of medicine and scholarship as well as in public affairs, becoming in turn President of the Medical Institution and Lord Mayor of Liverpool. Beck (297), who at the age of 32 became professor of Physiology at the University of Lvov, continued to work on the subject into this century, publishing with his old professor Cybulski, and interest was thereby aroused in Germany and in Russia. He met a tragic death during the German occupation of Poland.

Interest became widespread in 1929 with the first publication on brain potentials in man. In that year Hans Berger (298), a psychiatrist in a hospital in Jena, revealed to the scientific world the results of work he had been pursuing in secretive seclusion for over 5 years. He had repeated and confirmed the findings of Caton (to whom he gave full credit) and had extended them to man. He studied (and named) the electroencephalogram in normal man, finding the two major rhythms, alpha and beta, that Nemini-nski had found in dogs (299). He applied Caton's tests for the biological origin of the potentials he found, showing them to be affected by hypoxia and by anesthesia. He also found them to be changed by sleep.

Berger's outstanding contribution was the foundation of clinical electroencephalography. Having proved that brain waves could be recorded in man through the unopened skull, he went on to demonstrate that their characteristics could be used as an index of brain disease and thus he opened up a new line of approach for the physiologist and the clinician to the study of brain mechanisms. Berger's major discovery in the clinical field was that the electroencephalogram is abnormal in epilepsy. He did not with
tials. His instruments were a double-coil galvanometer and a string galvanometer, and in much of his initial work he used only two electrodes, these being large plates fixed one to the forehead and one to the back of the head. He thus missed the localizing potentials of the EEG, and in addition gathered in all the muscle potentials of the frontalis and trapezius muscles. In later experiments he changed to needle electrodes pushed into the skin. In his early experiments he tried a reference electrode consisting of a silver spoon held in the subject’s mouth. The development of concepts about the EEG concomitants of grand mal epilepsy had their grounding in Fischer’s (300) recordings during experimentally-induced seizures in dogs.

The demonstration of the 3 per sec. wave-and-spike formation so typical of the petit mal type of epilepsy was the achievement of the team of Lennox, Davis and the Gibbeses at the Harvard Medical School (301). This discovery (which Berger came very close to making), together with that of Grey Walter (302) published the following year (1936), namely that brain tumors can be located through the skull by the abnormally slow waves of their surrounding tissue, form the two main foundations of clinical electroencephalography. Altenburg & Foerster (303) had during a brain operation found abnormal potentials associated with a tumor, but Walter’s demonstration that neoplasms could be located by the reversal of sign of the slow waves recorded from the unopened head and his confirmation that the tumor itself was electrically silent made this a practical clinical test. The subsequent expansion and development of electroencephalography is part of the continuing story of modern times not yet history.

In the history of electroencephalography one other figure should be mentioned. One year after Caton’s discovery, Danilewsky, the Russian neurophysiologist, noted the same phenomenon of oscillating cortical potentials in the absence of applied sensory stimulation in five dogs on which he was experimenting. He did not publish this at the time and reported it only in retrospect (304) as a confirmation of Caton’s original observation. Danilewsky’s primary interest lay in the autonomic effects of stimulation of the cortex, such as arterial pressure changes (305), and in the mechanisms of temperature control (306), and he was active in the design of new instrumentation for electrophysiological experimentation (307). Together with his brother (Alexis Y. Danilewsky) he was prominent among the Russian physiologists at the end of the nineteenth century.

In the latter half of the nineteenth century, Russian neurophysiology saw a development that was to influence all future concepts about the brain and behavior. At this period it was usual for Russian physiologists to go to centers in Western Europe for training and experience under the outstanding teachers of the time, and to Müller’s laboratory in 1856 came I. M. Sechenov. Sechenov, later to be known as ‘the father of Russian neurophysiology’ was then 27 years old and during the next 6 years he received training from six of the more outstanding physiologists: Müller, du Bois-Reymond, Ludwig, von Helmholtz, Bunsen and Claude Bernard. The influence of these leaders can be traced in Sechenov’s later thought and development. Among them, only one, Müller, retained even a lingering trace of allegiance to the concept of a vital force, and with him Sechenov had the least contact, for Müller was at the end of his life, still lecturing but no longer experimenting.

In neurophysiology the most influential of Sechenov’s teachers were du Bois-Reymond and Claude Bernard. Sechenov took du Bois-Reymond’s course in animal electricity and in 1860 returned to St. Petersburg with one of his master’s induction coil stimulators and a galvanometer and with them introduced electrophysiology into Russian science. Two years later he was back in Western Europe, this time in Claude Bernard’s laboratory in Paris, and it was here that the experiments were made that were to mold his thinking and to suggest to him a concept of brain mechanisms later to flower in the hands of Pavlov into the theory that has dominated Russian neuro-
physiology ever since, the theory of conditional reflexes.

Sechenov’s experiments that proved so crucial to his future thinking were on the effect on reflex movements of salt crystals placed at various levels of the transected neuraxis (308). His preparation (309) was the decapitated frog, a toe of which he dipped into acid, a procedure that had been developed by Türck. He timed the interval between stimulus and onset of withdrawal of the frog’s foot by counting the beats of a metronome. In this way he got some index of the degree to which application of the salt crystal to the brain stem slowed withdrawal. Sechenov interpreted lengthening of withdrawal time as inhibition of reflex activity. The selection of a salt crystal as a stimulus seems strange in the hands of a pupil of du Bois-Reymond’s and is reminiscent of Marshall Hall’s use of it half a century earlier to study depression and augmentation of spinal reflexes. Only later (310) did Sechenov use electrical stimulation in his experiments on the ‘spontaneous’ variations of spinal cord potentials which he regarded as signs of activity in the spinal centers. This was the first experimental approach towards a centrally exerted inhibitory action on skeletal (‘voluntary’) muscle.

Although at this stage his own experimental evidence seemed slender, Sechenov must have been pondering its meaning in much wider terms, for a year later, on his return to Russia, he published as a series of articles the essay (311) that proved to be so influential in Russian physiology. This essay on the Reflexes of the Brain was later (1866) published as a book after a stormy period during which efforts were made to suppress its publication and censure its author. This opposition was stirred by Sechenov’s assertion that all higher brain function was a material reflex consisting of three sectors—an afferent initiation by sensory inflow, a central process entirely sub-


ject to physical laws and an efferent component resulting in a muscular movement. All reactions, however they might be described in common parlance as pleasure, fear, distress or other descriptive terms were, according to him, in essence muscular in expression. During the passage of the inflow through the central portion of the arc there could either be excitation which would augment the reflex motor response (as in so-called emotional states) or inhibition which would decrease the reflex muscular movement, the resultant being ‘rational’ controlled behavior. It is interesting that Sechenov conceived that inhibition could be learned and that with maturity an increase in the degree of inhibition exerted was achieved.

Thus, according to Sechenov, all human behavior was a balance between inhibition and excitation operating mechanically at the central link of the reflex arc. A so-called ‘willed’ movement according to him only apparently lacked the first component of the arc, its afferent inflow being material memory traces left by external stimuli in the past. It was in elaborating this part of his theory that Sechenov approached the concept of the conditional reflex, for he postulated that the memory trace of a past sensory experience could be evoked by the recurrence of any fraction of it even if this fraction were quite insignificant and unrelated in its apparent meaning. This is essentially the principle underlying the formulation of the conditional reflex theory, namely the potency of an indifferent external stimulus provided it is repeatedly time-locked to the original experience. One further point should be noted in this early attempt to relate mental processes to brain physiology. Sechenov believed that man had the special faculty of increasing the degree of inhibition exerted at the central link until a level of total inhibition of the efferent discharge was reached, and he held that thought was an example of this condition.

Although terms such as ‘cerebral reflexes’ and ‘psychical reflexes’ abound in the nineteenth century literature, they were mostly used by psychologists to describe automatisms. At this period only a few writers had broached the problem of explaining mental processes in physiological terms. Thomas Laycock (312), whose belief in cortical localization no doubt influenced his pupil Hughlings Jackson, wrote in 1845 a paper On the reflex function of the brain. In this he stated his belief that “the brain although the organ of consciousness, was subject to the laws of reflex action, and that in this respect it did not differ from other ganglia of the nervous system.” He too envisaged a three-component arc, the central link in the brain being one where ‘ideagenous’ changes took place that influenced the motor output. He came close to anticipating one of Sechenov’s postulates by stating that the actual sensory impression of an object or the mere idea of it could evoke the same ‘ideagenous’ change in the brain and result in a similar reflex motor effect. So firmly did Laycock believe in the neuronal basis of ideas that he calculated how many there could be to the square inch of grey matter (the answer was 8000) and argued that “as there must be an immense number of square inches of surface in the grey matter extended through the cerebrospinal axis of man, there is space sufficient for millions.” We find echoes of this kind of calculation in some of today’s conjectures about the number of possible interconnections in the brain.

Laycock did not test his hypotheses by experiment though he argued from a basis of clinical observation, for he said “an experiment is occasionally made by nature.” There is no evidence that Sechenov was aware of Laycock’s ideas, although he was influenced by the writings of two other nonexperimentalists, Herbert Spencer (313) and George Henry Lewes (314). These two men, united through their relationships with George Eliot, were influential not only on Sechenov but on Pavlov. Their writings, now largely unread, were translated into Russian almost immediately after publication and were everywhere highly regarded. Spencer’s work was an argument for cortical representation of mental function, and Hughlings Jackson was one who expressed indebtedness to him. Spencer based much of his argument on comparative evolution though he was writing 4 years before the publication of the Origin of the Species by Darwin (315), another writer whose books were extremely influential on Russian thought. Spencer stressed localization of mental processes, saying that “whoever calmly considers the question cannot long resist the conviction that different parts of the brain must in some way or other subserve different kinds of mental action.” When we find in his Autobiography (316) that

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he had the humps on his head read by a phrenologist
(with flattering interpretations) we perceive a deriv-
ing of his ideas from Gall and Spurzheim. Spencer
became hypochondriacal about his own head, believing
it to have an inadequate blood supply. To improve
the circulation he exercised at rowing and at racquets
in 15 min. spurts, dictating his books in the intervals
between exertions. His friend, Lewes (317) in his
Physical Basis of Mind was doubtful about the localiza-
tion of the various mental processes but convinced of
their physiological nature.

Pavlov, the towering figure of Russian neurophysiol-
ology, repeatedly throughout his life stressed his in-
debtedness to Sechenov®® and to Lewes®® (whose book
on physiology he read when a schoolboy). The
influence of these men, one too little known outside
Russia, one almost forgotten, was so great that they
feature not only in the scientific writings of the times
but in Russian fiction. Turgeniev is said to have
taken Sechenov as his model for the science student,
Bazarov, in Fathers and Sons and Dostoievsky cited
the reading of Lewes’ book as a sign of education in
the wife of a drunk in Crime and Punishment.

Pavlov dated his interest in the digestive system
(318) from reading Lewes, an interest that was to
occupy the first 25 years of his working life and to win
for him the Nobel Prize. And it was a feature of the
digestive system, the salivary apparatus, that was to
be drawn by him into the work suggested by Sech-

Principal Digestive Glands (in Russian). St. Petersburg:
Kushnercev, 1897; translated into English by W. H.
Thompson. London: Griffin, 1902.

enov’s theories of 30 years before. Fundamental in
Pavlov’s thinking (319) was the concept of temporary
connections established in the cortex by the repetition
of external stimuli linked only by a constant time
interval, although one gets the impression that he
thought more in terms of influence than of specific
neuronal connections. Thus, for example, in his
classical experiment, the repeated sound of a metro-
nome, at a fixed interval before food was made avail-
able to his experimental dogs, caused salivation to
begin with shorter and shorter latency and at an
increasing rate. Later more complex situations were
developed as laboratory procedures, and this type of
reflex was used for mapping the response of the
cerebral cortex to various sensory inputs, Pavlov
(319) naming the areas as “analyzers” for the various
modalities.

The instability and temporary character of the
conditioned reflex in contrast to that of the inborn

319. Pavlov, I. P. Lectures on Conditioned Reflexes, English
1928.

®® The opening sentence of the phrenologist’s report read:
“Such a head ought to be in the Church.” When we seek the
basis for this statement in the itemized score for Spencer’s
bumps, we find both Firmness and Self-esteem ‘very large,’
Language ‘rather full,’ and Wit and Amativeness only ‘moder-
ate.’

®® See Shaternikov, M. N. The life of I. M. Sechenov. In:
Sechenov, Selected Works. Moscow-Leningrad: State Publ. House,
1935.
®® See Babkin, B. P. Pavlov. Chicago: Univ. Chicago Press,
unconditioned reflexes serving instinctual movements for preservation of life led to Pavlov's ideas of cortical inhibition and its relationship to sleep and hypnosis. Pavlov distinguished between natural conditional reflexes learned in early life and the artificially

As the second half of the twentieth century unfolds the neurophysiologist in his search for brain mechanisms continues to use the three main categories of experimental procedure: anatomical, ablative and electrical. It is the great advance in electrical stimulation and recording that marks this era of investigation from its predecessors, although it is only through knowledge from all sources that progress can be achieved in an understanding of the brain.

Neurophysiology came into being as a specialized branch of endeavor when the nervous system no longer had to compete with the humors and with the blood as the principal coordinator of the body. With the recognition that sensation and motion were mediated by the nerves their position became unassailable, for movement was regarded as the sign of life. Slowly the concept of neural organization began to be pieced together and levels of integration were postulated, in the spinal cord, in the cortex and in the deeper structures of the brain. The period of analysis of the function of each structural unit, of each sector of the nervous system, was followed by a shift of emphasis towards a synthetic consideration of neural activity. The search began for the physiological mechanisms of mental processes, of consciousness, of memory—all terms and concepts that had belonged to another domain of thought. In the neurophysiology of today we find both angles of approach, ranging from analysis of the intimate physicochemical basis of nervous structure and dynamics to the synthesis of action that we call behavior of the organism.

The writer expresses her great indebtedness to the authors of many articles and books not listed in the abridged bibliography that follows. She adds her thanks to those who have sent her material in correspondence, and in particular would mention appreciatively: Dr. Maria Rooseboom for the use of many articles and microfilms from the National Museum for the History of Science at Leiden; Dr. Palle Birkeland, Director of the Danish Royal Library; Dr. Auguste Tourney for a photostat copy of Pourfour du Petit's Lettres; the Institution of Electrical Engineers and Miss Helen G. Thompson for access to material collected by Silvanus P. Thompson on Gilberd; Miss Anne Caton for family photographs and material from the diaries of Richard Caton; Dr. Andrei Jus of Pruszko for photostats of Adolf Beck's doctoral thesis; and F. Czubalski of Warsaw for information about Beck's works. For details of Beck's life the writer expresses warm appreciation to his daughter, Mme. Jadwiga Zahrzevska.

**A SHORT LIST OF SECONDARY SOURCES**

Space does not permit the listing of all the articles to whose authors the writer is indebted for information. The following books have been selected for the special interest they may have for the physiologist. Where possible, works in the English language have been chosen.


THE HISTORICAL DEVELOPMENT OF NEUROPHYSIOLOGY


Hamilton, W. The History of Medicine, Surgery and Anatomy from the Creation of the World, to the Commencement of the Nineteenth Century. London: Colburn and Bentley, 1831.


BIOGRAPHIES

For each of the following scientists one biographical study only has been listed. Again the choice has been made on the grounds of interest to the physiologist and, where possible, text in the English language.


Bichat, Marie François Xavier (1771-1802). Busquet, P. Les Biographies Médicales I: 37, 1827.


Dr. Brazier: I might take up just a few of the points, especially the ones Dr. Toman has presented relevant to his longer paper. Let me start with three rather obvious statements apropos the question that his two gentlemen were discussing. That was specifically whether electrophysiology is in fact a useful or appropriate tool with which to search for the mechanisms of drug action in the nervous system. I'm going to try to restrict my remarks to the tranquilizing drugs because that is the main purpose of our meeting. First, all of us presumably hold that behavior is dependent on nervous system activities whether directly or indirectly mediated; second, I suppose we all agree that nervous system activity is accompanied by electrical signs; and third, drugs work on cells and not on behavior, and here comes the point that Dr. Toman raised about the relevance of research with electrical techniques for the elucidation of drug actions on behavior.

It seems to me that there are different specific levels on which this problem can be attacked. One is the primary level of the cells on which the drugs are working, the kind of work that Dr. Grundfest has referred to. That is undoubtedly an absolutely essential level of investigation. Then there is the study of animal behavior, and (just to be provocative) I would like to question the value of that level for the specific topic of this meeting unless we are to be anthropomorphic in our interpretations. The third level is the study of behavior in man, and that is after all what we are meeting about today. The question I raise about animal behavior is, of course, based on many of the things which have already been said about species differences and so on.

Let me just take up the next point which Dr. Toman raised about how profitable electrophysiology has been in some other diseases, for example, epilepsy. He said, however, that it has not proved to be very profitable in the behavioral disorders. I suggest that in this context there are three questions to be considered. They are the problems of \textit{where} to look for the electrophysiological sign, \textit{what} electrical signs to look for, and \textit{how} to look for them.

Now what kinds of electrical signs are to be looked for? In man you may think we're very restricted in this area. We can look at the scalp EEG, we can look at the depth EEG, we can look for evoked responses to physiological or artificial
stimuli. There is, however, a whole new field involving a quite different approach that's been rather neglected until now, and that is what I may call the spatial and temporal relationships of electrical activity. We possibly may not find the abnormalities in electrophysiological characteristics that parallel abnormalities of behavior if we look at the activity of structures considered singly. If I may use a rather flippant term, perhaps what we should look for is "interpersonal relationships" of the electrical activities within the brain.

Now, as you know, some work on the surface of the brain in man has been started by John Lilly for temporal relationships, and also by Grey Walter using a toposcope, but I would suggest that methods are developing by which we can look at all these things in man with even finer tools.

Let me, however, first deal with an example illustrating the problem of where to look for the electrical sign. You will all be familiar with depth recording, but perhaps I may illustrate these techniques. Dr. Toman talked about epilepsy. An electroencephalographer who has been reading scalp EEGs for years, as I have, has in the past had some confidence in saying that a normal scalp EEG is a happy finding and helpful in ruling out epilepsy. Yet you find when you use depth recording that a seizure discharge of considerable severity can be going on in the depth while all is quiet on the scalp. This is illustrated in Figure 1 where the first four recordings, all from the amygdala, show a seizure discharge which is recorded from implanted electrodes inserted stereotactically. Compare these depth recordings

![Figure 1](image)

**Fig. 1.** Of the 8 channels of this record the upper four were recorded from electrodes placed stereotactically in the amygdaloid nucleus, the lower four are from the scalp in a case of temporal lobe epilepsy. From a collaborative study with Dr. H. C. Solomon and Dr. W. P. Chapman on the electrical activity of the amygdala.
with what is happening on the scalp. At the surface there is no sign of the seizure. That's just one example of the information that depth electroencephalography can add in studies in man.

The next point I want to raise concerns one kind of electrical sign that has been studied very fully in animals, the response evoked by sensory stimulation. That is supposed to be difficult to find in man, and it very frequently is with the routine method for recording EEGs. For example, in Figure 2 from a normal man (showing from top to bottom, leads from the left occipital, right occipital, mid-line high occipital, and mid-line low occipital) a flash occurred at each of the signal pips on the fifth line, but is is very difficult to be certain that any response occurred. However if this same EEG is analyzed by a technique of electronic averaging, not only does an evoked response appear, but its several components are clearly discernible. Figure 3 shows the average of 70 responses from this same EEG record. This electronic averaging technique emphasizes all those potentials that are time-locked to the stimulus and minimizes those that are randomly related to it (e.g., the background EEG). I shall not take time to give the details of this method since they have been published.\(^1\) Figure 4 makes this operation a little clearer. It illustrates a simulated experiment in which a sinewave hidden in background noise of equal amplitude is detected and its average waveform reproduced.

\(^1\) Brazier, M. A. B., & Barlow, J. S. Some applications of correlation analysis to clinical problems in EEG. *EEG clin. Neurophysiol.*, 1956, 8, 325-331.

Fig. 3. Same subject as in Fig. 2. Averaged waveform of the response to 70 flashes of which 5 are present in the 3rd channel of Fig. 2. The flash was coincident with the first pen deflection on the left. The pen deflections are 1 millisecond apart. The peak of the maximum deflection is at 87 msec. after the flash but events occurring earlier than this can be detected.

Fig. 4. Simulated experiment to illustrate the detection of a signal in noise by electronic averaging.

Now the last point I want to make deals with the question of what I called the "interpersonal relationships" between structures within the brain and the use of cross-correlation techniques to find whether any activity happening in one structure
Fig. 5. Cross-correlograms from pairs of points recording from within the basal ganglia in a patient with Parkinson's disease.

is related in time to the activity that is happening in another. Figure 5 is the analysis of recordings from electrodes implanted in the basal ganglia of a patient of Dr. William Sweet's with Parkinson's disease, and these are cross-correlations of the basal ganglia activity.

Cross-correlation consists of the comparison of two simultaneously occurring EEGs with each other. If activity in one of them leads that in the other, the maximum correlation indicated by the highest pen deflection will occur at an interval of time that can be read off from the graph (the pen deflections are 5 milliseconds apart). The height of the pen deflections are proportional to the degree of correlation between the two recordings that are being compared.
When the recordings of the two points in the medial globus pallidus were cross correlated the maximum correlation occurred at zero delay. In other words, within the medial globus pallidus the activity was simultaneous. But when the medial globus pallidus was cross correlated with the lateral globus pallidus, the medial was found to be firing 7.5 milliseconds before the lateral. Down below, the medial globus pallidus is compared with the putamen, and this shows the medial globus pallidus to be firing 5 milliseconds before the putamen. Those are examples from the basal ganglia, but obviously this technique can be used for many purposes. Finally Figure 6 shows the original record that was being analyzed, and I think I would defy anyone to tell me what the time relationships are between the activities from the various nuclei. There are the actual records from which these analyses in Figure 5 were made.

So the message that I wish to convey is that I feel we would get further in this particular problem of elucidating the action of tranquilizing drugs in man if we were to work on man. And from the point of view of available methods, I would say "Do not despair." New methods are developing all the time.
REMARQUES A PROPOS DE L’ENREGISTREMENT DANS LES DIFFÉRENTES COUCHES CORTICALES DE LA RÉPONSE PRIMAIRE À L’ÉCLAIR LUMINEUX CHEZ LE CHAT LÉGEREMENT ANESTHÉSIÉ,

PAR MM.

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INTRODUCTION.

Au cours d’une étude des réponses visuelles primaires chez le chat (Brazier, 1954) en fonction du degré d’anesthésie, nous avons pu constater par des explorations effectuées au niveau des différentes couches corticales des variations de forme, d’amplitude et de polarité du potentiel évoqué par stimulation lumineuse chez certains animaux dans un état proche des conditions physiologiques normales.

Ce travail a été effectué en 1954 alors que de nombreux travaux basés sur l’explo­ration oscillographique des voies optiques et de l’aire visuelle avaient été réalisés (Bishop et O’Leary, 1938 ; Marshall, Talbot et Ades, 1943 ; Chang et Kaada, 1950 ; Buser, 1950) et qu’étaient entreprises des études microphysiologiques (Jung et coll., 1952 ; Amassian, 1952 ; Brock et coll., 1953 ; Li et Jasper, 1953 ; Albe-Fessard et Buser, 1953).

Depuis cette date, l’emploi des microélectrodes (Tasaki et coll., 1954 ; Mountcastle et coll., 1957 ; Li, 1955 ; Buser et Albe-Fessard, 1955) apportait, en s’inten­sifiant, confirmation des hypothèses qui interprêtaient le potentiel visuel évoqué diphasique, sensoriel, comme l’expression d’un phénomène postsynaptique successi­vement orthodromique de dépolarisation et antidromique de repolarisation (Albe-Fessard, 1957) tandis que les repérages anatomiques, en particulier dans les enregistre­ments corticaux permettaient de souligner l’importance de l’orientation et de la densité des structures corticales, telles qu’elles étaient, d’ailleurs, précisées par certaines techniques anatomiques (Sholl, 1956).

Les résultats publiés ici, bien tardivement, concordent dans leur ensemble avec ceux des expérimentations plus récentes, ils gardent la particularité d’avoir été obtenus dans des conditions physiologiques quasi normales et d’être fondés sur des données anatomiques précises.

TECHNIQUE.

L’animal est anesthésié au Nembutal à 60 p. 1.000 (2/3 cm³/kg de poids, par voie intra-péritonéale). Une sonde trachéale est placée pour contrôler la respiration si l’usage de curare devient nécessaire.

La tête de l’animal est immobilisée devant un stimulateur lumineux, les conduits auditifs obturés. Une trépanation met à nu le cortex visuel primaire d’un côté. La pupille de l’œil controlatéral est dilatée (atropine) et ses paupières maintenues ouvertes par deux points de suture. L’activité cérébrale est contrôlée par une déri-
Évaluation EEG qui permet d'apprécier le niveau de l'anesthésie. Après ouverture de la dure-mère et de la pie-mère la micro-électrode exploratrice est mise en contact avec la surface corticale ; elle est reliée, après amplification usuelle (capacité-résistance), à un oscilloscope cathodique, une négativation de l'électrode active se traduisant par une déflection vers le haut du rayon cathodique.

L'expérimentation débute une heure et demie environ après le début de l'anesthésie ; les tissus opérés sont novocaïnisés. L'électrode faite d'un fil de platine de 10 µ gainée de verre mesure à sa pointe (aiguisée selon la technique de P. D. Wall) environ 40 µ. Elle est enfondée à l'aide d'un micro-manipulateur par étapes, sous contrôle d'un microscope binoculaire. Sa fragilité nécessite le choix d'une portion de cortex libre de vaisseaux. Le cortex exposé est protégé par de l'huile de paraffine retenue par une marge de matière plastique élevée sur les bords de la craniostomie.

A chaque palier d'exploration les oscillogrammes sont photographiés. Le balayage de l'écran, déclenché par le stroboscope, permet de superposer sur la même pellicule une trentaine de réponses succédant aux incitations lumineuses qui surviennent toutes les secondes environ. Des réponses sont également photographiées séparément. Les mesures ont été faites sur les courbes obtenues par la superposition des réponses. On a retenu pour illustrer cette publication des réponses significatives photographiées isolément.

A la fin de l'expérience, l'électrode est laissée en place, le chat tué par exsanguination et perfusion de 3 litres de sérum physiologique suivie d'une perfusion de 2 litres de Formol à 10 p. 100 (King, 1913) qui a pour effet de fixer le cerveau en place ; l'animal est conservé dans un réfrigérateur pendant 48 heures. Le cerveau prélevé est radiographié pour repérage macroscopique de l'électrode ; la portion intéressante de cortex est confiée à l'histologiste. Le repérage des couches (Rose, 1931, 1935 ; Jung, 1953) est pratiqué après coloration de Nissl et celui des dendrites et des axones après coloration à l'argent (Davenport, 1931 ; Ferreira, 1951).

Méthode de repérage.

Le plan de référence de l'exploration intracorticale est donné par l'oscillogramme qui se stabilise lorsque la pointe de l'électrode jusque-là baignée dans l'huile, atteint la surface corticale. L'électrode est enfondée par paliers de 250 µ environ et le niveau présumé de la pointe de l'électrode est lu sur le micromètre.

Les documents histologiques (sections effectuées tous les 70 µ) permettent de mesurer la longueur du trajet de la microélectrode dans le cortex et éventuellement dans la substance blanche (et de corriger les erreurs de niveau dues au micromanipulateur). Les coupes contenant le trajet de l'électrode permettent également de trouver les points de repère nécessaires à la reconnaissance des différentes couches corticales. Ces points de repère, comparés avec les coupes immédiatement voisines de la même portion de cortex et aux mesures données par Li et Jasper (1953) permettent de définir avec une erreur moyenne d'une soixantaine de µ, en tenant compte du coefficient de la rétraction due aux manipulations histologiques, l'épaisseur de chaque couche corticale.

Il est alors possible, en connaissant l'inclinaison du trajet de l'électrode qui n'est pas nécessairement perpendiculaire au plan des couches, de calculer la longueur du trajet de l'électrode dans chacune des couches corticales et donc le niveau de chacun des enregistrements (fig. 1).
Résultats.

Les réponses obtenues montrent au niveau de la couche I le classique potentiel évoqué primaire avec sa première « pointe » positive et l’ample déflexion négative consécutive. Nous avons dénommé « onde A » la « pointe » ; « onde C » l’ample déflexion consécutive, réservant la lettre B pour une encoche qui apparaît éventuellement à certains niveaux d’exploration sur la partie ascendante de l’onde C (fig. 2 A).

Nous n’avons pas étudié en détail les potentiels diphasiques qui succèdent parfois au potentiel primaire. Enfin nous avons recueilli des pointes unitaires cellulaires (« spikes ») de façon trop peu constante ou prolongée pour nous attacher à leur étude.

Fig. 1. — a) Les pointillés délimitent la zone de cortex visuel primaire (gyrus suprasylvien) habituellement explorée ; la croix représente schématiquement l’emplacement de l’électrode exploratrice.

b) coupe histologique (coloration de Nissl). La flèche indique sur cette coupe la portion visible du trajet de l’électrode.
Ces phénomènes rapides ont persisté une seule fois, assez longtemps pour n’être pas interprétés comme un effet lésionnel ; ils survenaient alors au niveau de la couche IV, par groupe de trois, sur la phase descendante de l’onde A. La rareté de l’enregistrement de ces potentiels unitaires s’explique sans doute par l’emploi de Nembutal et la relative grosseur des microélectrodes utilisées.

Pour chacune des ondes A, B et C nous avons étudié la latence, la polarité et l’amplitude à chacun des différents niveaux d’exploration correspondant aux différentes couches corticales. Cette étude, répétée le, a été effectuée sur les courbes obtenues par la superposition d’une trentaine de réponses. Le flou de l’« image composite » explique la relative imprécision des mesures en ce qui concerne la latence (évaluée au 1/4 ou au 1/3 de milliseconde) et l’amplitude. Les réponses superposées ont permis de dessiner des courbes schématiques moyennes (fig. 2 A) qui ont permis pour illustrer ces résultats de retenir les réponses photographiées d’ailleurs isolément qui s’en rapprochaient le plus (fig. 2 B).

**Fig. 2 A. — Représentation schématique d’une réponse dans les différentes couches corticales ; les lignes horizontales pointillées représentent les lignes de base. On n’a pas représenté l’artefact indiquant la stimulation qui se trouverait en dehors des limites des schémas.**

1. **Latence.**

La latence est mesurée au sommet des défections. Les différentes valeurs de la latence sont représentées dans le tableau 1.

a) Dans une préparation donnée elles varient peu :
   - onde A : variation de latence de l’ordre de 0,5 ms.
   - onde B : variation de latence de ± 0,5 ms.
   - onde C : latence particulièrement stable.

b) La comparaison de la latence des ondes A, B, et C dans les différentes préparations met en évidence des latences de valeurs comparables chez les chats légèrement anesthésiés (préparations 126, 127 et 123). 
   - préparation 126 : latence de l’onde A égale à 10,5 ms.
   - latence de l’onde B égale à 17 ms.
   - latence de l’onde C voisine de 22,3 ms.
préparation 127 : latence de l'onde A voisine de 13,3 ms.
latence de l'onde B voisine de 20,5 ms.
latence de l'onde C égale à 27 ms.
préparation 123 : latence de l'onde A voisine de 14,3 ms.
latence de l'onde B égale à 17 ms.
latence de l'onde C voisine de 21,2 ms.

Fig. 2 B. — Photographies de réponses isolées significatives (c'est-à-dire superposables aux courbes obtenues par superposition d'une trentaine de réponses sur un même cliché.) L'échelle des temps est donnée par l'enregistrement sur le deuxième rayon cathodique d'un courant à 100 e/s. L'amplitude est indiquée pour chaque série de réponse par l'enregistrement d'un signal de 100 ou 200 µV suivant les cas. Remarquer pour les préparations 127, 123 et 126 le renversement de polarité de l'onde A au-dessous de la troisième couche corticale, la difficulté d'individuer l'encoche B et pour la préparation 123 (chat profondément anesthésié) la stabilité de la polarité positive de l'onde A.
Par contre, dans la préparation 124, profondément anesthésiée la latence de l’onde A est égale à 25 ms et celle de l’onde C à 35 ms.
Les variations de latence dans les préparations 126, 127 et 123 sont vraisemblablement en rapport, elles aussi, avec des différences de niveaux anesthésiques bien que l’E.E.G. ait paru indiquer un état vigile comparable dans ces trois cas.
On peut enfin remarquer que les latences les plus stables, aux différents niveaux d’exploration, dans ces trois préparations, sont celles de l’onde C.

2. Polarité.

La polarité des ondes A, B et C (positive en dessous de la ligne de base, négative au-dessus) dépend évidemment de la stabilité de la ligne de base et sur les courbes réalisées par la superposition d’une trentaine de réponses de la stabilité de l’amplitude et de la latence de chacune des ondes étudiées.

a) dans les préparations légèrement anesthésiées :
   l’onde A positive dans les trois premières couches présente un renversement de phase en dessous de la couche III :
   l’onde B, qui n’est bien individualisée que dans la couche III (préparation 127) et IV (préparation 123), est négative ;
   l’onde C est négative.

b) par contre dans la préparation profondément anesthésiée, où l’onde B est absente et l’onde C négative, l’onde A reste positive dans toutes les couches corticales.

3. Amplitude.

La mesure de l’amplitude est très imprécise :

a) pour donner un ordre de grandeur on peut signaler que l’onde C, dont l’amplitude est relativement stable, est de l’ordre d’une centaine de microvolts, que celle de l’onde A est cinq ou six fois plus faible ; l’onde B a une amplitude encore moindre qui fait apparaître cet accident comme une simple encoche sur la partie ascendante de l’onde C ;

b) la comparaison de l’amplitude des ondes A, B et C dans les différentes préparations met en évidence des différences en rapport avec le degré d’anesthésie.

Chez les chats légèrement anesthésiés :
   l’amplitude de l’onde A reste à peu près stable dans les trois premières couches ; après le renversement de phase, l’onde devenue surface négative décroît progressivement d’amplitude entre les couches corticales IV, V et VI ;
   l’amplitude de l’onde B, inconstante, atteint son maximum dans la quatrième couche corticale ;
   l’amplitude de l’onde C est également la plus grande dans la couche IV.

Chez le chat profondément anesthésié, par contre, l’onde A qui ne présente pas de renversement de polarité diminue progressivement d’amplitude entre la première et la dernière couche corticale, l’onde B est absente, l’onde C reste stable dans les six couches corticales, ou semble prédominer aux niveaux inférieurs.

Remarque : l’onde B paraît se confondre dans la préparation 123 avec l’onde A au niveau des couches corticales VI, V et même VI et dans la préparation 126 avec l’onde C au niveau des deux premières couches corticales. Cette difficulté d’interprétation est non seulement due à la faiblesse de l’amplitude de l’onde B mais aussi au voisinage des latences des ondes B et A dans le premier cas, B et C dans le second.
DISCUSSION.


Deux remarques paraissent, cependant, nécessaires :

1° Les importants et nombreux travaux publiés jusqu'ici (Bishop, 1938-1953 : Chang, 1950) portent en général sur des potentiels évoqués par stimulation électrique directe à un niveau quelconque des voies optiques centripètes, recueillis par des électrodes relativement volumineuses et souvent en dérivation « bipolaires » ; quelques travaux plus récents, utilisant également un choc stimulateur électrique, font état d'enregistrements par micro-électrodes (Amassian, 1952 ; Thomas, 1952 ; von Baumgarten, 1953 ; Cohn, 1954). Il convient donc de souligner la limite des comparaisons à établir entre ces réponses entraînées par des modes de stimulation et d'enregistrement différents :

— la stimulation électrique par choc direct détermine, en effet, des volées hauteurment synchronisées d'influx qui entraînent une réponse polyphasique complexe où l'on reconnaît, en particulier sur l'onde initiale surface positive, des « pointes » d'une durée voisine de 1 ms de signification d'ailleurs discutée ;

— la stimulation lumineuse, utilisée dans ce travail parce qu'elle représente une excitation sensorielle physiologique, entraîne des influx intégrés de façon plus complexe dans le temps et l'espace et provoque, finalement, une réponse de morphologie assez simple comme nous l'avons vu.

Néanmoins, ces différences n'interdisent pas de discuter les résultats acquis ici, à la lumière des autres travaux, puisque nous voulons nous intéresser moins à la signification de la morphologie de la réponse qu'à ses modifications en fonction du niveau cortical.

2° L'utilisation d'une électrode particulièrement fine, en dérivation dite « monopolaire » (l'électrode de référence est située sur le muscle) et la protection de la préparation par de l'huile de paraffine réalisent, d'ailleurs, des conditions qui simplifient la discussion des résultats en permettant d'interpréter aisément la positivité ou la négativité de l'électrode exploratrice et en éliminant les risques de déshydratation de la préparation (Bishop et Claire, 1952).

Ces deux remarques étant faites, on peut admettre qu'une phase positive de la réponse exprime une positivité de l'électrode exploratrice par rapport à l'électrode de référence et qu'une phase négative de la réponse exprime une négativité de l'électrode exploratrice. Or, l'activation d'une structure nerveuse se traduit par une « négativation » de cette structure par rapport aux zones inactives, l'activation modifiant le champ électrique de telle sorte que le courant s'écoule des zones inactives vers la structure activée (ces modifications plus ou moins rapides se manifestant par des potentiels de durée correspondante). Donc l'étude de la polarité, de l'amplitude, de la durée et de la latence des différentes phases du potentiel évoqué primaire permet de définir la direction, l'intensité et la valeur instantanée du champ électrique au niveau de l'électrode exploratrice.

De plus, la comparaison des réponses obtenues au niveau des différentes couches corticales invite à définir le champ électrique instantané cortical comme le champ extérieur d'un dipôle formé par un pôle positif représenté par la zone inactive et un pôle négatif représenté par la zone active.

Encore faut-il bien préciser que ce dipôle :

— ne peut se définir comme tel que par l'apparition du seul pôle négatif (le pôle positif n'étant que relatif et dans son apparition et dans sa délimitation);
— n'a de valeurs qu'instantanées;
— est fonction dans son expression de l'« angle » sous lequel le système explo-rateur entre en rapport avec son champ;
— a pour substratum des structures anatomiques orientées de façons diverses et dont l'activation, successive ou simultanée, produit un champ électrique instantané dont on n'apprécie, en un point donné, que la résultante.

Ainsi peut-on figurer le potentiel évoqué primaire comme lié à l'existence de dipôles résultants et successifs que cette exploration permet de localiser avec plus ou moins de précision, en essayant d'en définir l'étendue et l'orientation dans les différentes couches corticales (fig. 3).

**Fig. 3.** — Courbes schématiques représentant les modifications de polarité des ondes A, B et C en fonction des différentes valeurs de leur amplitude dans les six couches corticales. En trait plein : courbes schématiques obtenues chez les chats légèrement anesthésiés : remarquer pour l'onde A, le changement de polarité entre les couches corticales III et IV ; le « gradient » très abrupt en dessous de la troisième couche, plus étalé en dessous de la quatrième ; pour l'onde B et l'onde C, le maximum situé dans la couche IV. En trait pointillé courbe schématique obtenue chez le chat profondément anesthésié : remarquer pour l'onde A l'absence de modification de polarité, le gradient étalé ; l'absence d'onde B ; pour l'onde C, la persistance d'une amplitude élevée dans les couches inférieures.

Chez les animaux dans une situation proche de l'état physiologique normal :
— l'onde A devient alors l'expression d'un dipôle normal au plan des couches corticales, dont le pôle positif se trouve dans les trois couches superficielles et le pôle négatif dans les trois couches profondes. Le passage de la positivité à la négativité se produit en effet au-dessous de la couche III avec un gradient abrupt ;
— l'onde B devient l'expression d'un dipôle de signes électriques opposés, entraînant une perturbation peu intense et dont le pôle négatif présente un maximum au niveau des couches III et IV ;
— l'onde C devient l'expression d'un dipôle de signes électriques également opposés à celui de l'onde A, assez étendu pour que le pôle négatif de ce dipôle intéresse toutes les couches corticales avec un maximum au niveau de la couche IV.

La profondeur de l'anesthésie influe sur ces dipôles ; en effet, en ce qui concerne la perturbation A, tout se passe comme si le pôle négatif intéressait alors des struc-
Les données anatomiques de leur côté montrent que les arborisations dendritiques (en particulier, celles de cellules stellaires) prédominent au niveau de la couche IV et que les cellules pyramidales étagées entre les couches II et V, prédominant en III et surtout V, ont une disposition radiaire. Cette architectonie laisse penser que les connexions synaptiques, directes ou non, de la voie de projection primaire avec les cellules pyramidales sont les plus nombreuses au niveau de la couche IV.

Ces deux ordres de faits, électrophysiologique et anatomique, apportent des arguments en faveur de théories déjà exprimées :

— qui interprètent l’onde A comme l’expression d’une dépolarisation postsynaptique des cellules pyramidales (Fessard, 1950 ; Chang et Kaada, 1950 ; Bishop, 1952 ; Brock, 1953 ; Cohn, 1953 ; Li, 1954) ; en effet, le gradient du phénomène A très abrupt en dessous de la couche III, est plus étalé en dessous de la couche IV ; le phénomène A semble donc bien lié à la dépolarisation due à des influx centrifuges des éléments cellulaires de la couche IV et des cellules pyramidales radiairement disposées jusqu’à la couche V ;

— qui font du phénomène C un potentiel antidromique (Bishop, 1953 ; Chang, 1953) en effet, indépendamment des arguments tirés de la latence et de la durée de l’onde C, les résultats de cette exploration montrent que le gradient de la perturbation prédominent bien au sein des structures dendritiques les plus denses (couche IV) et que le champ électrique correspondant à l’activité de structures non orientées, est assez étendu et ne présente pas d’« oppositions de phases ».

Ces corrélations électrophysiologiques et anatomiques, si l’on tient compte de l’influence du degré d’anesthésie, laissent penser que lorsque l’anesthésie devient plus profonde les dipôles ne paraissent plus s’établir entre les diverses structures corticales elles-mêmes, mais entre les structures corticales et sous-corticales, en même temps que disparaît le potentiel B. Cette encoche B, qui résiste mal à l’effet dépressurise des barbituriques, correspond d’ailleurs à un champ électrique relativement restreint (qu’une exploration normale au plan des couches voit d’ailleurs, peut-être mal) et paraît lié par sa topographie aux éléments responsables du gradient maximum de la perturbation A. Son signe négatif et sa latence d’autre part rapprochent cette encoche B de l’onde C. Il semble donc permi d’interpréter cette onde B comme un phénomène antidromique précoce intéressant les dendrites des cellules excitées les premières et les plus sensibles à l’anesthésie.

La valeur de cette hypothèse qui donne une signification comparable aux ondes B et C est dans une certaine mesure soulignée :

— d’un point de vue électrophysiologique par l’absence de ce phénomène B lors des stimulations éolières où la « récupération » de l’équilibre électrique est plus homogène en raison de la synchronisation des influx.

— d’un point de vue anatomique par la localisation du champ de l’onde B au niveau de la couche IV où siègent les cellules stellaires non orientées et les dendrites apicales verticales des cellules pyramidales de la couche V (1).

**Conclusion.**

Ces résultats préliminaires apportent un argument en faveur des théories, actuellement admises, sur l’origine et la nature du potentiel évoqué primaire. Les corrélation anatomiques établies ici ajoutent à la réponse primaire, déjà considérée comme un précieux témoin de la reconnaissance d’une aire réceptrice corticale, la qualité

(1) Il est intéressant de remarquer que les réponses répétitives, succédant au potentiel évoqué primaire, non étudiées ici, sont présentes chaque fois que la réponse primaire comporte l’encoche B.
de point de repère électrophysiologique de l'étage cortical où s'effectue une exploration en soulignant l'importance des notions architectoniques de densité et d'orientation des divers éléments cellulaires corticaux.

Les conditions quasi physiologiques de cette expérimentation permettent d'ignorer les discussions portant sur l'origine (rétine, relais sous-corticaux...) des divers éléments qui compliquent l'onde A lors des stimulations par choc électrique et surtout elles laissent envisager la possibilité de préciser les niveaux d'explorations corticales chez l'animal chronique et même, si les conditions s'y prêtent, chez l'homme non plus par des vérifications anatomiques mais par la seule électrophysiologie.

Nous tenons à remercier pour tout le travail histologique qui a permis ces remarques, le Dr Richardson et pour leur collaboration technique Mlle Pettersen M. Chock.

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LONG-PERSISTING ELECTRICAL TRACES IN THE BRAIN OF MAN AND THEIR POSSIBLE RELATIONSHIP TO HIGHER NERVOUS ACTIVITY

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D. Sc. 1960

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One of the most challenging of unsolved problems in neurophysiology concerns the mechanism of storage in the nervous system. 'Storage' seems a word preferable to 'memory' for it does not carry with it the connotation of awareness. The term is however inclusive of the various categories of memory such as short-term transient memories and the long-enduring ones that may last a life-time.

It seems unnecessary to expect the latter type to have an electrical sign during their dormant stage - only when a memory is being laid down or reinforced or evoked would it seem profitable to search for signs of neuronal activity. Similarly it would seem unlikely that the basis of long-term storage is one of continuing neuronal activation by impulses in reverberatory or self re-exciting chains, for these could hardly be expected to survive intracerebral holocausts such as electric shock, concussion or generalized convulsions. It is well known that the natural conditional reflexes of early life as well as the acquired learning of later life are not destroyed by these massive disruptions of central nervous system activity.

As a consequence of this type of argument physiologists and psychologists have been fertile with suggestions for some type of structural change with use, some protoplasmic growth of a nerve process, or at a more molecular level, some re-orientation of protein molecules or the formation of steric interlocking. That structural changes take place at synapses after birth as well as during embryonic development has been demonstrated, though such changes have usually been regarded as consequent to maturation rather than to persistent use (Tersuolo, personal communication). However, there may be some who prefer to regard all learning processes
As part of a continuum of maturation. purposeful learning or "unconscious" as in

Possibly the search for a structural change is being made in the wrong order of magnitude and perhaps one needs to seek it at the submolecular level where thermal agitation disperses aggregates below a certain size. Here it seems not implausible to envisage changes of a chemical nature (resultant on impressions received) that may increase the size of the aggregates sufficiently to make them invulnerable to thermal agitation so that in this way they may achieve some degree of permanence. Changes of this kind could influence the characteristics of the cell membrane both in terms of its (spatial) sieve-like qualities and in terms of chemical affinities. Tied behavior alluded to is one in which the animal receives food by press. No single postulate that has yet been proposed as a possible mechanism for storage covers all its phenomena. Structural changes of the magnitude of protoplasmic growth would seem unlikely to be formed rapidly enough to be the basic mechanism of immediate recall of singly occurring sensory experiences. Possibly this is an instance where an electrical concomitant might be reasonably expected, though its form might not necessarily be that of circulating impulses; an alternative form to example, might be a change in the safety factor for synaptic transmission, establishment of a change in the probability of firing across a synapse.

Speculations of this kind can run riot and scarcely bring us any closer to a but solution. In face of the phenomena we attempt to explain they all seem simple-minded. If one is prepared to postulate structural changes this implies that they occur somewhere, that they have a site, whether submicroscopically or microscopically on the nerve cell, on the dendrites, on the synapses or elsewhere, in other words that past experience has left its traces in a spatial representation. But this is not enough, for storage as we know has a temporal quality; there is a temporal integration that retains the serial incidence of the impressions at the receptor organs. Is this too, transmuted to a spatial form? The organization of
this sequence may be "conscious" as in purposeful learning or "unconscious" as in conditional reflexes. Whatever the mechanism of storage its organization embodies a temporal sequence. Expressed in another way, the coding in which past experience is stored is such that not only are events themselves represented but their serial incidence is preserved.

In the preliminary stage in which this code is being 'set' centrally, the "absolute" time-scale of this temporal sequence is preserved (as in some conditional reflexes) whereas in the long-term storage this may be compressed so that only the sequence parameter of time is preserved and not the duration parameter. An example of the conditioned behavior alluded to is one in which the animal receives food by pressing a lever a given interval after the conditioning stimulus. Only if the interval is exactly timed by the animal, does lever-pressing result in food becoming available.

It has been suggested by some psychologists that the storage of temporal sequence may be peculiar to man and that this may underlie his unique ability to use language. A case for this argument could be made in terms of long-term storage, but one has to grant the animal storage of temporal sequence on a short time-base or the establishment of conditional reflexes would be impossible.

Allusion has been made to the site of mechanisms in terms of micro-structure but more importantly one needs to recognize the process in terms of systems. Can electrophysiology aid in giving clues as to the systems involved? For example, let us take the laying down of storage. In sepia Sanders and Young have shown that this cannot be done after removal of some specific lobes of this animal's brain. In man this apparently cannot be done in the absence of interplay between the brain stem and the cortex, i.e. not in anesthesia or in sleep or in coma caused by lesions in the brain stem. And this is not because the message from the periphery fails to reach the cortex. It would appear to be due to failure to recode at the integration level.
On the principle of parsimony, one's first urge is to postulate a single input through which the storage is laid down, but this is a formidable task for any evidence of sufficiently long-lasting activity in the brain that entailing a coding in the same system for both space and time, but one wonders whether a more likely mechanism might not be based on the principle of redundancy, namely, that more than one afferent path into the integrating system is employed, each responding with a different code to the same stimulus, and therefore delivering to the storage system a multiple form of code.

In our laboratory we have been interested in whether there is any evidence of some rhythmic activity in the brain that could perhaps be secondary to the storage system a multiple form of code. Some of the more obvious ways by which redundancy operates in the nervous system are exemplified by the duplication of our eyes which gives us information about the third dimension of space (distance) and the duplication of our ears which gives us the clue to the direction from which a sound is coming. It will be noticed that, in the latter instance, although the information gained is of spatial attributes alone, to very minute subdivisions in certain experimental situations, the nervous system has had to use temporal coding to obtain it (the discrimination of the interval between arrival of stimuli from the two ears).

But the bilaterality of the brain and duplication of the distance receptors is not the only substrate for redundancy of input to the nervous system. Redundancy of corticopetal flow has been proven by the demonstration of the pathways from the specific nuclei of the thalamus to the cortex that are separate from those travelling through the brain stem to the cortex. From an electrical point of view we know that messages in these duplicated pathways are coded (distally to the cortex and in the thalamus) in different forms. Although neuronal activity is unlikely to be the physiological substrate of long-term storage, it must certainly must be the original neuronal process. Further proposal would involve, nevertheless, that agent of its initiation, the carrier of the original code (which, of course, bear no resemblance to the final stored integrated code).

The experimental neurophysiologist feels very humble in the face of a problem of this magnitude. How can he attack it? The finding of correlates and concomitants of neuronal activity, the frequency coding, of course, not necessarily have to be meaningful - is not enough, yet what else has he to offer? Eager for larger targets he has to...
content himself with first steps, and one of the most elementary of these is the
search for any evidence of sufficiently long-enduring activity in the brain that
would enable the organism to use it for prediction or for matching of experience
brain that reflects any mechanism that can be used for prediction can have to use
at one instant in time with what has gone before. It is with hope of approaching
a special tool, some form of analysis that tells one whether the parameter selected
this elementary step that the following experimental findings are presented.

In our laboratory we have been interested in whether there is any electrical
determined by the usual forms of automatic frequency analysis which lose informa-
trace of some rhythmic activity in the brain that could perhaps be secondary to
mechanism subserving the capability of the nervous system to estimate the pas-
several of phase mean not only from the theoretical concept of prediction but
sage of time. The techniques of conditional reflexes have shown that there is a
also from the practical evidence that the fluctuating potentials of the electro-
considerable range over which the nervous system can time an interval with great
encephalogram reflect excitability conditions in the cortex (and not unconsciousness).
This varies from a fraction of a second in the case of conditioned
the spinal potentials of discharging cells or slow). There is, however, frequent
eyeblink in man, to many minutes in some animals in certain experimental situations,
evidence that the probability of discharge of units in greater at a specific phase
though in the latter case the animal may be making for himself an external clock by
of each cycle of these slower oscillatory potentials, i.e., at the point in the
evolving a pattern of stereotyped movements adjusted during the period of training
rhythm may not be unwarranted. This and similarity of excitability is maximal.

until they just occupy the desired interval. One sees this more in lower forms (like
transmission of messages in the central nervous system and cannot be analyzed from
It has occurred to many that the apparently rhythmic electrical activity of the
any hypothesis that concerns itself with coding. Structures that do not themselves
brain may be a candidate for this role. It would, however, seem more plausible that
"manufacture" rhythmic potentials are passed into them by the arrival of raised dis-
the oscillations of the electroencephalogram, because of the many conditions in which
changes. Any form of frequency analysis that loses information about phase-locked
they can be blocked, are the sign of a secondarily driven oscillator rather than of
will clearly not be the adequate tool to use for this specific purpose.
the original enduring pacemaker. Either proposal would however, necessitate that
the rhythm should not only maintain a constant frequency but should in addition
on fluctuation of potential per unit time (i.e., usually per second). Analysis may
be either be present in a persistent phase-locked form, or, if it were to lapse momen-
tarily, that it should return correctly in phase with its previous oscillations. For
series throughout the whole length of the sample, enabling to find whether any
predictive use, the frequency would, of course, not necessarily have to be monorhythmic.
fluctuations occurring in the EEG are related in any consistent way to those it could be a pattern of frequencies provided the repetition of the patterning that have come before them. were periodic and were phase locked.

If there are characteristics in the EEG that are necessary consequences If one is to search for a characteristic of the electrical activity of the brain that reflects any mechanism that can be used for prediction one has to use a special tool, some form of analysis that tells one whether the parameter selected at a given time is a duplicate of its incidence at a previous time. Such cannot be determined by the usual forms of automatic frequency analysis which lose information about phase-locking. The neurophysiological necessity for insisting on constancy of phase stems not only from the theoretical concept of prediction but also from the practical evidence that the fluctuating potentials of the electro-

At the outset not too much could be expected of the alpha rhythm as a encephalogram reflect excitability conditions in the cortex (and not envelopes of long term measure, for as recorded from the outside of the skull of man, if the spike potentials of discharging cells or axons). There is, however, increasing is acutely vulnerable to changes in the state of the subject and especially evidence that the probability of discharge of units is greater at a specific phase of each cycle of these slower oscillatory potentials, i.e., at the point in the rhythm, as in sleep and anesthesia, does not interfere with time sequence cycle when excitability is maximal.

These facts are cited to make the point that timing of the occurrence of no laying down of new ones in these states. On the other hand, desynchronizes and troughs of oscillatory changes in excitability are of importance in the fashion of the alpha rhythms during conditions of alertness certainly does not transmission of messages in the central nervous system and cannot be excluded from transmits the temporal coding process. As indicated above however, there is any hypothesis that concerns itself with coding. Structures that do not themselves change the possibility of, to make it more emphatic, the probability that an "manufacture" rhythmic potentials are paced into them by the arrival of pulsed discharging. Any form of frequency analysis that loses information about phase-locking will clearly not be the adequate tool to use for this specific purpose.

With these a priori reservations we have applied in our studies of the types of frequency analyzers that we had previously used placed emphasis on fluctuation of potential per unit time (i.e., usually per second). Analysis by this kind of analysis gives information as to whether there are any characteristic autocorrelation on the other hand, yields information about the EEG voltage-time in the raw data whose statistical properties are independent of the interest in series throughout the whole length of the sample, seeking to find whether any
fluctuations occurring in the EEG are related in any consistent way to those that have came before them.

The principle of autocorrelation as applied to the EEG is that data will not be discarded if the same features occur in the EEG that have preceded them (characteristics that can be predicted by extrapolation from a previous section of the record) the EEG would have some of the features of the phenomena known as stationary time series. The possibility that there is some process of this kind in the brain suggests one conceivable mechanism by which some of the coding of time sequences of experiences might be mediated. Such a process could be the central pacing mechanism for several forms of driven oscillations of which the alpha could be one.

At the outset not too much would be expected of the alpha rhythm as a long term measure, for an recorded from the outside of the skull of a man. It is notoriously vulnerable to changes in the state of the subject and especially to the degree of his vigilance. Complete (apparent) suspension of the alpha rhythm, as in sleep and anesthesia, does not interfere with the coding of time sequences that have already passed into their stored form, but there would seem to be no laying down of new ones in these states. On the other hand, desynchronization of the alpha rhythm during conditions of alertness certainly does not impede the temporal coding process. As indicated above however, there is always the possibility or, to make it more emphatic, the probability that in examining the alpha rhythm we are studying an epiphenomenon of (and not the phenomenon of) the brain's time sense.

With these a priori reservations we have applied in our studies of the electroencephalogram the form of analysis that is known as autocorrelation. This kind of analysis gives information as to whether there are any characteristics in the raw data whose statistical properties are independent of the interval in being reported here is only a small part.
The principle of autocorrelation as applied to EEG has been described in several publications and will not be detailed again here.

In the simplest possible terms, autocorrelation consists of comparing a time series (in our case, an electroencephalogram) with itself displaced in time. This comparison is made by a computer (from the EEG recorded on magnetically tape) at a great number of steps of time displacement, it being possible for these delay steps to range progressively from a fraction of a millisecond to many seconds. Thus if there is a periodic event present in the EEG, the correlation of the EEG with itself will be strongly positive when it lags by a delay time equal to the repeating period of this event and at all multiples of this. At all other delay times the correlation will be less than maximal. This higher correlation with the same periodicity as the repeating event will be present even if the periodic activity is of considerably lower amplitude than that of competing potentials of a random nature that may completely mask the oscillations in the standard EEG tracing (for these will average out if the interval sampled is adequately long). It should be emphasized that in averaging techniques of this kind the unavoidable use of finite samples introduces errors. A special study of this point is being made by members of Professor Rosenblith’s laboratory at Massachusetts Institute of Technology. Indices would in fact alter either of

Since making our first pilot studies, phase in which we had to adapt to our use a digital computer designed for another purpose, we have had the use of an analogue computer designed for the autocorrelation analysis of EEGs, and constructed in collaboration with our colleagues at the Massachusetts Institute of Technology who are participants in the program of research of which the work we are reporting here is only a small part. Averaged over several stimuli, are phase-look.

If we restrict ourselves to the subjects who are to the best of our knowledge...
physically and mentally normal we find that their autocorrelograms can be roughly classified in three categories: those who have a markedly periodic recurrence of high correlation persisting for some seconds, those who have a marked periodicity in a range of short delay times, but not persisting beyond a second or so, and those who have little or no rhythmic recurrence of high correlation (i.e. minimal, if any, trace of a phase-locked rhythm).

In the context of the discussion with which this paper opened it is clearly the first category of autocorrelograms - those of a long persisting periodic character - that are of the most interest. Examples of two subjects in this category are shown in Figure 1. But before leaving the other two categories aside, it may be pointed out that an investigation into the conditions under which these subjects can be induced to yield periodically fluctuating correlations is of great interest, and one which we are only just beginning to explore. This work will not form a part of the present report. It might perhaps be remarked that individuals in the third category, i.e. without any rhythmically occurring correlation, are rare. In the individuals from whom rhythmic autocorrelograms can be obtained it has been found that samples taken several months apart usually yield very similar analyses.

Having found this persisting periodicity of the autocorrelation function when averaged over the whole 5-minute samples of EEGs, the next step was to determine whether an imposed sensory stimulus would in fact alter either of the parameters mentioned above; i.e. the phase or the frequency.

The subjects were therefore flashed with a slowly repeated flash. In order not to set up a resonance or cyclic conditioning, the flash was delivered at random intervals. The resultant EEG was then cross-correlated with a pulse signal-led by the flash onto one channel of the magnetic tape. The computer, in this case, reports only those potentials which when averaged over several stimuli, are phase-locked to the flash. All unrelated random potentials are rejected provided the
sample is adequate in length. An example of this type of analysis for detecting "signal to noise" is shown in Figure 2. This technique gives the envelope of the averaged response, and as can be seen from the figure, a great amount of detail emerges when the random background is eliminated. There is a primary response of short latency (between 15 and 20 msec) initially occiput positive. There is also a large late response. After the main complex is over, we see a periodic after-discharge, such as has been described in animals by many writers. The after-discharge in man has also been described previously, but the point for emphasis here is that the after-discharge is phase-locked to the stimulus. The usual methods of harmonic analysis in the frequency domain cannot give this information.

This finding, of a rhythm phase-locked to the stimulus shows that the brain now has a rhythm that has been imposed on it through a sensory system. Has this imposed rhythm supplanted the 'endogenous' one, or is it the same rhythm with a shift in phase to carry the message, or is the basic rhythm still there and this one added? In the latter case the brain would have its own rhythm against which to match this one for both frequency and phase.

A test for whether the original rhythm is still present is to run autocorrelations on the EOG of the subject while being flashed aperiodically. Since the stimulus-evoked oscillations are locked to the flash, and since this is occurring randomly, they will not appear in an autocorrelation at values of delay larger than the intervals between flashes.

Figure 5 (center strip) shows that there is some clear periodic oscillation that is independent of the influence of the flash. Here then is a measure against which the brain can match the new oscillations that are going on at the same time. This match can be made for phase and for frequency.
The two forms of analysis shown in Fig. 3 are of the same recording of
the EEG - the identical sample having been analyzed in these two ways for
selective extraction of these two contrasting characteristics, and hence it
is the same neuronal (and electrical field) of the brain that has been sampled.

It is not, of course, being suggested that the brain has only one endogenous
rhythm. Autocorrelation bears out the electroencephalographer's impression
from ink-written records that rhythms of different frequencies may be present
simultaneously in other parts of the head (see for example Figure 4), and this
gives the brain yet more possible tools for matching time sequences. This sug­
jects that some of the complexities introduced by flash stimulation may be
altering the relative dominance of these real rhythms as recorded from our
electrodes. In other words, information may be being carried by the relative
dominance of the various rhythms.

Of the different rhythms so far discussed, the sensory after-discharge
seems to be the most labile, by which is meant that in the same person consider­
able variability may be found, especially in the degree of regularity of the oscilla­
tion. In relation to this, one may well ask whether this lability may not in
fact be basically due to a great variation of cortical response from flash to
flash, a variation lost sight of by the use of an averaging technique. This varia­
tion might be expected to include, among others, the decrease in response with
familiarisation, such as has been described by Artemiev, by Hernández-Peón
and by Galambos.

We have recently been able to make some first steps towards a quantifiable
study of variation in the laboratory of Professor Rosenblith where we have been
privileged to use a new type of computer. This is an instrument with transis­
torized circuits that gives a write-out in digital form of the averaged response
to a stimulus within a minute of so of receiving the input. The computer
has in addition, other circuits that display(either on an oscilloscope or
on a write-out) a histogram of the distribution of values, the mean of which
appears as a single plotted point on the curve of the averaged response. His-
tograms can be obtained for each plotted point, and thus the degree of scatter
around the median can be assessed for any part of the response.

Our studies on the variability of response in man are not yet complete
enough to report, though we have some material of this nature on animals.

Figure 5 illustrates the type of information one gets about the variability
of cortical response to flash in the cat, with and without anesthesia. The
records show the response in 1 millisecond steps following the flash.

The averaging process brings out the response that follows the primary
by about 11 milliseconds and which presumably travels to the cortex by the
non-specific route uncovered by the work of Magoun and his group. This response,
unlike the primary one, has no counterpart in the lateral geniculate nucleus and
is abolished by barbiturate anesthesia.

In order not to overload the figure, histograms for only 6 points of each
curve are shown - namely for the record on the left are data for the scatter of
values found at intervals after the flash of 15, 25, 35 and 45 milliseconds. In
the righthand record the histograms are shown at intervals after the flash of
10, 20, 30 and 40 msec. after the flash.

The much greater range and hence larger standard deviation of the values
in cat when unanesthetized than when barbiturized is very clear. This analysis
alone does not however differentiate between variation of background activity
again which the response is occurring and variability of the response itself.
For this differentiation further analysis is required.

This figure is shown for the hearing it has on the suggestion that in the unanesthetized organism, animal or man, a stereotyped response to flash cannot be suspected. This may result in the lability that we find in the after-discharge for which only by more careful the temporal lobe recorded with

In the context of the main subject matter of this paper, we conclude from the type of experiments outlined so briefly above, that incoming sensory impulses may register on the brain by a contrast in phase to that of its alpha rhythm and by a complexity of frequency change that cannot be assigned to a single factor.

The proposal that is being made is that short-term temporal sequence as distributed around the "specious present" may have its neural mechanisms in the phenomenon described here. In no sense is it suggested that these are correlates for that it would seem, one could not be certain at all for the same degree long-term memory or for any of the mechanisms of storage that survive such disruption. Memory of recollection is retained and probability that when, of course, these types of the alpha rhythm as occur in anesthesia, in concussion, in electric shock would change, but not by its effect to sleep or in the same case, could perhaps

In this context, it may perhaps be of interest to show the autorcorrelograms of a subject awake and sleep. On the left of Fig. 6 is a normal subject awake and in natural sleep. For comparison, on the right are the autorcorrelograms in a normal subject awake and in a hypnotic 'sleep' in which all the outward behavioral signs were those we associate with the sleeping state. It will be noticed that in normal sleep all periodic oscillations are lost both in the autorcorrelogram and after the flash, although the primary response is still present.

In summary then, we are exploring the proposal that the periodic phase-locked component of the alpha rhythm may contribute to the factor of exact repetition necessary for probablistic measurement of time intervals over a period of seconds with a considerable degree of accuracy, and that sensory stimuli register against this time-base by initiating a rhythm differing in phase and also as a frequency
change of great complexity which may in fact be a modification of the relative
dominance of the several frequencies present at all times in the head, as evi­
denced, for example, by those recordable in the temporal lobes compared with
those in the occiput.

It should be emphasized that in the conceptual background against which these
experiments were designed, a distinction was drawn between general awareness of
the passage of time and an exactness of time sense that can be gauged only by
a mechanism. The subjective experience and the objective behavior is usually one

No less interesting, however, is the other, but related problem of the awareness
of temporal sequence, of the reversibility of time's arrow. For
this, it would seem, one does not need to call on the organism for the same degree
of accuracy of repetition; a mechanism based on probability that must, of course,
be recognized as a problem for students of the nervous system, one finds that
exceed chance, but not by so great a degree as in the other case, would perhaps
have been considered as being paid in the past to how the nervous system handles
suffice. The body has several extra-neural candidates for this role, the heart
rate being the most obvious one. Others are respiration, blood sugar levels,
the sleep cycle, sexual cycles, etc. etc. These are all variable, but variable
within ranges sufficiently limited, to permit them to be used on a probability
basis for approximate estimations.

All of them have a degree of homeostasis operated by the autonomic nervous
system and all of them have nerve supplies that can report to the central nervous
system the degree of maintenance of, or departure from, a balanced homeostasis.
But surely this would imply some time gauge, some rhythm or resonance against
which these reports are to be matched for estimation of probability.

Most of the processes mentioned exert their action outside of what we usually
define as "awareness", but there are situations where the departure of an
external rhythm from its predicted periodicity is subjectively experienced
as a departure from probability. All composers, musicians, conductors
know that they can evoke a sensation in their listeners by imposing a rhythmic
technique of preponderant-argoisique, utilising a structural insensitivity of wave
beat, and then either anticipating it, which has what is described as a rousing
effect, or delaying it which has a subjectively anxiety-making effect.

Similarly subjective effects can be induced in the laboratory by flashing
5. a subject at a constant rate until the electroencephalogram shows a steady rhythm
and then suddenly introducing randomly delivered (and hence unpredictably occurring)
flashes. The subjective report and the objective behavior is usually one
in uncorrelated electrodes. J. Physiol. 111. 226, 1951
of anxiety and may have definable autonomic components, such as a change in

Although man's time sense has always been of interest to philosophers, and has
been recognized as a problem for students of the nervous system, one finds that
far less attention has been paid in the past to how the nervous system handles
time than to how it handles space. As one searches back through the history
of man's recorded thoughts and looks at the development of his concepts about
his nervous system, one finds the emphasis in the neurological sciences to
have been in terms of spatial attributes of perception. The experimental work
described here is presented as a preliminary foray into the time domain.

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Figure 1: Autocorrelograms of two normal adults.
RESPONSE TO FLASH IN MAN
(AVERAGE OF 180 RESPONSES)

0 85 170 225 milliseconds

Figure 2.
Response to flash in man. The envelope of the curve gives the average of 180 responses sampled at 5 msec. intervals and recorded by unipolar linkage from the occipital region of the skull. The first 3 pen deflections that stand alone on the left, and the detached group on the right, are for calibration of the baseline. The flash was coincident with the first pen deflection of the continuous series. Note early occipital-positive response and late rhythmic after-discharge, phase-locked to the flash.
Figure 3.
Analyses from a subject while being stimulated with an aperiodic flash.

Above: Autocorrelogram while being flashed.
Below: Averaged response to the random flash.
The two analyses were made from the same sample of EEG.
Figure 4.

Autocorrelograms of EEGs run simultaneously from bipolar temporal leads, a unipolar lead from the vertex and bipolar occipital leads.

Note rhythm of different frequencies present at the same time in different parts of the head. (Analyses made in 5 msec. steps of delay).
Figure 5.

Below left: Averaged response to flash in the visual cortex of an unanesthetized cat with implanted electrodes. Primary surface-positive response (latency 12 msec.) is followed by a second (latency 23 msec.). Analyses have been made in 1 msec. steps of delay.

Above left: Four histograms showing the degree of scatter of the individual readings that gave the average value depicted at 15, 25, 35 and 45 milliseconds (respectively) after the flash.

Below right: Averaged response from the same cat when anesthetized with pentobarbital sodium. Note lengthening of latency to primary response and absence of the second surface-positive response with consequent unmasking of large surface negativity.

Above right: Histograms of the scatter of points for the averaged values at 10, 20, 30 and 40 msec. after flash. Note the much tighter distribution under anesthesia than in the awake cat.
Figure 6.

LEFT Above: Autocorrelograms of a normal subject, awake and asleep.
Below: Averaged responses to flash of the same subject, awake and asleep.

RIGHT Above: Autocorrelograms of a normal subject, awake, and in a hypnotic 'sleep'.
Below: Averaged responses to flash of the same subject, awake and in a hypnotic sleep.
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Those physiologists whose field of investigation lies within the brain, have long been reactive with black box models that strive to relate all the characteristics of the output to the extracorporeal parameters of the input. Such a line of argument derives from the past— from an earlier era of laboratory procedure, one in which the experimental animal was anesthetized to a level at which the brain no longer met the incoming stimuli with its own modifying excitatory and inhibitory reactions.

Modern physiology tells us that in such experiments centrifugal control of inflow, ascending reticular and mid-line thalamic influences, cerebellar modification and limbic system influence, as well as more complex factors introduced by the circulatory and humoral systems have all been distorted by the experimenter, and the stimulus-response data that he collects are information, not about the functioning brain, but about a laboratory artifact that he has, in part, constructed.

In the normal animal the extracorporeal stimulus impinges on a nervous system already under stimulation from its proprioceptors, its interoceptors and its milieu interieur, and we are not justified in regarding it as being in a steady state.

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*U.S.P.H. Senior Research Fellow.
As techniques have developed that enable the investigator to study the electrophysiology of the brain in unanesthetized, freely behaving animals, evidence has grown that the changing degrees of interplay between the three great systems of the brain are paramount in determining the response to a given stimulus.

Of these three major functional systems of the brain we have heard in these sessions much about the specific afferent systems, something about the midline non-specific system but unfortunately there has been nothing about the limbic system, for all are involved in the subject that gives its title to this symposium. The purpose of this preamble is to emphasize the background of variables within the functioning brain against which the experiments that are to be reported have been designed, for these introduce yet another consideration, namely: variation with serial time. The results are being presented to emphasize that the response of the brain to a stimulus whose parameters are held constant, is modified by the past experience of the organism. In other words, the output of the black box depends on its past history.

With the slow realization by Western scientists that the conditional reflex technique can give them a method for imposing a controlled experience on the animal, has come an increasing wealth of information as to the changing interaction of the various brain systems in the serial stages of training in the learning of a task.

The initial recognition of these serial changes came essentially from electroencephalographers skilled in the recognition of pattern in the records of both animal and man, and at first they had to meet considerable skepticism.
of electrographic condition. With the exception of Stage II, this work will not be described in more detail as Dr. Morrell's presentation of it to the American EEG Society's Symposium on "EEG and Conditioned Behavior" is shortly to appear in print.

Somewhat similar observations have been made by several workers and the suggestion has been made by some that the rhythmic wave that appears so evanescently in Stage II may reflect an anticipation by the brain of the flicker frequently heralded by the conditioning stimulus. In order to determine this point the Average Response Computer in the Laboratory of Communications Biophysics was called in as consultant.

We were fortunate in having Dr. Morrell come to work for a brief period in our laboratory at the Massachusetts General Hospital where he and Dr. John Barlow ran a series of rabbits through a similar experience, recording the EEGs on a 7-channel magnetic tape recorder, and submitting the recordings later to analysis by the computer at M.I.T.

Figure 1, reproduced from Dr. Morrell's paper, shows the result of averaging the records from one of the rabbits in the series. These are all averages of the electrocortical activity in the period between the tone-signal which triggers the sweep and the onset of flicker. Averages of 10 trials, each 2 seconds in length, are shown in each trace, their serial incidence being indicated on the right. The beginning deflection on the extreme right of each trace is caused by the first flash of the train.

The rhythmic activity which Dr. Morrell had perceived in his ink-written traces in Stage II is clearly seen. In this rabbit it appeared most prominently in the averages of the 60th to the 70th trials.

(*) This computer, designed and constructed at the Lincoln Laboratories of M.I.T. has been described by its designer in reference #2.
What is this rhythm? It may bear no direct harmonic relationship to
the frequency of the flash that the brain is being trained to expect, and
in our experience is a phenomenon that can be unrelated to the specific flash
frequency. Rather we would propose that this may be a reflection of a tran-
sient dominance of limbic system arousal at this certain stage of training.
In the rabbit the hippocampus lies little more than 2 mm. below the visual
cortex (from which these recordings were made). We know from the work of
Green and Arduini that activation of the reticular formation either by
direct electrical stimulation or by normal stimulation of peripheral receptor
organs, evokes a theta rhythm of high voltage, high enough, it is being sug-
gested, to be recordable about 2 mm. distant in a volume conductor.

The second series of experiments to be presented as examples of changing
interplay between systems within the brain as the result of repetition of
constant stimuli concern situations developing during the establishment of
a conditional reflex. The average in each case of 432 responses of the

A paper has been published this year by John and Killam in which were
reported many and subtle changes in the electrical recordings from multiple
sites within the brain as well as from its cortex, during conditioned avoid-
ance training. To summarize the great amount of data presented, one may say
that during conditioning stages were found where potentials arose in struc-
tures previously unresponsive to the stimulus, and modification was seen in
the response of structures initially responsive.

One of the many interesting findings reported by John and Killam was
a change at different stages of the training period in the potentials of
the lateral geniculate nucleus to the repetitive flash that they were using
as the conditioning stimulus. This was surprising, for all of the structures
in the brain one would perhaps expect the classical relay nucleus of the visual system to be the most conservative in its response.

It was fortunately possible for one of these authors (K.F.K.) to come to work in the laboratory at the Massachusetts General Hospital for a period, so that some of the recordings could be put on a tape-recorder and played back into the computer at M.I.T. The experiment was in many ways similar to those reported by John and Killam from work at Los Angeles, but in the experiments about to be reported the conditioned response was not avoidance of a shock but lever-pressing rewarded by milk. Electrodes were implanted in several sites within the brains of the cats in this series, but the present comments will be restricted to the events recorded at the lateral geniculate nucleus. These recordings were made some weeks after the implantation when the animals were unanesthetized and freely moving.

The signal was a 10/sec. flash and the average response curves shown in Figure 2A, B and C are the averages in each case of 432 responses of the lateral geniculate. This computation was processed in the Laboratory of Communication Biophysics at the Massachusetts Institute of Technology by the same computer that was used for the experiments of Morrell that have just been described. The computing procedure increases the signal-to-noise ratio so that detail previously hidden in background activity can now be studied.

In Figure 2A is shown the average response of the lateral geniculate nucleus to 432 flashes during an early stage of learning when the cat was beginning to master the first step in responding appropriately to the 10/sec. flash. At this stage no limit of time was forced on the animal, the train of flashes being continued until he pressed the lever.
Averages of this kind are obtained by cross-correlating the electrical trace (recorded on magnetic tape) with a pulse timed by the flash. Thus the curves shown represent the average of only those potential changes whose phases are consistently locked in time to the occurrence of the flash. Randomly occurring ERG potentials unrelated to the flash are averaged out.

The sweep starts at a constant interval before the incidence of each flash and the flash artifacts are not included in the record. Since the signal is a 10/second flash there is a 100 msec. interval between the primary response and the change in the complex that follows it and that presumably represents, and hence the first 25 msec. of each of these curves represents the effects of the elaboration procedure. Note also that the average effect of the early residual effect in the lateral geniculate nucleus of each previous flash is now very long-lasting, occupying the whole of the 100 msec. interval.

In Figure 2A this is negligible, i.e., the effect of each flash has died out in the geniculate by the time 75 msec. have elapsed from the previous flash.

One notices in Figure 2A that after the initial response there is another event, triple in form and building up to an amplitude as great as the initial signal is a 10/second flash there is a 100 msec. interval between the primary response. If the primary response represents the initial arrival of the signal, this subsequent complex may be described as an electrical concomitant of the processing of that signal.

Figure 2B represents the average response from the same electrodes when the cat had fully learned the procedure and had become an automaton, responding correctly every time with a fully elaborated reflex. As these are averages, the differences in the curves are significant. One notes an augmentation of the primary response, but an even greater augmentation of the complex that is being suggested for consideration as the sign of the processing that follows the receipt of the signal. Again one sees from the early part of the sweep that the average disturbance created in the geniculate by the flash does not last for the full 100 msec. interval between
flash es.

Figure 2C gives the curve obtained when this same fully-trained animal was confronted with the necessity to discriminate between 10/second and a 6/second flash. Only with the former frequency was lever-pressing rewarded by milk. The brain now had to match the frequency it was experiencing against some stored information of a previously experienced frequency. The changes in the average response from the lateral geniculate apparently reflect this demand for a new form of processing. The primary response has become distorted, but more striking is the change in the complex that follows it and that presumably reflects a part of the elaboration procedure. Note also that the average effect of a flash is now very long-lasting, occupying the whole of the 100 msec. interval and even invading the rise of the curve of the newly entering subsequent flash. The stimuli are the same but the reactivity has changed.

The last set of experiments to be reported here also have bearing on the effect that the past experience of the brain has on the response that a given stimulus will evoke from it. These experiments were begun in Los Angeles on a visit to Dr. Magoun’s laboratories and they have been continued since at the Massachusetts General Hospital.

It has been shown by Livanov and since by several other workers on intersensory conditioning, that if one exposes an animal to trains of synchronous flashes and clicks, after a given time the same flashrate, without any click will produce a repetitive response in the auditory cortex. This result can be readily confirmed in cortical recordings but it seemed to us of interest to know whether this intermixing of the sense modalities could be detected in the deeper structures of the brain.

If one exposes an unanesthetized cat with implanted electrodes to a
standard flash rate (without sound) many times, an inkwriting oscillograph
indicate that the number of deep structures that respond may increase, but
provided the flash is silent (and for these experiments a silent argon tube
was used), the specific auditory pathway will remain apparently unresponsive
light was off and a drop when it came on again. In the top record there
except to the “on” of the brain.

From experiences with an automatic frequency analyzer in experiments
that have no place in this report, it would appear that the various struc-
tures, if they react at all to repetitive stimulation with a repetitive response,
do not necessarily adopt the stimulus frequency. Each structure responds within
its preferred frequency band which is usually rather narrow. The reticu-
lar formation, for example, responds in a frequency band grouped around a lower
center frequency than the response of the specific relay nuclei. Undoubtedly
this is directly related to the longer recovery time of reticular neurons.

One cannot determine this from unanalyzed records such as this, but
Figure 3A is introduced to show that although the reticular formation gradually
assumes a rhythmic oscillation no trace of rhythm can be detected in the audi-
ary system in these ink-written records from a cat who has never experienced
a click paired with the flash.

Quite a different result is obtained from the cat when he has experienced
a click coincident with every flash of the train (Figure 3B). With a past
history of this kind the auditory system reacts to flash alone with clearly
marked responses, and even in this unanalyzed record there is a strong sug-

gestion that the change is not restricted to the auditory cortex alone, for
the medial geniculate is now clearly disturbed by the flash.

We were interested to study this interaction of sense modalities with
the flash. The slow waves seen in the previous experiment are again present.

The lowest record is with click alone in the cat after experiencing the
called ‘driving’ with its implications of resonance.
paired. Figure 4 shows on the left, superimposed oscillograph traces derived from the auditory system. The cat was in a sound-reduced compartment in a steady silent argon light. A rise in the signal line indicates when the light went off and a drop when it came on again. In the top record there was no response in the auditory system either to the “off” or the “on” of the light.

In the center trace a click has been introduced at the “off” of the light. An initial response in the auditory cortex and medial geniculate is followed by two slow waves in both these structures. The 4th beam is recording from a position in the reticular formation where large responses to click were always present. Histology showed the tip of the electrode to be in a site analogous to that which, in the marsupial phalanger, was found by Adey, Dunlop and Sunderland to give large evoked responses to click. This was a part of the subparafascicular system.

In the lowest record, the stimulus was identical with that in the top record, but the experience of the brain had changed; a flash alone now evoked the two slow waves in both auditory cortex and thalamus. Not only does the auditory system give this mixed response to flash, it also gives a mixed response to click, once it has had the experience of pairing. This can be seen in Figure 4 in the right hand column of records. These are recordings from the same sites as in the left hand column. The response to click in the animal who has experienced no pairing appears in the top record. In the center record the click has been timed to coincide with the “off” of the flash. The slow waves seen in the previous experiment are again present. The lowest record is with click alone in the cat after experiencing the
paired modalities. The slow wave brought in by the flash in the past is reproduced by the brain, although there is no flash stimulus in the present.

On return to our laboratory at the Massachusetts General Hospital, a new series of experiments was begun along these lines with the object of processing the control recordings were analysed by the computer, it was found, the recordings through the computer in order to facilitate the detection of as we had begun to suspect, that all these sites responded both to click alone responses hidden from us in the single trace, or even in the superimposed traces and to light alone even before the animal had experienced these stimuli paired, for, of course, these latter do not in any way reduce the amplitude of the back—(Figure 7). Although it may be possible to assign to the components of ground activity.

In this series of experiments on unanaesthetised cats with implanted electrodes, in the reticular formation and superior colliculus), this explanation cannot be made to fit control runs were made to record responses to click alone and to flash alone before all the data, especially when amplitude as well as phase is taken into account, allowing the animal to experience any pairing of stimuli. The stimuli were in all cases delivered at a rate of 1 per second. The cat was in a sound-reducing box, actually an old refrigerator cabinet lying on its side with one end replaced by a transparent plastic window. The stroboscope used was built into a sound-reducing box to muffle its click, and a second glass was placed in front of its light, so that an air space lay between the two glass fronts. The stroboscope was placed outside the cabinet containing the cat. In all experiments a masking 'white' noise is evoked before the brain had experienced pairing. (In all figures the numbers were delivered, its intensity being regulated for each experiment by calibration to the left of each trace are inversely proportional to the scale used in one of the input voltage to the loudspeaker. Clicks when used were also calibrated placing the animal.

to a standard intensity at each experiment. The duration of each click was

The late slow wave response detected in the superimposed traces of the 100 μsec.

Oscilloscope records can be seen in Figure 9 and were present in deeper structures as well as in the cortex.

Computer-averaged responses to flash after the cat had experienced pairing are shown for the auditory system, reticular formation and centre median in Figure 5. None of these sites is unresponsive to flash. The response of the reticular formation was of such high amplitude that it is reproduced at half the scale used for the other positions. The response of the reticular formation is, of course,
merely confirmatory of the responses first demonstrated by French, Amerongen and Magonn. In whatever stage it is evoked and whether by single or multiple sensory stimuli, will always depend on the state of the animal. In working with the fully functioning brain we are faced with a system that does not contrast with response of the same electrode site to click. The same scale for long tolerate the isolation of a single variable. Difficult as it is to accomplish, the experimenter must attempt to keep his animal at the same level of general anesthesia in all the tests if his results are to be causal as we had begun to suspect, that all these sites responded both to click alone and to light alone even before the animal had experienced these stimuli paired. When the control recordings were analyzed by the computer, it was found, as we had begun to suspect, that all these sites responded both to click alone and to light alone even before the animal had experienced these stimuli paired.

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response, at whatever stage it is evoked and whether by single or multiple 
sensory stimuli, will always depend on the state of the animal. In working 
with the fully functioning brain we are faced with a system that does not 
for long tolerate the isolation of a single variable. Difficult as it is 
for the experimenter to accomplish, the experimenter must attempt to keep his animal at the same 
level of general alertness in all the tests if his results are to be com­ 
parable. Although hard to achieve, this is easy to monitor, and for this 
reason simultaneous EEG records have been run in all the experiments re­
ported here.

Space limits the display of changes found in all the brain centers 
may be superficial. Should this eventually prove to be so, we would be 
from which responses were obtained in these experiments, but perhaps enough 
have been presented to explain why these records have suggested to us that 
of new anatomical pathways as necessary mechanisms for the development of 
the intersensory response after pairing is an augmentation of one already 
there, and that the major changes are probably in the late slow fluctuations 
such as were noticed in the oscilloscopic records. It would appear probable 
that all parts of the brain take their individual part in the subject of 
this symposium, namely sensory communication.

Much further work is needed before a more definite statement can be 
made, but the possibility may be proposed that the so-called 'temporary con­ 
nections' set up by intersensory conditioning are not, in fact, temporary 
connections, but already existing ones. It is interesting in this context 
to recall the proposals made by Gastaut and by Fessard and others 
since, that conditioning may be explained on the basis of a center of con­ 
vergence in the reticular formation.

The suggestion is made here that before conditioning the electrical
signs of activity in these connections often lie below the noise level of the brain’s on-going activity, and that the influence of the pairing is to increase their amplitude to a level at which they can be seen.

The connection may be only one of very many somewhat diffuse pathways but its repetitive use may result in a facilitated transmission — perhaps a membrane change — that brings it into dominance.

The possibility may even be entertained that further experiment may reveal similar electrophysiological information about other forms of conditional reflexes and that the concept of temporary connections may be superfluous. Should this eventually prove to be so, we would be relieved from speculations about protoplasmic outgrowths and the formation of new anatomical pathways as necessary mechanisms for the development of conditional reflexes.

Summary:

The position is taken that the response of the brain to sensory stimulation depends more importantly on events within the brain than on the extracorporeal parameters of the stimulus. Not only do current activities in brain mechanisms influence the response, but past experience also has its effect.

Three series of experiments illustrating the influence of past experience on the reactivity of the brain to standard stimuli are reported. The first of these was carried out with Dr. Frank Morrell and Dr. John Barlow; the second with Dr. Keith Killam and Dr. Barlow, and the third in collaboration with Dr. Keith Killam and Dr. James Hance in the Department of Anatomy at the University of California at Los Angeles, continuing
at the Massachusetts General Hospital with Miss Ruth Carpenter and Miss Margaret Magavern.

As a general conclusion the proposal is made that the so-called temporary connections set up by intersensory conditioning are not in fact temporary, but already existing connections whose responses are augmented by use. These responses often lie hidden below noise level of the usual recording but can be revealed if processed through a computer that increases the signal-to-noise ratio.

It will be clear to the reader that there is one to whom we are very greatly indebted: Prof. Walter Rosenblith. It is a pleasure to have an opportunity to express our appreciation to him and to his group, among whom we would especially like to mention Mr. Frank Nardo who has been responsible for operating the computer in most of these studies.

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-15-


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Figure 1. Analysis by the Average Response Computer of the cortical potentials occurring in the visual cortex of a rabbit between a conditioning stimulus (cone) and the onset of light flickering at a rate of 16 per second. The sequence of trials averaged in each trace is indicated on right.

(From Russell, Barlow and Bronfer. EEG Clin. Neurophysiol. 1963.)
Figure 2. Average of 432 responses of the lateral geniculate nucleus to 10 per second flash used as the signal that lever-pressing will yield milk.

A: At an early stage of training when the cat is not yet pressed to respond within any given time limit.

B: When the same cat has perfected the reflex response, including a time-limit for reward by milk of response within 15 seconds of onset of flash.

C: The same cat, having reached 100% correct responses to 10/second flash is now required to discriminate between this frequency and a 6/second flash that brings no reward.

For interpretation see text. Averages computed by the Average Response Computer at the Laboratory of Communications Biophysics, Massachusetts Institute of Technology. (Clark, W.2).

(Unpublished records: Kilman, K.F. and Barlow, J.E.).
Figure 3.

A: Responses following the 6/sec. flash-rate in the visual system, but not in the auditory system in an unanesthetised cat which has not experienced clicks paired with flicker.

B: The response of the same cat to 10/sec. flash alone after experiencing clicks paired with the flash at this rate. Note following by the auditory system in the absence of clicks.

(Kilham, Nance and Brazier. Unpublished records).
Figure 4. Superimposed traces from three sites in the brain of an unanesthetized cat showing:

On the left: Response to flash before, during and after pairing a click with the flash.

On the right: Response to click before, during and after pairing a flash with the click.

(Killam, Hance and Brazier. Unpublished records).
Figure 5. Computer-averaged responses to 1/sec. flash alone in an unanesthetized cat who had experienced 4 trains of 500 flashes paired with clicks at 1/sec. The figures on the left are inversely proportional to the scale at which the traces are displayed, i.e., the response in the reticular formation was of such high amplitude that it is reproduced at half the scale used for the other sites. Length of trace 175 msec. Unipolar recordings. The small numbers indicate latency times from the flash for various points on the curves.
Figure 6. Computer-averaged responses from the auditory cortex of an unanesthetized cat to 1/sec. click alone before pairing and to 1/sec. flash alone after experiencing click paired with flash 500 times. Length of trace 250 msec. Unipolar recordings from middle ectosylvian gyrus. The numbers in parenthesis indicate the scale factors used for the computation, and the smaller numbers latency times from the stimulus.
Figure 7. Computer-averaged responses to 1/sec. click from four deep structures and from the visual cortex in an unanesthetized cat that had not experienced flash paired with the click. All were recorded at the same amplifier gains and are displayed at the same scale factor, (4). Length of traces 150 msec. Unipolar recordings.
Figure 8. Computer-averaged responses to 1/sec. click recorded in the reticular formation of an unanesthetized cat (1); before pairing; (2): during pairing on the first day of intersensory conditioning; (3): on the 11th day; and (4); (Lowest tracing) response to click alone after this experience. The responses to paired stimuli are of such high amplitude that they are reproduced at 2 the scale of the top record. Note increase in response of reticular formation in last trace for which the write-out is at half the scale used for the top record from the 'naive' cat. Length of traces 185 msec. Unipolar recordings. Each test day consisted of 4 trains of 300 paired stimuli.
Figure 2:
Average responses to flash before (above) and after pairing (below) the flash with the click. Note development of late wave.

These records have been plotted by the computer at 1/5th of the time-base used used in previous illustrations in order to demonstrate the late wave. With this time-base the resolution of the early events is lost. Length of each trace = 350 msec. To aid the eye the 100 msec. and 500 msec. intervals from the flash are marked at the top and bottom. The small figures (16 and 32) at the beginning of the traces indicate the scale used for the computer write-out (the smaller the number the greater the amplification). Note that the responses from the visual cortex increased in size after pairing (and hence are reproduced at half the original scale used in the upper record).
THE EEG IN OPEN-HEART SURGERY AND IN SURGERY FOR AORTIC
AND CEREBRAL ANEURYSMS

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The role of the electroencephalographer in the operating room during open-heart surgery is that of a monitor and a Cassandra. If he cannot warn the operating team of impending trouble his findings will be solely of academic interest. The academic interest will be limited because it will be difficult in the stress of the operating conditions to obtain sufficiently quantitative information to correlate with the observed EEG changes.

The electroencephalographer must therefore have the knowledge of what changes to expect from each of the manipulations that may be made in the patient's cerebral circulation and be able to recognize when these changes exceed the margin of safety. In Figure 1, the danger in hypothermia is that there are three major categories of circulatory manipulation that the electroencephalographer has to be prepared to meet in open-heart surgery.

They are:

1. Hypothermia
2. Extracorporeal circulation
3. A combination of hypothermia and extracorporeal circulation

The choice between these methods will lie with the surgeon but will essentially be dictated by the type of defect from which the patient suffers.

From the Neurophysiology Laboratory of the Massachusetts General Hospital (aided by grants from the National Institute of Neurological Diseases and Blindness (B 569 Physiology) and the U. S. Navy (Office of Naval Research NR 101-445), and the U.S. Air Force (Office of Scientific Research, AF-49- (639)-98), the Communications Biophysics Laboratory of the Massachusetts Institute of Technology (supported in part by the U.S. Army (Signal Corps), U.S. Air Force (Office of Scientific Research, Air Research and Development Command, and the U. S. Navy (ONR)), and the Department of Neurology at the Harvard Medical School.
Hypothermia. The use of hypothermia alone is restricted to those cases where the surgeon is confident before surgery of the type of defect he will find and where it is of a simple nature that can be repaired in about 6 minutes. Almost the only condition that meets these restrictions is an atrial septal defect, an operation with a low mortality rate. Any defect demanding surgical repair in the neighborhood of the conduction bundle, such as a cushion defect of the atrium, must involve a long operative period and therefore must have extracorporeal circulation.

What must the electroencephalographer expect as the result of hypothermia alone? Should there be any change from the patient's normal record? In the years that have followed the pioneer work of the Toronto group there have been many studies made, and it is now recognized that, if all is going well, the most change that should be tolerated is a slight slowing of the rhythm (as is seen, for example, in Figure 1). The danger in hypothermia is that when the temperature falls to 27°C the heart may go into ventricular fibrillation. Fortunately the electroencephalogram is a highly sensitive monitor and usually gives signs of impending trouble before ventricular fibrillation begins. It is the task of the electroencephalographer to familiarize himself with these warning signals. There is one further advantage of EEG monitoring in hypothermia. Shivering, which is of course to be avoided, is usually detectable on the EEG trace before it is clinically visible.

Since this colloquium is devoted to consideration of cerebral anoxia in general, some observations on monitoring the EEG during carotid occlusion performed for the excision of cerebral aneurysms under hypothermic conditions may be reported. Figure 2 shows the EEG of a patient being operated on for a cerebral aneurysm; the first record on the left at the top was taken 20 minutes after
cooling had begun, when neck surgery for exposure of the carotids had been
started under pentothal and curare. She was on a Jefferson respirator. The
most likely indicator of C2o stagnation, for a drop of 0.2 in the pH is a frequent
EEG shows high voltage slow waves of pentothal anesthesia. We find, as others
result of cooling. Measurements of pH values of the blood sample in vitro have,
have before us, that hypothermia potentiates the EEG signs of this anesthetic,
of course, to be corrected for the temperature of the blood when taken, and it must
probably owing to the fall in liver metabolism caused by the cooling. At the
time of this first record an arterial blood sample showed her carbohydrates to
be 56 mg.%, Lactate 12.5 mg.% and phosphorus 5.65 mg..%. The second record on
of pentothal in the EEG, (which is certainly an undesirable sign) can be avoided,
the upper right is a sample taken after craniotomy had begun (each EEG excerpt
in the case shown in Figure 3. For example, the arterial pH just before double
is 3 seconds in duration). Her temperature was at that time 30.8° and a blood
sample showed that her carbohydrates had risen to 70 mg.%. without coincident
the patient made a very satisfactory recovery.

increase in products of glycolysis and her total serum inorganic phosphorus

In another patient (Figure 4), who was being operated on for an aneurysm of
had dropped to 2.2 mg.%. The lower two photographs show a further drop in tem-
peratures. All effect of the anesthetic drug has gone and some slowing due to the
blood sample showed that her carbohydrates had risen to 70 mg.%. without coincident
cooling is seen.

Renneman, Bunker and Brewster have reported that in general during hypo-
and on release there was immediate recovery at the EEG activity. After moderate
thermia decreased carbohydrate respiratory oxidation takes place without coincident
hyperpolarization the pH was raised to 7.51 and carotid occlusion repeated in order
increase in glycolysis and that in these circumstances the total serum inorganic
phosphate was found in an anesthetic with either ether, pentothal, or cyclopropane. With these
breakdown of glucose to lactic acid and the reduction of
pyruvic acid to lactic acid occur readily under anaerobic conditions, but the
breakdown of lactic acid requires oxygen. This metabolic situation, which
further breakdown of lactic acid requires oxygen. This metabolic situation, which
must be the chemical counterpart of what the EEG reflects, contrasts with that
must be the chemical counterpart of what the EEG reflects, contrasts with that
another sign of danger, namely the development of large delta waves which are
found in anesthesia with either ether, pentothal, or cyclopropane. With these
because of carotid hypoxia rather than of C2o accumulation. They are very ominous
anesthetic the carbohydrate in the arterial blood falls and the lactate increases.
signs are not as obvious as before. The change was not sustained, but total occlusion was then
further breakdown of lactic acid requires oxygen. This metabolic situation, which
This warning sign, of a sudden drop in amplitude of the EEG, contrasts with that
another sign of danger, namely the development of large delta waves which are
found in anesthesia with either ether, pentothal, or cyclopropane. With these

In some of our cases the change in the EEG on carotid occlusion has been a
will be replaced by a flat record, i.e., not merely a loss of amplitude but a loss
moderate slowing only, as in Figure 5. In this case the duration of the double
occlusion was 11 minutes, and the EEG slowed but did not flatten. It would
The accumulation of carbon dioxide is a rare occurrence in these cases, and it is most likely indicates a CO₂ stagnation, for a drop of 0.2 in the pH is a frequent result of occlusion. Measurement of pH values of the blood sample in vitro have, among other abnormalities developing especially in cases where the patient's condition is being taken, and it must be remembered that more CO₂ is held in solution in the blood at low temperatures.

In another patient (Figure 4), who was being operated on for an aneurysm of the anterior communicating artery, the arterial pH was 7.45 and the CO₂ 28 meq/l. Unilateral occlusion did not affect the EEG, but bilateral occlusion produced an immediate drop in amplitude. Total occlusion was therefore held for only 5 minutes before surgery. After moderate hyperventilation the pH was raised to 7.51 and carotid occlusion repeated in order to proceed with the surgery. (Figure 5). There was some change in the EEG, but not nearly as severe as before. The change was not maintained and total occlusion was then held for 5 minutes during which time surgery was completed.

The warning sign, of a sudden drop in amplitude of the EEG, contrasts with another sign of danger, namely the development of large delta waves which are heralds of cerebral hypoxia rather than of CO₂ accumulation. They are very ominous signs and cannot be regarded lightly. If the hypoxia becomes severe the slow waves will be replaced by a flat record, i.e., not merely a loss of amplitude but a loss of activity.

This sign of a sudden drop in amplitude of the EEG, contrasts with another sign of danger, namely the development of large delta waves which are heralds of cerebral hypoxia rather than of CO₂ accumulation. They are very ominous signs and cannot be regarded lightly. If the hypoxia becomes severe the slow waves will be replaced by a flat record, i.e., not merely a loss of amplitude but a loss of activity.
The accumulation of carbon dioxide is a rare occurrence in these cases and is usually satisfactorily avoided by controlled hyperventilation but may sometimes develop during rewarming. The electroencephalographer should be alert for abnormalities developing especially in those cases where the patient's own lungs are being used for ventilation with artificial respirators. This is a danger one meets very occasionally in all types of surgery carried out with muscle relaxants.

The EEG sign of inadequate removal of carbon dioxide is a drop in amplitude that is rapidly reversible when ventilation is increased. If the gains of the recording amplifiers are adjusted for study of the EEG in this condition, it will be seen that the trace has the low voltage, high frequency suggestive of an activated record, and the patient gives signs of lightening anaesthesia.

In a case, not of heart surgery, but of abdominal surgery for hernia, an opportunity was obtained for checking on this interpretation by sampling the blood gases and obtaining the pH values. The patient had gone through the operation under light anaesthesia with succinyl choline as a muscle relaxant. Usually a patient will resume his own respiratory contractions within a few minutes of stopping the infusion of this drug. This the patient failed to do in this case and electroencephalography was requested. The record proved to be of low amplitude, with high frequencies and no apparent alpha activity. The patient was being given pure oxygen and though unresponsive in terms of skeletal muscle movement, there was pupillary dilation in response to pinch. A blood sample was taken for analysis which revealed a pCO₂ of 125 mm Hg and a pH of 7.03. Increased ventilation was therefore requested. Within 1 minute a strong alpha rhythm appeared in the EEG and the patient moved, responded to his name and resumed spontaneous respiration. Another blood sample was taken.
and it was found on analysis that the pCO₂ had fallen to 46 mm Hg., the pH being now 7.30. (Figure c).

In this particular case a Jefferson respirator had been used during the action of the succinyl choline. This instrument works on positive pressure and the unforeseen difficulty that arose was owing to the patient's having a bronchial obstruction that resulted in the respirator working on the pressure in the bronchus rather than in the lung. The resultant inadequacy of expiration had raised the blood CO₂ to a high level with a concomitant fall in pH. There was an apparent prolongation of the effect of the muscle relaxant and a lightening of the anesthetic level.

In open-heart surgery, however, respiratory acidosis such as that just described is rare, but hypoxia itself, if not avoided, causes an acidosis owing to the extraordinary unusual site of the patient's beginning to be deoxygenation to the production of acid metabolites resulting from the incomplete oxidation of carbohydrates. The control of the CO₂ level is doubly important because not only is an excess a danger, but an insufficiency in the arterial blood can also cause difficulties by increasing the cerebrovascular resistance. One of the points to remember in using hypothermia is that cerebrovascular resistance rises as body temperature falls. It is also the opinion of those who have studied the threshold for ventricular fibrillation that the CO₂ level must be controlled, for either too high or too low a pH is dangerous. From the studies of others one gathers that the optimal range lies between 7.4 and 7.6.

(2) Extracorporeal circulation. A brief report will now be given of experience with the EEG in extracorporeal circulation. If this procedure can be maintained effectively by the team in charge there is no reason for the patient's brain to suffer and hence no reason for the EEG to change. The task of the team is however not simple. It is not merely a problem of supplying adequately oxygenated
blood at the correct pressure and the correct temperature. There is some inevitable damage to the blood by all pumps, though the degree of hemolysis can be reduced to make this hazard negligible. Another technical problem is the effective removal of foaming. The degree of foaming depends on the method of oxygenation and is greatest with bubblers, and less with disc oxygenators or stationary screens. The defrothing process takes some antifoam into the circulatory system and may cause minute emboli. These though small, could however be serious in the brain, and coronary arteries and the kidneys.

Some of the defects for which extracorporeal circulation is used necessitate very long periods of surgery, for example, ventricular septal defects where great care has to be taken to avoid damaging the conduction bundle and during this lengthy ordeal signs of the patient's beginning to go down hill must be vigilantly watched for. The hazards are increased in patients where the defect is acquired rather than congenital, for example, in aortic stenosis.

Whatever the method used, the electroencephalographer if he is asked to monitor must be prepared for warning signs. These are essentially the same as those that have just been discussed but their relationship to blood chemistry is not as yet as clear. The writer has not in her experience encountered any abnormal signs during the period in which the patient has been on the pump. Sometimes in the early days one encountered accidental interference with the circulation during the operative manipulations preparatory to switching the patient to the extracorporeal blood supply, for example, during insertion of the catheters, etc. The EEG is a very sensitive indicator - far the most sensitive we have - of interference with cerebral blood supply and is therefore of the greatest value as a monitor, but experience and practice have eliminated this hazard. In the author's opinion the EEG is the most valuable indicator, but the patient's clinical condition also has to be watched closely.
The EEG in Figure 7 is from a patient in whom the recording was made from 10 needle electrodes in the scalp from induction of anesthesia, during chest surgery, and throughout the whole period on the heart-pump. The patient was being carried on pentothal anesthesia and her EEG reflected this throughout. With each added injection of pentothal slow waves developed for a few minutes—a normal reaction that was to be expected. The operation was for the repair of a large superior and a small inferior atrial septal defect in a woman of 29. The total period on extracorporeal circulation was 11 minutes, and no EEG change other than that to be expected at this level of pentothal anesthesia was encountered.

Monitoring of the EEG during heart-pump cases at our hospital is now carried out by Dr. Phillips Hallowell of the Anesthesia Department as a standard procedure, and his wide experience has added greatly to that derived from the first cases in the series.

(5) Combination of Hypothermia and Extracorporeal Circulation.

From the viewpoint of an electroencephalographer monitoring the well-being of the brain, a combination of the two procedures, as has already been given EEG changes solely due to hypothermia and extracorporeal circulation. The combination suggested here is desirable for use in severe cases, as it may be to electroencephalographers charged with monitoring a patient in an operating room, where extracorporeal circulation is used in the recovery phase.

The electroencephalographer then needs to know what he should expect from each of these factors and be able to assess their degree of success in protecting the brain. In our hospital we have not yet used this combined method, but the preliminary stage of experimentation on animals has been undertaken by Dr. William Brewster.
To summarize: Our experience in recording the EEGs of human subjects with extracorporeal circulation leads us to conclude that there need be no adverse effect on the brain of the procedure but that it is desirable to monitor the EEG for the unexpected mishap, and this is now routinely undertaken by the anesthesia department. In operations at normal body temperatures we have found that slowing of the EEG is most usually the sign of hypoxia, though if this becomes severe it will be followed by flattening. A sudden drop of amplitude without the intermediate stage of slow waves is more usually the sign of acidosis, and gives the appearance of an activated record. In human blood during hypothermic anesthesia. Proc. Int. Physiol. Soc., Brussels, 1956.

In the interests of brevity a rather sharp and certainly oversimplified differentiation has been made in this report between the effects of hypoxia and hypercapnia in these cases, but it should be remembered that the living organism is a system that will not tolerate the isolation of a single variable, and as soon as one factor begins to change, compensatory mechanisms are marshalled by the body to restore homeostasis. Our artificial manipulations with hypothermia and anesthesia impede and impair but do not abolish the restoration of this balance, and hence it would be an exaggeration to describe a given EEG change as solely due to hypoxia and another as solely due to CO₂ accumulation. The differentiation suggested here is presented for what practical use it may be to electroencephalographers charged with monitoring cases in the operating room.

The writer would like to thank the anesthesia Department of the Massachusetts General Hospital for the opportunity to make these observations. She is especially indebted to Dr. John Bunker, Dr. Phillips Hallowell, Dr. Torquil Anderson and Dr. William Brewster: though they should not be held responsible for opinions expressed here. She is also grateful to Miss Elizabeth Peterson for her patience and skilful technical help with all the recordings made in the operating room.


Figure 1: Four levels of hypothermia recorded before the beginning of surgery. Pentothal anaesthesia used at the start and lightened later. Lowering of the temperature introduces a slight slowing of the activity to just below the alpha band (i.e., about 7 per second).
EEG DURING HYPOTHERMIA IN MAN

<table>
<thead>
<tr>
<th>Condition</th>
<th>CHO</th>
<th>LACTATE</th>
<th>INORG P.</th>
</tr>
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<tbody>
<tr>
<td>LMT-LPT</td>
<td>56 mg%</td>
<td>12.5 mg%</td>
<td>3.65 mg%</td>
</tr>
<tr>
<td>LPT-LP</td>
<td></td>
<td></td>
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<tr>
<td>LPT-LMT</td>
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<tr>
<td>LP-LMT</td>
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<tr>
<td>LO-LMT</td>
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</tbody>
</table>

Temp: 35.5°
High voltage slow waves of pontal stage 2.

Temp: 30.8°
Less pontal activity. Last dose 30 min before.

Temp: 29.6°
Slowing of EEG and heart.

Temp: 28.5°

**Figure 2:** CHANGES IN EEG AND BLOOD CHEMISTRY DURING HYPOTHERMIA.
(see text).

**Figure 3:** CAPSULE SOLEUSUM.
by controlled hypothermlation the patient's blood base was raised to 7.61. On removal of the capsule there was no sign of any symptoms of the MUS. There was no appreciable loss of consciousness (Fig. 2).
Figure 3: CAROTID OCCLUSION.

By controlled hyperventilation the patient's pH had been raised to 7.61. On occlusion of the carotids there was slowing of the EEG without appreciable loss of amplitude. (Pt. E.).
EFFECT OF CAROTID OCCLUSION ON EEG IN MAN

• (Rectal temperature 28.2°C.)

![Graph showing EEG changes with different carotid occlusion scenarios.]

Neither Occluded
pH 7.45

Right Carotid Occluded

Both Carotids Occluded

Both Carotids Have Been Occluded for 2 Minutes

Left Carotid Released

Right Still Occluded

Both Carotids Released

Figure 4: CAROTID OCCLUSION.

With a blood pH of 7.45 occlusion of both carotids caused a marked change in the EEG. (Pt. T.).
EFFECT OF CAROTID OCCLUSION ON EEG IN MAN
(Rectal temperature 28° C.)

1-3
3-5
5
1 sec
5-7

NO OCCLUSION
pH 7.51

BOTH CAROTIDS OCCLUDED
1 MINUTE PREVIOUSLY

BOTH RELEASED

Figure 5: CAROTID OCCLUSION.
Same patient as in Figure 4. Occlusion after hyperventilation had raised the pH to 7.51. (Pt. T.).
Figure 6: EEG AND BLOOD CHEMISTRY IN A CASE OF RESPIRATORY ACIDOSIS.
(see text).
EEG RECORDING DURING CARDIAC SURGERY ON HEART PUMP
(PENTOTHAL ANESTHESIA)

<table>
<thead>
<tr>
<th>CHEST OPENING (PENTOTHAL)</th>
<th>DURING CARDIAC REPAIR</th>
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</thead>
<tbody>
<tr>
<td>LF-LO</td>
<td></td>
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<tr>
<td>LC-LO</td>
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<tr>
<td>RF-RC</td>
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<tr>
<td>RC-RO</td>
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<tr>
<td>LT-LC</td>
<td></td>
</tr>
<tr>
<td>RC-RT</td>
<td></td>
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<td>L.Arm-L Leg</td>
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11TH. MINUTE ON PUMP

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<tr>
<th>DURING CHEST CLOSURE</th>
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The patient was being carried on pentothal anesthesia and the record reflects the fast and slow waves resulting from this anesthetic. There was no loss of activity during any part of the procedure, eleven minutes of which were during extracorporeal circulation. Interference from stitching of the heart muscle is reflected in the recording at the upper right. (Pt. E.).

E.K.G.
IN Press: American Physiological Society, Washington DC.

Mary A. B. Brazier
D.Sc. 1960

SOME ACTIONS OF ANESTHETICS ON THE NERVOUS SYSTEM

The first point to which I would like to draw attention is the effect barbiturate anesthesia has on the flexibility or pliability of the response systems of the central nervous system. Under this anesthetic certain pathways are blocked off, others are released from inhibition, responses in the specific pathways become more rigidly synchronized, and the general balance of activity in the brain is changed. It is recognition of these effects that has made physiologists so wary in recent years of applying localizing findings made under anesthesia to their conception of normal brain function.

For example, the finding of French, Verseano and Magoun that the specific primary response to a sensory stimulus is followed within 8 to 10 msec. by another response that has travelled via the reticular formation and non-specific thalamic system, can only be adequately demonstrated in the unanesthetized animal. We have examined this point for responses to flash.

Figure 1 illustrates the response to which I refer. I should add, perhaps, that these records are averages of about 150 to 200 responses, the average being electronically computed by a device designed and constructed by my colleague, Dr. John Barlow. The isolated columns that stand at the beginning and end of each record are for calibration only. The flash occurs from the Neurophysiological Laboratory* of the Massachusetts General Hospital and the Research Laboratory of Electronics** at the Massachusetts Institute of Technology.

*Aided by grants from the U.S. National Institute for Neurological Diseases and Blindness (B 369 Physiology), the U.S. Navy (Office of Naval Research NR 101-445) and the U.S. Air Force (Office of Scientific Research AF-49-(658)-99).

**Supported in part by the U.S. Air Force (Office of Scientific Research, Air Research and Development Command) the U.S. Army (Signal Corps) and the U.S. Navy (Office of Naval Research).
at the beginning of the continuous record and the curved lines on the graph are at intervals of 20 milliseconds. The envelope gives the wave-form of the average response.

In Figure 1A the response that has travelled through the mid-line structures can be seen very clearly following the primary response in the cortex of the unanesthetized animal. Fig. 1B, recorded simultaneously, shows equally clearly that the response has not travelled up through the lateral geniculate nucleus. With a moderate degree of barbiturate anesthesia (15 - 50 mg./Kg.) the surface negative wave is not only no longer cut into by the positivity of the non-specific response (Fig. 1C) but it is also augmented. We have previously suggested that this increase in surface negativity under light pentobarbital anesthesia appears to be an impairment by the drug of an ascending inhibitory influence acting in the unanesthetized animal through the nonspecific system. The sketch on the lower right superimposes the unanesthetized and anesthetized records to bring out this augmentation.

By use of another computer which we have been privileged to use in the Research Laboratory of Electronics at M.I.T. we have been able to obtain some measure of the variability of the responding cortex. This instrument, which has been described by its designers elsewhere, not only gives the curve of the averaged responses, but can also display histograms showing the scatter of the individual responses that went to make up the average reading at each point on the curve. For clarity in Fig. 1 histograms are reproduced for only 4 of the points averaged in each curve.

On the left (Figure 1,E) in the recording from the unanesthetized animal, histograms are reproduced showing the scatter of values that went to make up the average at 15, at 25, at 35, and at 45 milliseconds respectively after the flash.
On the right, (F) from the same cat under pentobarbital, histograms are shown for the scatter of responses at 10, 20, 30 and 40 milliseconds. The much tighter distribution of values under the anesthetic can be very clearly seen.

The question does arise however as to whether this is due to variation in response mechanisms only, or also to variation in background cortical activity into which the impulses enter. The latter is an important component in the variability seen in the unanesthetized record but when the histograms for all points along the curve are studied there is found to be a greater variability during the medially conducted response than during the primary specific wave. Space limits the reproduction of all these histograms here but some impression of greater scatter can be seen in the 3rd sample of the unanesthetized record, i.e. 33 msec, after the flash.

I would not wish to suggest that the introduction of the anesthetic has left open only the classical specific route to the cortex through the geniculate, for exploration of the responsivity of mid-line thalamic nuclei has revealed a response to singly occurring flashes that is resistant to anesthetics, at least at the levels we have used. In fact, ether is the only agent which in our hands so far has depressed at all appreciably the large slow-wave response of the centre median to flash, though not completely abolishing it. (See Fig. 2). This result is in keeping with the finding of Dr. Eve King that ether was the only anesthetic of those she examined that depressed the recruiting response evoked by stimulation of the centre median.

The wide wave-like form of this averaged response in all anesthetics would suggest a great scatter in time of the responses that went to make up the average, and in fact, with greater resolution, i.e. by averaging more responses, one can show that the response in the centre median is bimodal.
as has been reported elsewhere.

One is, of course, interested in whether this response in the center median is passed on to the cortex, and we have been especially interested in cortical areas outside the specific receiving cortex. The averaging technique that we use has allowed us to see responses that we have been unable to detect in our cathode ray traces. Figure 3 shows the wave-like responses to flash that we find in the averaged recordings made from the cingulate cortex of a cat unanesthetized, and in the same animal under each of three anesthetics. These are strikingly different in form from the familiar primary responses at the specific projection cortex.

Taking our electrodes further down the brain stem we find by this averaging technique, that responses to single flashes are recordable also in the reticular formation. Figure 4 shows responses under pentobarbital. The wave-like response in the reticular formation reaches a peak at about 20 msec. after the flash. Meanwhile in the visual cortex impulses arriving in the specific radiations have already caused the surface-positive deflection (beginning 12 msec. after the flash). The wave-like responses of the non-specific cortex reach their peaks at approximately 37 msec. In this instance they are being recorded from the sensori-motor cortex. Similar responses are found in the reticular formation in tribromethanol anesthesia and in ether.

In describing these results I should emphasize that this report has been restricted to single stimuli. It is when repetitive stimulation is used that the effect of anesthetic agents and the role of the reticular formation become most marked, for it is the recovery phase that is usually most severely impaired.

The work reported here has been that of a team including Miss I. Sugiura, Miss S. Wing, Miss M. Sugiura, Dr. J. S. Merz, as well as our colleagues in the communications bio-physics laboratory at M.I.T., among whom we would especially like to mention Mr. Frank Rudo.
In this brief note there is not time to follow this point further or to describe our later experiments, but I should perhaps emphasize that these subcortical responses that have just been described are to be differentiated from the well-known and much later Forbes-Morison "secondary discharge", which with varying level of anesthetic has its own pattern of waxing and waning, both cortically and subcortically.

In closing I would like to refer to the intrinsic rhythms in the various regions where cells aggregate in the brain. When autocorrelation is used to sort out periodic components from the mixture of potential changes recorded from these sites we find different periodicities in the various centers in the unanesthetized cat. For the principles and technique of this kind of analysis, see reference (4).

Figure 5 is an example from a cat awake but not alerted, showing clear rhythm of 13 c/s in its motor cortex. In the visual cortex such poorly defined rhythm as can be detected at all is 11.5 c/s. A faint rhythm in the reticular formation has a frequency of 12 c/s. When this unanesthetized cat becomes spontaneously drowsy (i.e. without any drugs), all parts of the cortex and the reticular formation have the same slow beat. I might remark in passing that we have found a similar result with light anesthesia, although of course at deep levels all rhythmic phenomena are lost.

This result will probably not surprise electroencephalographers who are familiar with the great variety of patterns that the EEG may exhibit in the waking man and with the fact that we all become electroencephalographically indistinguishable from each other when we fall asleep. The same is true of man in the anesthetized state, as Dr. Bickford has so clearly shown.

The work reported here has been that of a team including Miss R. Carpenter, Mrs. L. King, Miss M. Magavern, Dr. J. S. Barlow, as well as our colleagues in the Communications Biophysics Laboratory at M.I.T., among whom we would especially like to mention Mr. Frank Nardo.
REFERENCES


Figure 1: Averaged responses to flash in a cat with and without anesthesia.

A. Visual Cortex: no anesthesia.
B. Lateral Geniculate Nucleus: no anesthesia.
C. Visual Cortex: pentobarbital anesthesia.
D. Superposition of A. and C. Electrode positions verified post-mortem.
E. and F.

Above records A and C are mounted 4 histograms showing the distribution of amplitude of the responses averaged at 4 chosen points in each. Note the decrease in variability induced by pentobarbital (see text).

Figure 2: Averaged responses recorded from implanted electrodes in the centre median in an unanesthetized cat, and in the same animal under four different anesthetics. With equal amplification there is impairment of response to single flash only with ether. (Electrode position confirmed post-mortem).
Figure 3: Averaged responses from the cingulate cortex of a cat with implanted electrodes. Pentobarbital 30 mg./Kg. Choloralose 20 mg./Kg. Tribromethanol 50 mg./Kg. Multiple peaks on wave-like responses suggest multiple input, and the lack of the shorter latency peak in the unanesthetized state suggests some release of these pathways by the drugs from an inhibitory restraint.
Figure 4: Averaged responses to flash recorded from 4 positions of implanted electrodes in a cat's brain. The onset of the initial deflection at the visual cortex is noted. The onset of the non-specific responses is less easy to define so an approximate value for the peak of local negativity has been indicated, (pentobarbital anesthesia).
Figure 5: Autocorrelograms processed to extract from the mixed rhythms of the cat's electroencephalogram those components which hold their frequency and phase relationships for an appreciable time. In the awake cat the rhythms of the motor cortex are of different frequency and have more persistence than those of the other two sites depicted. The motor cortex also shows some evidence of two competing frequencies. These rhythms drop out when the cat falls asleep and only slow undulations all of the same frequency appear in the autocorrelogram.

The curved lines of the graph paper are 20 milliseconds apart and the abscissa is not time but the length of delay at which each autocorrelation was computed. In these curves the value of the autocorrelation (ordinates) was computed in delay steps of 5 msec, increasing from left to right. The autocorrelation function is, of course, highest (i.e. 1) at zero delay on the extreme left of the continuous curve. For further details of this technique see reference (7).