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A STUDY OF ABSORPTION IN THE STOMACH AND SMALL INTESTINE.

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Introduction.

This thesis purports to consist of a general description of the work on absorption in the alimentary canal that I have been engaged in since 1920. In several cases the results of such work have already been recorded in the Journal of Physiology. In certain sections of the work my junior colleague, Miss M. Murray has collaborated with me.

The investigations to be considered include a study of:-

1. The gaseous interchange in the stomach of anaesthetised and pithed animals.
2. The absorption of alcohol by the stomach and small intestine and the influence of CO_2 on this absorption.
3. The influence of alcohol on the absorption of glucose (a) in decerebrate animals and (b) in animals under amytal anaesthesia.

Gaseous Interchange in the Stomach as regards CO_2 and O_2 in the anaesthetised and pithed animal.

Introduction.

The object of this 1st investigation was to ascertain:-

1. Whether there was evidence of any differential active absorption of gases, such as CO_2 and O_2, in the stomach, i.e. whether the disappearance of gases in the stomach was simply the result of a difference in partial pressure of the gas in the cavity of the stomach and that in the mucous membrane, or whether it was due to some active process of absorption in some region of the mucous membrane.

2. Whether the appearance of gas in the stomach, as for example CO_2, was due to a process of active secretion or was simply the result of a comparatively high pressure of the gas in the mucous membrane.

3. By whatever means gases in the cavity of the stomach underwent change in composition, whether the rate of change was dependent in any degree upon the condition of the mucous membrane as far as rest and activity were concerned?

It must be remembered that in certain catarrhal conditions of the stomach at any rate, large numbers of microorganisms may be present. Appreciable quantities of CO_2 and perhaps other gases might be a consequence of the vital processes of these organisms. The observations, detailed later, tend to show that any production of gas, or at any rate of CO_2, by microorganisms in the healthy stomach under the conditions in which the experiments were carried out, is unimportant when compared with other agencies normally operating. In about 75% of the animals used the spiral organism (spirella regaudi) was present, but variations in the pressure of gases observed seemed in no way related to its presence or absence.

Previous investigations.

Previous investigations do not seem to have thrown much light on this subject. Planer[1] in 1860 concluded that CO_2 was not secreted into the stomach but Schierbeck[2] from numerous experiments on dogs, came to the conclusion that the gastric mucous membrane could actively secrete CO_2 and that the amount secreted depended on the functional activity of the mucous membrane.

He In introduced boiled out water at 37·5°C. into the stomach through a sound and at different intervals he withdrew portions of the water and analysed them for CO_2 by means of baryta water. In fasting animals he found the tension to be 30-40 mm. Hg. but during digestion the tension rose rapidly and at the height of digestion it reached a pressure of 130-140 mm. Hg. As digestion proceeded the tension diminished till it again reached the low level found in the fasting animal. He estimated the acidity of the stomach contents at different intervals and found that there was a parallelism between the rise and fall of the tension of CO_2 and the acidity of the contents. In certain of the experiments the possibility of gas coming from the intestines was precluded by separating the intestines from the stomach by a rubber tampon, but the values for CO_2 tension were not altered.

Schierbeck first washed out the stomach with boiled out water. In order to observe the influence of activity, water and food were introduced and at different stages of digestion liquid was withdrawn and analysed for acid and CO_2. It should be pointed out that this does not preclude fermentative processes taking place, brought about by the bacteria introduced with the food, and a considerable quantity of the CO_2, Schierbeck found, may apparently have been due to bacterial agencies.

More recently Ylppo(3) has performed experiments on human beings introducing large quantities of gas into the stomach but the disappearance of gases cannot be regarded as necessarily affected by the gastric mucous membrane alone since the intestinal canal was in communication.

It would clearly be of advantage in testing for any interchange of gas during activity that the complication of the presence of food in the stomach should be avoided. In my experiments I was able to achieve this by injecting gastrin intravenously whilst the stomach contained only introduced gas and isotomic saline.

Since the publication of these results McIver, Redfield and Benedict[4] have repeated my experiments using similar technique but anaesthetising the cats with amytal instead of urethane. They have come to the same conclusions as I recorded with respect to the tension of CO_2 in the stomach. With regard to O_2 they merely state that it is absorbed by the gastric mucous membrane but little attention seems to have been paid to its tension in the stomach.

Methods.

In these experiments on gaseous interchange after preliminary anaesthesia with chloroform and ether the animals (Cats) were under the influence of urethane unless specified.

The abdomen was opened, a ligature was tied round the oesophagous, an opening made in the duodenum just beyond the pylorus and a cannula ligatured through the pylorus into the stomach. Through this cannula recently boiled out warm saline was introduced for washing out the stomach cavity, and by careful manipulation all gas was expelled. A gas sampling tube, containing a known volume of gas of known composition was attached to the pyloric cannula and the space between the stomach and the tube rendered gas free by withdrawing the remains of the washing out saline in the stomach through the side tube of the sampler.

Care was taken to prevent exposure of the animals to cold and most of the animals were kept in a saline bath at 37°C. only the head and shoulders being uncovered by the liquid. Fasting animals were used in these experiments and any small quantity of hair present in the stomach was removed in the washings.

When gas was used, this was introduced into the stomach by means of a mercury reservoir attached to the gas sampler and after the desired interval it was removed in the same way. The gas thus withdrawn was then transferred to the burette of a Haldane gas analysis apparatus and left disconnected from the rest of the apparatus for one hour to cool before the volume was determined. It was found in some preliminary experiments that after a period of two hours the gas, itself free from CO_2, introduced into the stomach, attained a certain percentage of CO_2 and this showed no increase as the result of more protracted exposure to the gastric mucous membrane.

In some experiments 25 cc. of sterilised saline were introduced in addition to gas and both were later analysed for CO_2 while the former was also analysed for HCl. A known volume of the liquid from the sampler was run under the surface of a known volume of baryta water and the excess of alkali titrated with standard oxalic acid. A similar volume of the liquid was then boiled carefully for five minutes to get rid of the CO_2 treated with baryta and titrated with oxalic. The value of HCl in terms of the oxalic used was thus determined and the percentage of CO_2 and HCl calculated. In all these experiments control titrations of the sterilised saline employed for experiment were made. In a few cases sterilised saline only was introduced and the liquid withdrawn after an interval of two hours and analysed by the method just described. In experiments in which the gastric mucous membrane was rendered active by gastrin injections, both gas and saline were introduced. In all cases it was found that the tensions of CO_2 in both the gas and the liquid were identical.

The effect of manipulation of the stomach in removal of any solid matter present before the stomach had been washed, was investigated by giving the animal a meal of meat about an hour before anaesthetising it. In these cases there was found to be an increase in the CO_2 produced. The mucous membrane of the stomach was almost invariably examined for micro-organisms at the end of the experiment and in some cases obvious catarrhal changes were found to be present. Such experiments were excluded. A certain number of experiments were performed to compare the tensions of CO_2 in the stomach and in alveolar air, taking as alveolar air, the last portion of expired air. In these cases the tracheal tube was replaced by a T-tube of somewhat narrower bore with a two-way tap at the angle of the T piece. One arm of the T piece was connected to a gas sampler which was filled with Hg from a reservoir and Hg was brought up to the tap. The tap was turned so that the trachea was connected with the air during inspiration and at the end of expiration it was rapidly turned on and off to the sampler, so that by having a slight negative pressure (about 1 cm.Hg) in the sampler about 0·1 or 0·2 cc. was collected at each breath. Repeating this for about 4'-5' about 20-25 cc. of alveolar air could be collected. Some practice was required before this method of collecting the ultimate expired air could be relied on, and if the animal were breathing at all rapidly the difficulty of collecting in this way rendered the method impracticable. There was no difficulty up to a rate of 50 respirations per minute.

Experimental procedure and results.

1st series of experiments. Introduction of 20 cc. of N_2 with variable periods of exposure. Animal not in warm bath.

In these experiments the cat was fixed to an animal stage and the abdomen was kept warm by hot flannels repeatedly applied.

Exposure 1 hour. A slight gain in volume was noticed. The percentage of CO_2 was about 7 and of O_2 about 0·65.

Exposute 2 hours. The gain of total volume was slightly greater, the percentage of CO_2 averaged 10 and O_2 was generally higher than after 1 hour.

Exposure 3 hours. The values obtained were of the same order as after 2 hours.

2nd series. Introduction of 20 cc. of a mixture of N_2 and O_2 with 2 hours exposure.

In these and subsequent experiments the standard period of exposure was 2 hours. Nine experiments of this order were made which are illustrated in the sample experiment adduced.

Gas introduced 17·4 cc. containing 2·27% O_2 and the remainder N_2.

Volume on removal 17·95. Percentage of CO_2 in removed gas 9·7 and of O_2 1·39.

In all these experiments there was a large gain of CO_2 and a loss of O_2.

Note. I am not disposed in the 1st and 2nd series of experiments to regard the animal in a normal condition. Though the temperature of the room was never low, usually about 17°C. yet the more consistent results which were obtained when the animal was entirely immersed in a warm bath kept at 37°C suggest that the heat loss under an anaesthetic with the animal exposed, had considerable influence on the CO_2 production.

3rd series. Animal previously fasting. Activity of gastric mucous membrane induced by injections of gastrin. Animal immersed in warm bath at 37°C.

In these experiments 2 cc. of a gastrin extract, neutralised immediately before use so that it had a PH of about 7·4, were injected into the femoral vein at intervals of 15 minutes for the first 1½ hours of the experiment. To test the activity of the gastric mucous membrane as the result of these injections the method adopted was to introduce with pure N_2 about 20 cc. of sterile normal saline. The gaseous interchange was estimated as before, (the gas coming in contact with the anterior mucous membrane of the stomach without the intervention of the liquid). The liquid was subsequently removed, analysed for total acidity and acidity after boiling out the CO_2, as described previously.

As was anticipated the conditions resulting from immersion in a warm bath largely prevented heat loss from the surface of the animal, and the CO_2 percentage in the removed gas was lower and showed very much less tendency to vary than in the previous experiments.

In three experiments in which gastrin was used, the CO_2 percentage was 7·2 to 7·9 (tension 51·3 to 56·3 mm Hg), the O_2 about 1 and the HCl about 0·1. In the liquid the CO_2 tension was identical (for the temperature) with that in the gas mixture shewing complete equilibrium between the two.

4th series. Animal fasting. N_2 and saline introduced.

In this series the gastric mucous membrane was at rest but though the time of exposure was frequently raised to 3 hours, the percentage of CO_2 varied between 5 & 5·5 and the O_2 between 0·75 and 1·4. The tension of CO_2 was identical both in the liquid and the gas mixture.

5th series. Animal fasting. N_2 and O_2 latter averaging about 1·6% introduced.

The CO_2 remained about the same as in the 4th series but the O_2 fell to 1% or less.

6th series. Animals in full digestion.

In this series the animals were fed with minced meat an hour before the experiment was begun. At the commencement of the experiment the food was removed through the pylorus which involved sometimes considerable manipulation of the stomach walls. The experiments in this series were designed to ascertain whether this manipulation affected the production of CO_2. The CO_2 percentage in these cases averaged 6·5% but the question here arises as to whether the higher percentage of CO_2 was due to the manipulation necessitated or to the fact that the stomach was in a condition of activity at the beginning of the experiment. Without further elucidation of this point there is no reason to believe that the increased production of CO_2 was due to other causes than the fact that the stomach was in a state of activity at the beginning of the experiment.

Observations were also made with a view of seeing whether the quiescent stomach evolved CO_2. The stomach was washed with boiled out sterile saline to remove any gas present. The liquid was withdrawn and the stomach was left free of both gas and liquid for 3 hours. At the end of this period gas free saline was again introduced into the stomach for the purpose of washing out any accumulated gas and as rapidly as possible removed. No gas was obtainable and the liquid on analysis was found to contain no appreciable CO_2.

From this experiment it would seem that there is no recognisable secretion of CO_2 into the cavity of the stomach during a resting period of the stomach.

In contrast with this, experiments have been performed with liquid alone in the stomach and in these cases the liquid was found at the end of the experiment (2 hours) to contain 3% of CO_2, equivalent to a tension of 41·8 mm.Hg.

7th series. Introduction of acid saline and N_2 into stomach at rest.

The question arose whether the presence of liquid containing HCl in the stomach could account for some accumulation of CO_2 from the action of acid on bicarbonates present in the mucous membrane. Could the increase of CO_2 in activity be explained in this way or is it connected with the work of secretion during activity?

This series of experiments was devised to throw light upon this point.

After two hours the CO_2 varied between 5·5%and 6·3% indicating that the rise in CO_2 during secretory activity is not due to the mere presence of HCl in the stomach reacting with carbonates or bi-carbonates in the stomach wall.

8th series. Alveolar air analysed at intervals throughout the experiment.

The alveolar air was collected at about ½ hour intervals throughout the experiment. In most cases gastrin was injected.

In all cases it was found that the average percentage CO_2 alveolar air throughout the experiment was about 0·3 - 1·1% lower than that found in the stomach. In other words the pressure of CO_2 in the tissue of the stomach was greater than that in alveolar air (ultimate expired air).

Series 9.

The experiments in Series 3 were repeated using decerebrate or pithed animals instead of anaesthetised. After preliminary ether anaesthesia tracheotomy was performed, the carotids ligatured and the animals decerebrated by Langley's method, (injection of 10% starch suspension in gum-Ringer). As soon as respiration ceased the trachea was connected with an artificial respiration pump. About 20 cc. of neutral boiled-out saline was introduced into the washed-out stomach together with about 20 cc. of nitrogen gas. In some experiments gastrin was injected during the two hours. The liquid and gas were then removed and analysed for CO_2 and the liquid was also tested and estimated for hydrochloric acid. In many of the experiments in which no gastrin was injected the liquid gave a positive reaction with Gunzberg's reagent and the analysis showed the presence of 0·01 - 0·04Mg HCl. (This point was further investigated later). The tension of CO_2 in the gas and liquid varied between 41·2 mm.Hg and 44·9 mm.Hg. (Average of six experiments was 42·7). This was when no gastrin had been injected and the amount of HCl in the liquid was not greater than 10 mgms. When the amount of HCl in the liquid withdrawn was greater than 16 mgms the pressure of CO_2 varied between 57 mm.Hg. and 62·6 mm. Hg. (Average of 8 experiments 58 mm.Hg.) These results are similar though slightly higher than those obtained from the urethanised animals, this probably being due to a slower metabolic rate of the animals under the influence of an anaesthetic.

Conclusions.

From the experimental results obtained, it would seem unnecessary to explain the presence of CO_2 in the stomach as due to the active secretion of this gas by the gastric mucous membrane. When the stomach was washed out and completely emptied, there was no accumulation of CO_2 even after an interval of three hours as would have been expected had the mucous membrane the power of secretion of CO_2. Whether N_2, N_2 and O_2, or N_2 and saline, were introduced into the fasting stomach, the CO_2 was found to reach a fairly constant level which would apparently be that of the tension of CO_2 in the superficial gastric mucous membrane and it is more probable that the presence of CO_2 is due to a passive diffusion of the gas from the tissue of the walls of the stomach rather than a secretion of CO_2 from the walls into the cavity of the stomach.

The experiments indicate that normally with the stomach at rest the tension of CO_2 varied between 5·5% and 6·5% of an atmosphere = 39·2 mm.Hg - 46·2 mm.

During activity and under conditions which involve no other source of CO_2 as would be the case if food were present in the stomach, the CO_2 rose to about 7·5% = 53·4 mm. Hg. and the O_2 remained at about 1% = 7·2 mm.Hg.

Since alveolar CO_2 pressure was always found to be lower than gastric CO_2 and O_2 very much greater, it seems permissible to regard these experiments as comparable to the use of a tonometer for the purpose of gauging the tension of CO_2 and O_2 in tissues or at any rate in the tissue of the gastric mucous membrane.

Further the conclusion may be drawn that the tension of CO_2 in this tissue is greater than that in venous blood and the tension of O_2 is of a very low order.

Argyll Campbell[5] has recently shewn that the tension of CO_2 in the bladder of rabbits and in human urine was between 40-45 mm.Hg. In rabbits the tension of O_2 was found to vary between 33-45 mm.Hg but in human urine it was much lower, being about 14-25 mm.Hg.

The CO_2 tension in the bladder thus corresponds with that found in the non secreting resting stomach but the O_2 tension even in the human bladder is much higher than in the stomach. This is to be expected since one organ has a purely passive mucous membrane and the other an active one.

In the course of an investigation on the effect of CO_2 on the absorption of alcohol from the stomach to be described later, it was found that when a dilute solution of alcohol containing 50-60% CO_2 was introduced into the stomach after one hour all the CO_2 had disappeared from the liquid which was withdrawn. This suggests that the presence of alcohol in the stomach causes CO_2 to disappear rapidly and completely through the gastric mucous membrane and that it prevents the liquid in the stomach equilibrating with the CO_2 tension of the tissues.

There is no reason to believe that the living condition of the mucous membrane is abolished, since it is called upon in ordinary life to meet media of the type employed. Nevertheless the effect of the alcohol is to cause what may be regarded as a diffusion membrane to be permeable in one direction only.

This point was further demonstrated by introducing unbuffered Ringer's solution containing CO_2 at a tension approximately equal to that in arterial blood. This was left in the stomach one hour when it was withdrawn and analysed for CO_2 and HCl. The CO_2 was found to be 3·6% = 50 mm.Hg. A similar solution of Ringer and CO_2 containing alcohol was introduced and after an hour the CO_2 had fallen below 1%. (Details of these experiments are recorded later on page 32).

The effect of driving CO_2 from a region of low to one of higher tension is remarkable but it is, however, transient, apparently depending in some way on the simultaneous absorption of alcohol.

Summary.

A gas mixture introduced into the stomach and restricted to that cavity undergoes a change in composition which appears to be the result of a simple physical process of gas diffusion from the gastric mucous membrane.

The tension of CO_2 in the stomach is greater during activity than at rest, varying between 40-46 mm.Hg. at rest and 51·5 - 56·5 mm.Hg. in activity.

The tension of O_2 is extremely low, but seems slightly lower during activity than at rest (about 7 mm.Hg at rest and 6 mm.Hg. in activity).

If the temperature of the anaesthetised animal is allowed to fall at all the tension of CO_2 in the stomach rises higher than during activity of the gastric glands.

In the pithed animal the tension of CO_2 is slightly higher at rest and during activity, and the O_2 lower.

In the presence of alcohol large quantities of CO_2 can be rapidly absorbed by the gastric mucous membrane, the tension of CO_2 becoming markedly lower (usually zero) in the stomach than in the blood.

There is no evidence that CO_2 is actively secreted into the stomach.

THE EFFECT OF CO_2 ON THE ABSORPTION OF ALCOHOL FROM THE STOMACH AND SMALL INTESTINE.

Although there have been extensive researches, notably by Pavlov, Edkins, and numerous American and Edinburgh workers, on the secretory functions of the stomach, it has remained somewhat doubtful from their work whether a neutral liquid such as Ringer's solution would cause secretion of gastric juice in an animal in which the vagi had been destroyed by oesophageal ligature.

J. S. Edkins[6] performed his "acute experiments" on anaesthetised animals and found that neither water nor saline were absorbed or caused any appreciable secretion of acid. This might also be true of the normal animal, but it is scarcely permissible to deduce this fact from the experiments of Edkins when anaesthetics are known to alter secretory activity in a very marked degree.

For all the experiments performed in the course of the investigations which are to be described, decerebrate or pithed animals were used. In this way it was anticipated that a more normal condition of the secretory activity of the mucous membrane would be attained.

This study of secretory activity was however not the initial object of the experiments. Originally it was intended to investigate the limits of the absorption of certain solutions through the gastric mucous membrane. In "acute experiments" reliance had hitherto been placed on anaesthetised animals. It is permissible to regard the stomach as predominantly a secretory structure, its function as regards absorption being secondary. Mendel(7) and other workers have shewn that alcohol, and certain other drugs, may be absorbed by the stomach.

A good deal of work has been done on the absorption of alcohol into the blood from the alimentary canal in the normal animal under varying conditions, but the degree of absorption that took place in the stomach could not be determined in this way.

In many of the recorded experiments very high concentrations of alcohol have been used and such as man would never have to deal with in ordinary life. These high concentrations of alcohol in the stomach were avoided in the present experiments as likely to promote too abnormal a state.

It is an ordinary experience that alcoholic beverages taken with aerated waters produce their characteristic effects much more rapidly than when taken in ordinary water. The scientific basis of this fact was investigated by experiments on the effect produced on the absorption of alcohol by the presence of CO_2. Later some of these investigations were extended to the intestinal mucous membrane.

The work to be described falls into two main divisions. In Part I. the points studied were (a) the degree of absorption of physiologically inactive liquids, and (b) the secretion of hydrochloric acid as indicating the secretory activity which these liquids caused. In Part II. the absorption ~~was considered.~~ of alcohol, & the effect of CO_2 on the amount of absorption was considered.

Throughout the experiments great care was taken to keep the animals as nearly normal as possible in order that the deductions made from the results might be physiologically sound.

Part I.

Method.

All the experiments were performed on cats. The animals wherever possible were kept in the laboratory for several days preceding the experiment and during that time fed on lean meat in order that the alimentary canal might be in a good condition.

In the early experiments the animals were first anaesthetised with chloroform but later ether was used as it was found that with ether the blood supply to the stomach was much better. This preliminary anaesthesia was for the purpose of preparing the animal for decerebration or pithing, the method of which has already been described. Then the abdomen was opened, a tight ligature tied round the oesophagus, great care being taken not to include obvious blood vessels. The intestine was then clipped off with Spencer-Wells forceps, an incision made across the duodenum about a centimetre below the pylorus and the stomach well washed out with several injections of warm saline. A T-shaped tube with a tap on one limb was then tied into the opening.

The liquids placed in the stomach were introduced at a low pressure and during the whole time kept at a pressure within the stomach of 5 cm. of water.

In the first group of experiments the apparatus used for introducing the liquid into the stomach was similar to that previously used. The animal was connected with the apparatus throughout the experiment and the total amount of liquid introduced noted. After an hour, two measured samples of liquid were withdrawn at the tap and the rest drawn back into the apparatus in order to measure the volume recovered. In this way the amount of absorption of liquid could be measured. Further by analysis of the second sample withdrawn by the tap the amount of HCl secreted could be calculated.

In the experiments of the first group simple inert liquids were used such as Ringer or saline. The idea was to cause as little stimulation to the mucous membrane as possible and to eliminate osmotic effects. Saline might have been suitable, but it was thought that since in the kidney the presence of calcium is an absolute necessity for the normal condition of the cell membrane that a more physiological liquid would be Ringer's solution. But as the estimation of HCl was to be performed by simple titration it was not possible to include the usual amount of bi-carbonate because of the buffering effect. For this reason the Ringer's used throughout the experiment was "unbuffered" and had the following composition.

·9g NaCl
·042 KCl Water to 100 cc.
·024 $CaCl_2$

The hydrochloric acid was detected by Gunsberg's test and estimated by boiling out a known volume of the stomach liquid to drive off the CO_2 and then titrating with $\frac{N}{100}$ NaOH till just alkaline to phenolphthalein.

The experiments of the first group fall into two series. In the first an endeavour was made to compare the absorptive and secretory effect of (1) saline and (2) unbuffered Ringer. For this reason each whole experiment consisted of two separate one hour parts in which Ringer and Saline were successively used.

In the second series similar experiments were made on loops of intestine isolated by first clipping off then cutting across and tying in cannulae, and comparisons were made between the absorptive functions of the gastric and intestinal mucous membrane.

Absorption in the Stomach.

Series I.

A. Absorption of Ringer and secretion of HCl.

Volume of Ringer introduced.	Volume of Ringer removed after 1 hr.	Difference in volume.	Gunsberg's Test.	HCl secreted
86 cc.	85 cc.	1 cc (loss)	+	7 mgm.
1. 79·9	73	2·9 (loss)	slight	1·3 "
2. 81·5	82·5	1 (gain)	"	3 "
3. 58·6	54	4·6 (loss)	+	10 "
4. 91·4	93	1·6 (gain)	++	18 "
5. 64·9	65	-	+	10 "
6. 60	60	-	++	19·7 "
7. 68·8	70	-	+	5 "

B. Absorption of normal saline and secretion of HCl.

Volume of Saline introduced.	Volume of Saline removed.	Difference.	Gunsberg's Test.	HCl secreted.
1. 68·2 cc.	68 cc.	0 cc.	slight	2·6 mgm.
2. 64·8	64	·8 (loss)	slight	2·6
3. 46·6	48	1·4 (gain)	+++	33
4. 86·5	88	1·3 (gain)	++	21
5. 59·3	58·5	·8 (loss)	+	9
6. 56·7	54	2·7 (loss)	-	0
7. 71·0	71	0	+	3

(Nos. 1 to 7 in A and B indicate corresponding 1 hour experiments on the same animal; the order being alternated in successive experiments).

Series II.

Comparison of the degree of absorption of Ringer, in the stomach and the small intestine of the same animal.

Intestine. Stomach.

No. of Expt.	Volume introduced.	Volume Removed	Difference.	% Absorption.	Volume introduced.	Volume Removed	Difference.	HCl secreted
12.	7·8 cc	2·3 cc.	5·5 (loss)	70				
13.	22·6	trace	22·6 "	100	54·5	56	1·5 (g)	18 mgm.
14.	15·8	7·4	8·4 "	50	51·5	51·5	0	0
15.	36·3	7	29·3	80	53	53	2·20(1)	14 "
16.	24	18	6 "	25	68·2	66	2·2	4 "

The connections with Ringer were made first with the stomach (one hour), then with the intestine (one hour).

Deductions from these experiments.

It is quite clear that the method of experiment does not in any way interfere with the intestinal absorption, therefore it is safe to conclude that the stomach is also functioning normally as regards absorption. There is certainly no appreciable absorption of either saline or Ringer in the stomach; and this confirms for decerebrate animals the results of other workers on anaesthetised. But it is quite obvious that these liquids do cause in the decerebrate animal a certain, though perhaps small, secretion of HCl, amounting only to a very small volume of actual secretion juices.

Part II.

(a) The absorption of Alcohol from the stomach.

(b) The effect of CO_2 on the absorption of alcohol.

The foregoing experiments have confirmed the view that the stomach is not to be regarded as possessing the power of absorbing water. As already stated alcohol is one of the substances which the stomach can absorb, and it is generally admitted that the absorption of alcohol is increased when taken with aerated water as compared with water not aerated. The characteristic quality of aerated water is the CO_2 content.

Starting with these facts as a basis, two points were the object of investigation:-

(1) To obtain accurate experimental evidence of the absorption of alcohol from the stomach when administered with non-gaseous liquids.

(2) To investigate the effect of CO_2 on (a) the degree of absorption and (b) the rate of absorption.

After washing out the stomach, the diluted alcohol, (which in most experiments was a 5 per cent solution in unbuffered Ringer) was introduced.

Each of the experiments consisted of two parts:-

(a) The absorption of alcohol in Ringer freed of CO_2 by previous boiling out.

(b) The absorption of alcohol in Ringer containing a high concentration of CO_2.

Each part of an experiment was allowed to run for one hour and since the second part might be considered influenced by fatigue the order of (a) and (b) was alternated in successive experiments.

Method of Estimation of Alcohol.

Our method of estimation was the process of distillation under reduced pressure devised by Cannan and Sulzer.[8] Their special form of apparatus was used and the alcohol vapour drawn into a mixture of equal parts of 0·15N Potassium bichromate and concentrated sulphuric acid.

Under these conditions, given a large excess of acid bichromate over alcohol the oxidation is complete to acetic acid, probably to the extent of 90% and over.

The alcohol oxidised was estimated by titration of the excess bichromate. For this purpose we did not use the usual ferrous amm. sulphate but made use of the oxidation of KI with acid bichromate and titration of the iodine by sodium thiosulphate with soluble starch as indicator.

All the alcohol estimations were done on the same day as the experiments. This is considered a very important point because in the first few experiments when this was not the case alcohol was lost in proportion to the "age" of the sample, making the absorption appear considerable in some cases. When it was realized that the alcohol did disappear in this way the early experiments were disregarded.

This disappearance of the alcohol is probably due to gastric lipase* which undoubtedly exists, as has been shown by Hofmeister and other observers.

The % of CO_2 was estimated by means of baryta water and titration with oxalic acid as already described in the first section of this thesis.

The Rate of Absorption and Influence of CO_2.

To obtain evidence upon these points liquid was withdrawn immediately after introduction and at 20 minute intervals, each sample was analysed for alcohol and CO_2 content by the methods described. In all, eight of the experiments were carried out on these lines and the results of some are given below.

Table II. Rate of absorption of alcohol in presence or absence of CO_2.

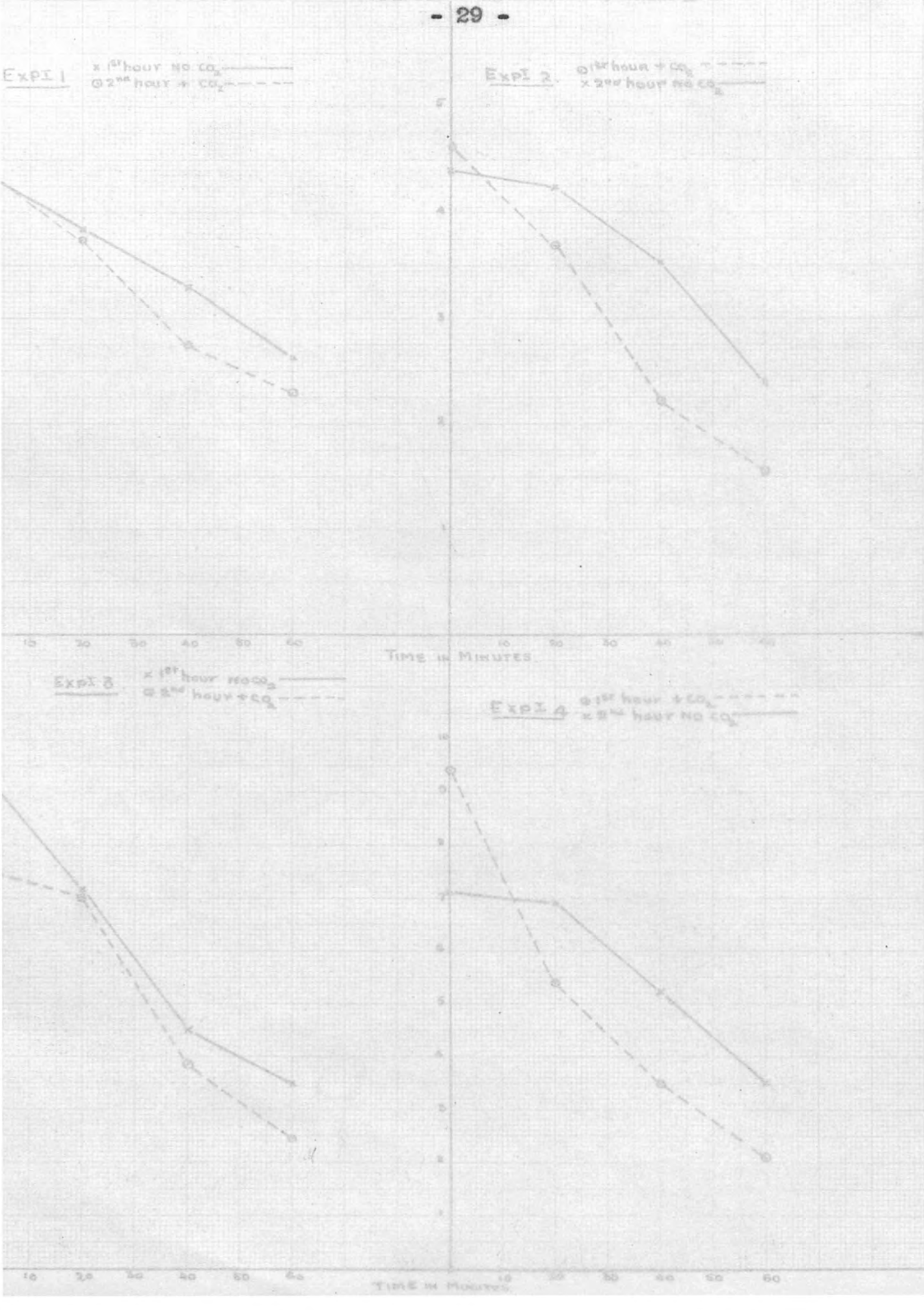
(a) = No CO_2 present. (b) = With CO_2 present.

Exp.	CO_2 at beginning. %	CO_2 at end of 1 hour %	Conc. alcohol at time 0 (introduction). %	Conc. alcohol after 20 min. %	Conc. alcohol after 40 min. %	Conc. alcohol after 60 min. %
1. (a) 1st hour	None	None	4·38	3·83	3·34	2·61
(b) 2nd "	66	4·4	4·41	3·77	2·74	2·31
2. (b) 1st hour	50	None	4·63	3·68	2·20	1·55
(a) 2nd "	None	None	4·44	4·26	3·53	2·41
3. (a) 1st hour	None	2·6*	4·77	3·56	2·33	1·75
(b) 2nd "	52·4	None	3·8	3·53	1·93	1·22
4. (b) 1st hour	46·4	None	9·36	5·35	3·46	2·10
(a) 2nd "	None	None	7·11	6·87	5·23	3·46

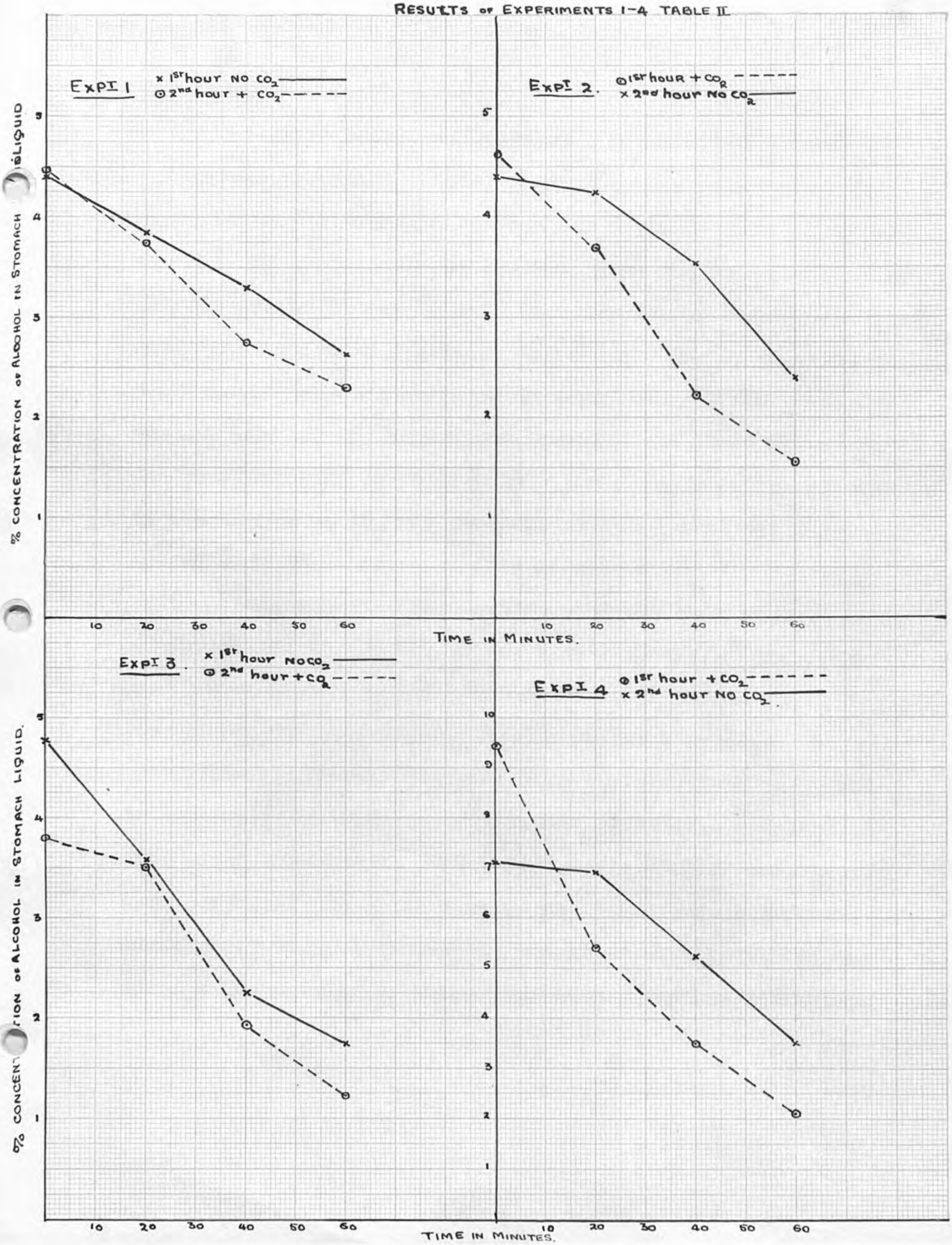
*This was about the only case where CO_2 initially absent was found to have diffused out from the gastric mucous membrane into the stomach.

RESULTS OF EXPERIMENTS 1-4 TABLE II

- 29 -



RESULTS OF EXPERIMENTS 1–4 TABLE II



Deductions.

The experiments need careful consideration before deductions are made. Every precaution was taken to ensure that the only difference between two parts of each experiment was the CO_2 content of the liquid. From the table of results and the graphs it may be said that alcohol is clearly absorbed more rapidly and to a greater degree when CO_2 is present. The results are more striking in experiments 2 and 4 because the CO_2 part of the experiment occupied the first hour. But the fact that the absorption in 1 and 2 was slightly greater in the hour when CO_2 was present, although this was the second hour, also supports this deduction.

Having obtained this evidence of the rate of fall in concentration of alcohol in the liquid in the stomach, the next point of interest was to ascertain if the actual absorption was also greater in the presence of CO_2.

Another series of experiments was therefore performed to determine the quantity of alcohol absorbed throughout the time of an experiment. For this purpose similar experiments were performed, in which samples of liquid were withdrawn immediately after introduction and after an interval of one hour. The results of these experiments are the following.

Table III. Absorption of alcohol in presence or absence of CO_2.

(a) = No CO_2 present. (b) = With CO_2.

	Conc. of CO_2 at beginning. %	Conc. of CO_2 at end %	Volume of alcohol at beginning. c.c.	Volume of alcohol at end. c.c.	Actual amount of alcohol absorbed. c.c.	HCl secreted in mgm.
Exp.						
1. (b) 1st hour	42·6	None	2·17	·8	1·67	36·7
(a) 2nd "	2·5	None	1·84	·6	1·24	48·94
2. (a) 1st hour	None	0·5	1·79	·39	1·4	21·5
(b) 2nd "	76·8	2·0	1·53	·43	1·11	31·1
3. (a) 1st hour	0·45	None	2·24	·5	1·74	3·79
(b) 2nd "	51·8	None	2·18	·52	1·66	37·85
4. (b) 1st hour	46·5	1·3	2·43	·71	1·72	7·6
(a) 2nd "	0·6	None	1·97	1·03	0·94	0·38
5. (a) 1st hour	0·6	None	2·07	·56	1·51	2·96
(b) 2nd "	40	None	2·38	·67	1·7	4·74
6. (b) 1st hour	42·0	None	2·5	·68	1·7	27·0
(a) 2nd "	3·3	·28	2·53	1·09	1·46	11·5

Concentration of alcohol solution in Expts. 1, 2, 3 roughly 5% (actual amount estimated) and Expts. 4, 5, 6 roughly 6%. In each experiment the difference between the liquids introduced was solely in CO_2 content.

A consideration of these figures also confirms the results of the previous series of experiments, i.e. that alcohol is absorbed more completely with CO_2 present.

Besides this observation two other points may be noticed if the results of the experiments are carefully studied.

One of these is that the presence of alcohol appears to have a rather striking effect on the gastric mucous membrane with respect to the passage of CO_2.

It has been proved in the first section of this thesis that CO_2, in quantities not differing greatly from the normal amount will diffuse until an equilibrium is established, but it appears that when alcohol is present in the stomach this is no longer the case. The figures for the CO_2 conc. in the liquid at the beginning and the end of each hour are given below.

Exps.		CO_2 at beginning %	CO_2 at end 1 hr.
1.	(a)	None	None
	(b)	66	4·4
2.	(b)	50	None
	(a)	None	None
3.	(a)	None	2·6
	(b)	52·4	None
4.	(b)	46·4	None
	(a)	None	None
5.	(a)	·45	None
	(b)	51·8	None
6.	(b)	42·6	None
	(a)	2·5	None
7.	(a)	·6	None
	(b)	40	None

From these results it seems that there was a rapid passage of CO_2 inwards across the gastric mucous membrane giving in most cases a fall of from 45% to nothing in an hour. When there was little or no CO_2 in the liquid initially there was, with only one exception no CO_2 at the end. Here there seems to be therefore an exception to the view that the gastric mucous membrane is a passive membrane for the passage of gases. The presence of alcohol seems to have altered the passive character profoundly and made the mucous membrane "a one way" membrane. That is, CO_2 passes in rapidly and completely, but it is prevented from coming out into the stomach liquid. Since we found no CO_2 present in the liquid removed, regardless of whether CO_2 was originally present or not, we endeavoured to determine whether the presence of alcohol influences the rate of disappearance of CO_2 from the liquid when the CO_2 was present in larger quantities initially.

(My previous experiments were all made with a low tension of CO_2). For this a few experiments were made similar in all respects to the others, but alcohol was omitted.

Exp.		CO_2 at beginning %	CO_2 at end %	HCl secreted mgm.
1.	(a) 1st hour	0·23	0·5	0·4
	(b) 2nd "	55·2	8·2	0·34
2.	(a) 1st hour	None	2·3	3·4
	(b) 2nd "	67·2	16·0	0·36
3.	(b) 2 hours	48·2	3·6	3·9

These results show that though there is considerable loss of CO_2 from the liquid the gas never disappears so completely and entirely as in the alcohol experiments, moreover, there is a tendency for the CO_2 content of the stomach liquid to equilibrate with that of the CO_2 tension of the gastric mucous membrane.

The second point is that although a considerable quantity of alcohol is absorbed there is very little absorption of water. If we consider side by side the quantity of alcohol absorbed and the amount of liquid which disappears from the stomach we obtain the following data:-

	Conc. alcohol at beginning. %	Conc. alcohol at end. %	Vol. of liquid introduced.	Liquid absorbed.
(a)	4·38	2·61	76 cc.	1·5 cc.
(b)	4·41	2·31	63 "	incr. 1 cc.
(b)	4·63	1·55	79 "	1 cc.
(a)	4·44	2·41	71 "	incr. 1 cc.
(a)	4·77	1·75	67·5	None
(b)	3·8	1·22	73·7	3·5 cc.
(b)	9·36	2·10	75·9	1 cc.
(a)	7·11	3·46	77·9	None.

The absorption of alcohol was approximately speaking just over half the amount, whereas the liquid absorbed was negligible. It is assumed that the volume is not altered by secretion of gastric juice. Apparently, therefore, the alcohol does not pass through to the mucous membrane accompanied by water, since that would involve a considerable diminution in volume of the liquid in the stomach, whereas practically no alteration in volume occurs. It is possible that the alcohol may accumulate in the mucous membrane and it may be on this account that the membrane exhibits the peculiar character with regard to the passage of CO_2.

This point was tested in some unpublished work by taking a blood sample from the animal ~~first~~ just before the stomach liquid was removed, then taking further samples of blood at intervals and estimating the alcohol content of each sample. In these experiments the strength of the alcohol was greater than in the previous ones hence the amount absorbed was greater. To quote one experiment as an example of others performed. The liquid introduced contained 3·6 cc. of alcohol and that removed contained 1·1 cc. of alcohol so that the volume of alcohol which disappeared from the liquid was 2·5 cc. The % of alcohol in the blood just before the liquid was removed from the stomach was 0·178 %. A half hour later the alcohol of the blood was 0·142%. An hour later it was 0·086%. This indicates that alcohol is not held up in the gastric mucous membrane since the % of alcohol fell in the usual manner after the solution had been removed from the stomach.

Discussion and Summary.

From the experiments we can conclude that alcohol and CO_2 mutually affect one another with regard to their passage across the gastric mucous membrane.

Certainly CO_2 in the alcoholic solution introduced hastens the rate of absorption of alcohol from the stomach and also causes a greater total absorption.

The total amount of alcohol absorbed in either part of an experiment, i.e. (a) in the absence of CO_2 or (b) in presence of CO_2 depends on which part occupies the first hour.

The presence of alcohol also causes the CO_2 to disappear more rapidly and completely and prevents the liquid in the stomach equilibrating with the CO_2 tension of the tissues.

The passage of alcohol in some way profoundly changes the character of the mucous membrane as a diffusion membrane for the transit of CO_2. This gas passes from the cavity into the tissues very rapidly and completely in the presence of alcohol. It even seems to pass from a region of lower to one of higher tension, since it disappears entirely from the liquid in the cavity. Moreover since an equilibrium is not established between the stomach liquid and the tissues, with respect to CO_2, it appears that the gas is barred from passing out to the cavity from the mucous membrane.

The results confirm the view that alcohol stimulates the secretion of HCl & it can be noted from the figures given that alcohol in the presence of CO_2 has an even greater stimulating effect.

Part III.

THE EFFECT OF CO_2 ON THE ABSORPTION OF ALCOHOL AND THE INFLUENCE OF ALCOHOL ON THE DIFFUSION OF CO_2 IN THE SMALL INTESTINE.

A former investigation had shown that CO_2 increased the absorption of alcohol by the gastric mucous membrane in the cat and that the presence of alcohol in the stomach had the curious effect of apparently making the mucous membrane of the stomach permeable in one direction only. The present investigation was undertaken to determine whether these effects were also exhibited by the mucous membrane of the intestine. (At the same time the opportunity was presented of making a comparison between the effect of alcohol on stomach and intestine.)

Method.

The method employed was similar to that in dealing with the stomach. The animal was anaesthetised with ether and decerebrated or pithed by Langley's starch injection method, artificial respiration being generally applied. Eight inches from the pylorus a piece of gut 55 cm. long was measured and clamped off. At each end a cannula connected with a tap was ligatured into the loop; and the loop was washed out with warm unbuffered Ringer's solution. The upper cannula was connected with a side tube between it and the tap, and through this tube the liquid to be investigated was introduced and kept at a constant pressure of 5 cm. of water.

The basic experiments as in the case of the stomach were done with unbuffered Ringer only. The table given below shows results which enable us to compare the absorption of Ringer only from the stomach and intestine in the same animal. The intestinal absorption though very variable is always considerable.

Table I.

	Intestine.				Stomach.			
	cc. Ringer introduced.	cc. Ringer removed.	Difference.	% absorption.	cc. Ringer introduced.	cc. Ringer removed.	absorption.	HCl g
12.	7·8	2·3	5·5 loss	70				
13.	22·6	trace	all	100	54·5	56	1·5 gain	·018
14.	15·8	7·4	8·4	50	51·5	51·5	-	-
15.	24	18	6	25	68·2	66	2·2 loss	·014
16.	36·3	7 cc.	29·3	80	53	53	-	·004

These experiments are similar in results to those which have been obtained by former observers, the reason we introduce them is that the animals having been either decerebrated or pithed the influence of the anaesthetic is largely eliminated.

The absorption of Alcohol in the Intestine.

The alcohol experiments were done on the same lines as in the case of the stomach only, i.e. each experiment consisted of two parts, each part was only of ½ hour's duration. In (a) about 8% alcohol in unbuffered Ringer was used and in (c) the same alcoholic solution to which about 44% of CO_2 had been added. In some experiments solution (a) was used first and then solution (c) and in others the solutions were used in the reverse order.

Table II.

		ccs. alcohol absorbed in Intestine.	Total Volume liquid absorbed.	CO_2 at beginning.	CO_2 at end of expt.
Exp. 1.	(a)	1·565	16·6	0	?
	(c)	2·38	23·2		?
2.	(c)	1·53	19·8	abt. 44	?
	(a)	1·08	2·4	0	?
3.	(c)	1·287	9·9	40	1·7
	(a)	1·121	4·3	0	1·6
4.	(a)	1·0	5·2	0	2·0
	(c)	1·0	1·5	43	2·0
5.	(c)	2·03	25	43	3·9
	(a)	1·399	3	0	3·5
6.	(a)	·755	-2·4	0	1·4
	(c)	·686	-9·5	43	1·7
7.	(c)	1·275	4·6	44	1·4
	(a)	·696	-3·6	0	1·6
8.	(a)	1·04	2·0	0	1·2
	(c)	1·11	-1·0	48	1·2
9.	(c)	1·06	8·6	0	3·2
	(a)	1·06	0·0	48	2·0
10.	(a)	·714	6·3	0	1·6
	(c)	.513	0.0	48	2·0
11.	(x)	--	11·4	0	1·4
	(y)	--	9·3	24	1·9
12.	(y)	--	7·2	56	3·1
	(x)	--	7·9	0	3 2

From the above table which presents a sample of the results obtained from numerous experiments it is clear that as far as CO_2 is concerned either the mucous membrane of the small intestine is acting merely as a passive membrane, or the CO_2 is the result of secretion. We endeavoured to settle this point by estimating the carbonate ion content of the boiled out liquid, assuming that, if the CO_2 present at the end was some of the gaseous CO_2 introduced, then the liquid on boiling out would have been free of CO_2 whereas, on the other hand, if there was a taking up of baryta after boiling then the CO_2 must have been fixed either as $NaHCO_3$ or Na_2CO_3. It was difficult to estimate the CO_2 after boiling because of the very mucilaginous character of the liquid, but the results, though too unreliable to emphasize figures, suggest that the CO_2 was fixed, probably as $NaHCO_3$. This fact was deduced because the alkalinity of the liquid increased on boiling though the CO_2 decreased. The explanation is, we consider, that a little Na_2CO_3 was secreted by the intestinal mucosa and this then met a large excess of H_2CO_3 in the lumen, $NaHCO_3$ was formed, $Na_2CO_3 + H_2CO_3 = 2NaHCO_3$ which on boiling lost CO_2 and the liquid therefore became more alkaline.

With regard to the absorption of alcohol in the presence of CO_2 there seems to be a tendency for more alcohol to be absorbed in the presence of CO_2 though the effect is not nearly so marked as in the stomach.

In the second part of the experiment peristalsis always occurred and usually less alcohol was absorbed, but the difference was less marked when there was CO_2 in the liquid in the last part of the experiment than when it was introduced first.

Re-stating some of the results already presented in Tables I. and II. it can be seen that the presence of alcohol has an effect on the actual absorption of liquid.

Absorption of Liquid from the Intestine.

% Absorption in 1 hr.		% Absorption in Successive ½ hrs.			
Ringer Alone.	Ringer + Alcohol.	Ringer Alone.		Ringer + Alcohol	
		1st ½hr.	2nd ½hr.	1st ½hr.	2nd ½hr
70	25	38	30	25	0
100	16	75	68	20	5
50	31	22	22	27	0
25	20				
80	37				

We can conclude that alcohol does not hasten the absorption of liquid but has rather the reverse effect, since the figures for the absorption of liquid with alcohol are usually considerably lower than in the case of unbuffered Ringer alone. Moreover alcoholic absorption seems to slow down the absorption of liquid very rapidly, since in the 2nd part of an alcoholic experiment there is very often no absorption at all, whereas in the 2nd half of a simple Ringer experiment there is very little difference from the first.

From all these considerations we may remark that alcoholic liquids are probably not as efficient as water in quenching the thirst.

Summary.

1. The effect of CO_2 on the absorption of alcohol is not so marked as in the stomach.
2. It cannot be stated whether the presence of alcohol affects the diffusion of CO_2 because of the possible secretion of Na_2CO_3 into the lumen.
3. Alcohol appears to retard actual absorption of liquid in the intestine.

THE INFLUENCE OF ALCOHOL ON THE ABSORPTION OF GLUCOSE FROM THE ALIMENTARY TRACT.

Part I.

It is generally stated in modern textbooks of Physiology that the Stomach has no power of absorbing either water or dissolved substances with the exception of a few compounds such as alcohol, chloral hydrate and strychnine.

Examination of older literature shows that Tappeiner[9] (1881) investigating the absorptive power of the stomach in cats and dogs concluded that glucose and peptone were both absorbed slightly from water solution and definitely absorbed to a greater extent from dilute alcoholic solutions.

Anrep[10] and later Segall[11] working with dogs with gastric fistulae concluded that the stomach absorbed both glucose and peptone.

v. Mering[12] and simultaneously Brandl[13] studied absorption from the stomach also in dogs with gastric fistulae. v. Mering came to the same conclusion as Edkins[6], that water was not absorbed: with regard to dissolved substances he found considerable absorption of glucose and peptone from water solutions and an increased absorption of glucose in the presence of alcohol. Brandl, whose experiments were all performed on one dog records very high figures for the absorption of glucose, peptone and sodium iodide with a definite increase in the presence of alcohol. His work is open to adverse criticism since he found absorption of water from quite concentrated solutions which was denied by v.

Mering. Other workers such as Ryan[14] and Brequet[15] state that alcohol does not enhance the absorption of strychnine by the stomach and according to Tschcknounow[16] saccharose is not absorbed in the slightest degree from water or alcoholic solutions in the stomach.

Most experiments carried out on the effect of alcohol on intestinal absorption, with the exception of those of Nakamura[18] have been done on dogs with Thiry-Vella fistulae. It must be urged against this method that there always results a catarrhal condition of the gut and therefore it cannot constitute a reliable method for studying physiological absorption. (See the discussion in Seäfer's Textbook of Physiology 1898. i. 557).

Scanzoni[17] employed T.-V. fistulae and found that various drugs which acted as stimulants (including alcohol) had a much smaller effect on intestinal absorption than on gastric absorption, Nakamura's conclusion (working with the "acute" experiment) with animals anaesthetised with A.C.E. was that alcohol does not promote intestinal absorption.

The above brief review of past work on absorption by the stomach and the effect of alcohol on absorption from the alimentary canal generally shows that no definite statements can be made.

Using decerebrate animals in the absence of anaesthetics (ether was used in the operation of decerebration) alcohol accelerated the absorption of CO_2 in the stomach. Experiments were then undertaken with the same operative procedure to see if alcohol accelerated absorption generally.

In this part of the investigation attention was first directed to the disappearance of glucose alone from the stomach cavity and then to the effect that alcohol exhibited on the rate of disappearance.

Method.

Cats were anaesthetised with ether, the carotids ligatured and decerebration performed by trephining. The respiratory centre functioned spontaneously. The animals were immersed in a saline bath at 37°C. The stomach was exposed, the oesophagus ligatured and a tube tied into the pylorus. Great care was taken to maintain the circulation intact, the appearance of the blood vessels readily informing on this point. The stomach was thoroughly washed out with warm saline, 25 cc. of glucose solution with or without alcohol was introduced, the glucose remaining in the introducing tube was washed into the stomach. Every experiment consisted of two parts, each part lasting for an hour, in one period glucose alone was given, in the other both sugar and alcohol. The actual concentration of the sugar was practically identical in all cases, viz. 20%. The strength of the alcohol was 10% in most cases, the actual amount of alcohol present being 2·5 cc. In some of the later experiments this strength was doubled. At the end of the hour the contents were withdrawn into a 200 cc. graduated flask and the stomach washed out with water until the volume was approximately 200 cc. The order of the administration of glucose alone and glucose with alcohol was alternated in successive experiments. The estimation of glucose in the solutions introduced and removed were made by Bertrand's method. All solutions removed from the stomach were freed from any protein by the Folin-Wu technique. Any loss that might have occurred in the process of introduction and removal by adsorption or mechanical adhesion to the gastric mucous membrane was estimated by introducing a known volume of solutions and immediately removing the same ~~and~~ Such determinations showed that any error in the results from this cause should not exceed 0·05 grm.

Results.

Periods of one hour; 25 cc. of 20% glucose introduced either in water or in 10% alcohol. Total glucose 5 grms.

Disappearance of glucose from stomach.

A. 1st hour glucose plus alcohol. 2nd hour glucose alone.

Exp. I.	0·881 grm.	0·46 grm.
" II.	0·625 "	0·0 "
" III.	0·475 "	0·0 "
" IV.	0·72 "	0·58 "
Mean	0·68 "	0·26 "

B. 1st hour glucose alone. 2nd hour glucose plus alcohol.

Exp. V.	0·41 grm.	1·006 grm.
" VI.	0·31 "	0·31 "
" VII.	0·28 "	0·58 "
" VIII.	0·38 "	0·44 "
" IX.	0·28 "	0·60 "
" X.	0·28 "	1·06 "
Mean	0·32 "	0·67 "

From the foregoing table it can be seen that glucose disappeared from the liquid in the stomach to the extent of approximately 0·3 grm. per hour. Also that with one exception the disappearance of glucose when given with alcohol was greater irrespective of whether the glucose alone was in the first or second period. In the presence of alcohol the absorption of glucose was 0·67g per hour, that is, the disappearance with alcohol was at twice the rate that it was alone.

Other experiments to test the rate of absorption of glucose with or without alcohol in the intestine showed that the influence of alcohol was here less marked. In these experiments about 100 cms. length of small intestine was taken distal from the duodenum. Tubes were tied into either end and the loop was well washed out to remove all contents. Into the loop was introduced either glucose or glucose plus 10% alcohol. In these experiments the periods were half-hours.

Results.

Disappearance of glucose from small intestine.

	1st ½ hour glucose plus alcohol.	2nd ½ hour glucose alone.
Exp. I.	0·813 grm.	0·541 grm.
" II.	0·733 "	0·46 "
" III.	0·645 "	0·432 "
" IV.	0·88 "	0·81 "
" V.	0·82 "	0·66 "
Mean	0·78 "	0·59 "

These experiments were complicated by the fact that in some cases tape-worms were not completely removed. No great stress can therefore be laid upon the precise values of the estimations, they can only be regarded as indicative.

It is better perhaps to speak of the disappearance of glucose than its actual absorption. J. Mellanby[19] has pointed out that etherisation and decerebration will cause variable fluctuations of the blood sugar level. No reliance therefore could be placed on simultaneous estimations of the blood sugar as far as relationship between disappearance of sugar from the alimentary canal and variations in the amount in the blood were concerned.

It seems however permissible to state that alcohol influences the rate of disappearance of glucose from the stomach and in work which is now proceeding the effect of alcohol is being further studied under conditions in which etherisation and decerebration are eliminated and the results so far indicate that the disappearance corresponds definitely to absorption into the blood.

THE INFLUENCE OF ALCOHOL ON THE ABSORPTION OF GLUCOSE FROM THE ALIMENTARY TRACT.

Part II.

In Part I. of this communication it was pointed out that the only satisfactory way of studying absorption from the alimentary tract of such substances as glucose would be to recognise the presence of the absorbed substance in the blood stream and not rely simply upon its disappearance from the gut. In the case of sugar absorption this presents difficulties when working with anaesthetised or decerebrate animals because of the attendant variations of blood sugar evoked by the technique employed. There remain two alternatives, either to work with normal unanaesthetised animals or to use some hypnotic which does not cause variations in the blood sugar level. The first of these methods is naturally ideal and some preliminary experiments on normal rabbits showed that giving a constant amount of glucose caused the rate of absorption, as estimated by the blood sugar level, to be greater when alcohol was simultaneously supplied. This method was however rejected since different individual animals showed considerable variations at different times. Recourse was had therefore to animals under amytal (ethylisoamylbarbituric acid) for the production of anaesthesia since this substance is stated by Page[20] to maintain deep anaesthesia without producing hyperglycaemia. Moreover it gives according to Deuel Chambers and Melhorat[21] after an initial fall a constant blood sugar level, slightly lower than the normal, over periods as long as six to eight hours.

In the series of experiments about to be described amytal was employed as the anaesthetic throughout.

Method.

Cats were employed after eighteen hours deprivation of food and without any preliminary anaesthetic were given an intraperitoneal injection of a 10% solution of amytal, made by dissolving 1 grm. of amytal in 8·85 cc. half normal NaOH with gentle heating and adding water to 10 cc. The dose for the production of anaesthesia in a cat was 0·8 cc. of this solution per kilo. of body weight. Almost invariably the animals went under in 10 minutes. Great care was taken during the experiments to keep the animals warm by means of constantly renewed hot water bottles and hot flannels. (It may be mentioned that amytal is said to lower the body temperature). After tracheotomy the carotid artery on one side was exposed but not ligatured. A tube was tied into the oesophagus at the neck. A canula was placed in the femoral vein by which injections could be made. Directly these operations were completed a sample of blood was taken by syringe from the carotid artery and the hole made, closed by a clip without occlusion of the vessel, thus the cerebral circulation was in no way interfered with. After the lapse of half an hour another blood sample was taken and the glucose solution introduced. The quantity of glucose given was comparable to that of the glucose tolerance test, that is, two grms. per kilo body weight in a concentration of 20%. This solution was administered by means of the tube tied into the oesophagus and then the remains were washed in with half the volume of water or, in experiments with alcohol, half the volume of 30% alcohol. Thus a final concentration of glucose in the gut was reached of about 13%. Blood samples of 0·8 cc. were taken at definite intervals in the way described above and were followed by the immediate injection of an equal amount of saline to make up the blood volume.

The sugar was estimated by the method of Hagedorn and Jenson, using 0·2 cc. for each estimation and performing each estimation in triplicate.

The experiments fall into three series.

Series I.

Realising that there would probably be wide differences in the amount of alimentary hyperglycaemia caused by the administration of glucose in different animals it was anticipated that a rather large number of experiments would have to be done, in some cases with glucose alone in others with glucose and alcohol, in order to obtain a reliable average for any conclusion to be drawn with precision. The first set of experiments were carried out as follows. Glucose was given and the blood sampled at regular intervals until the sugar level was either constant or falling slightly, then alcohol was introduced in the quantity and concentration described above and the blood sugar again determined at intervals of half an hour. The expectation was that when the blood sugar was at its maximum height alcohol would, if it aided absorption, cause a further rise. This anticipated rise was observed to take place as shown in the table of observations and graphs annexed.

Table I.

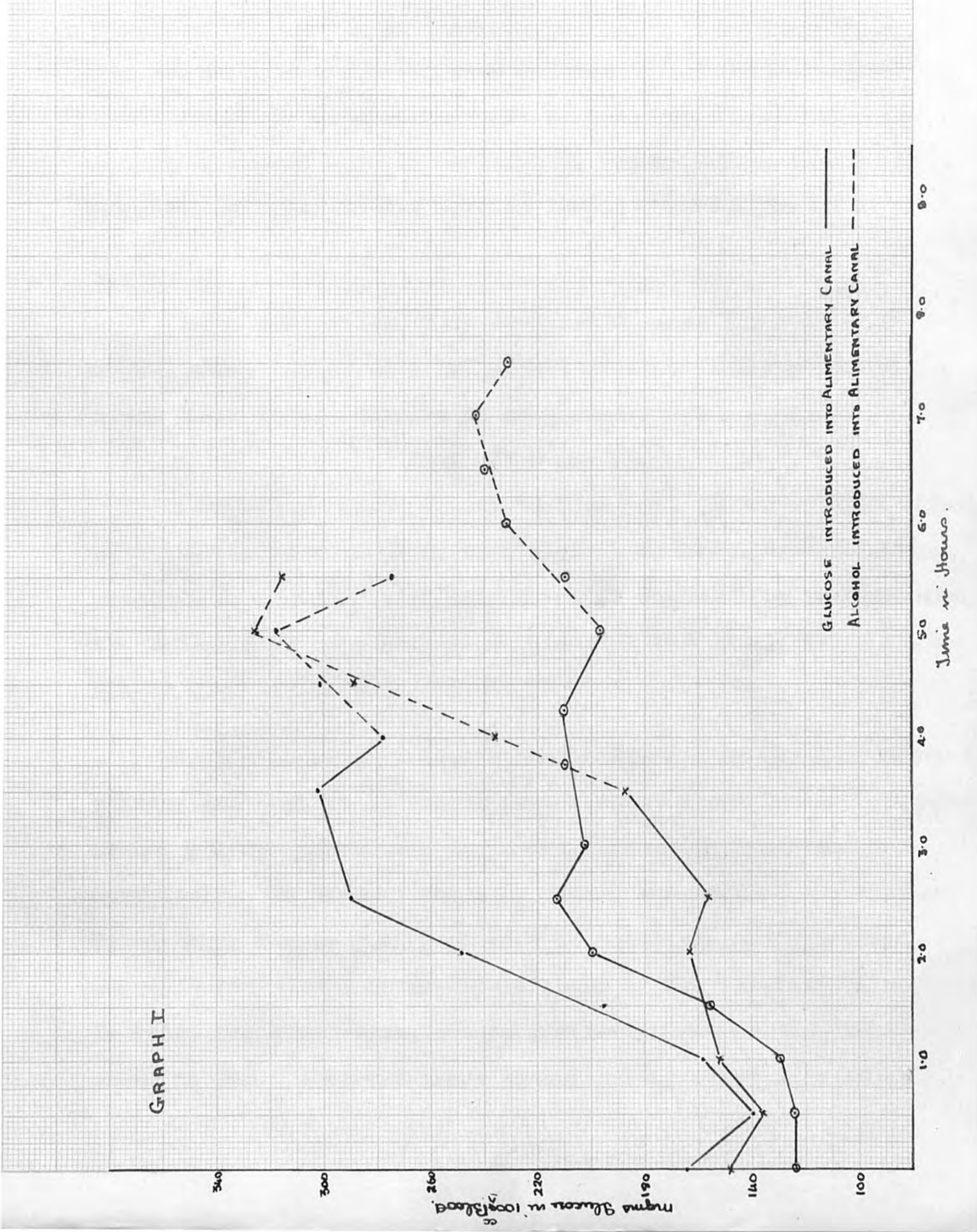
Experiment.	Initial blood sugar (mgms. per 100 cc.)	Maximum blood sugar with glucose alone.	Maximum after alcohol.
III.	136	187	326
V.	138	278	318
VI.	120	210	252
VII.	103	193	215
XI.	129	197	242
XII.	163	209	255
Average	132	212	268

Graphs of course of changes in III., V. and XI. are presented.

(Graph I. see next page)

In considering these results there is first the obvious criticism that the effect of the alcohol when absorbed might have been to turn out glucose from the glycogen of the liver and muscles, and that the increase did not represent augmented absorption. If this were so then alcohol introduced directly into the blood stream should cause a similar or even a greater increase. In two cases when alcohol was introduced directly into the blood stream (via the carotids) a fall and not a rise was obtained. But

GRAPH I


GRAPH I
mgms Glucose in 100cc Blood.
100
140
180
220
260
300
340
1.0
2.0
3.0
4.0
5.0
6.0
7.0
Time in Hours.
GLUCOSE INTRODUCED INTO ALIMENTARY CANAL
ALCOHOL INTRODUCED INTO ALIMENTARY CANAL

to show definitely that the alcohol was not acting by glycogen mobilisation several experiments were made where alcohol alone was passed into the oesophagus and the effect on the sugar level noted. The alcohol would be very rapidly absorbed in a fasting animal (see E. Mellanby[23]). Nevertheless no marked rise resulted as shown in the next series of observations.

Series II.

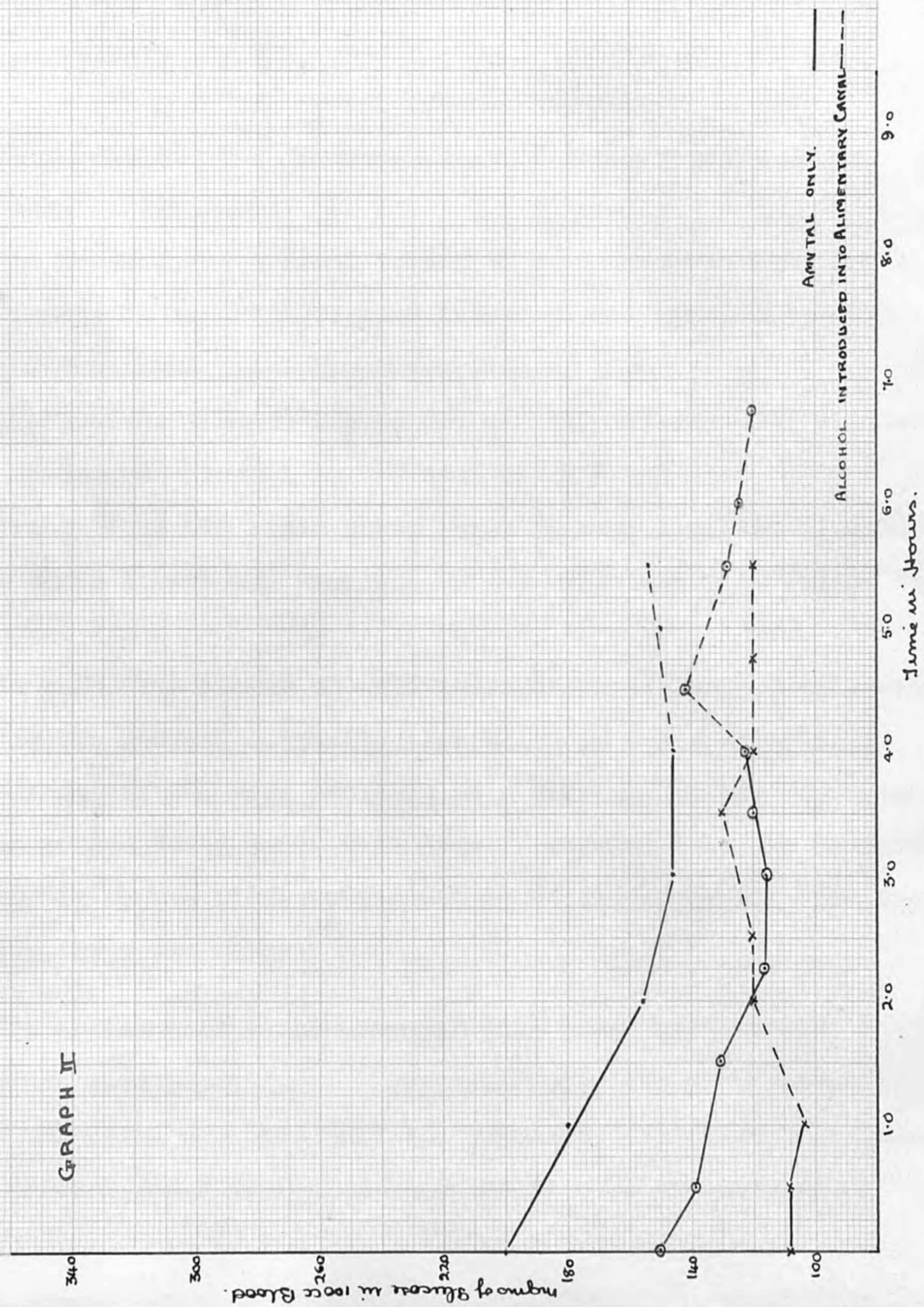
These experiments were designed to show the effect of amytal alone and further the effect of alcohol alone on the blood sugar level. Graphs of this series are presented.

(Graph II See next page)

From these graphs it can be seen that the invariable effect of amytal is to produce an initial fall in blood sugar and then maintain a constant level in cats as in dogs. (See D. Chambers and Melhorat[21]). The giving of alcohol alone causes but a very slight rise in the sugar level.

Having obtained evidence that alcohol aids the absorption of glucose and that it increases postprandial hyperglycaemia, another series of experiments was performed to confirm the point definitely. In these a complete record was made of the rise of blood sugar due to giving glucose as described and wherever possible the return of the blood sugar to the original value. In short, these experiments were similar to the glucose tolerance tests in man. A fairly large number of experiments on these

GRAPH II


GRAPH II
AMYTAL ONLY.
ALCOHOL INTRODUCED INTO ALIMENTARY CANAL
Time in Hours.
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
mgms of Glucose in 100cc Blood.
340
300
260
220
180
140
100

lines proved to be necessary before any generalised statement could be made and before a standard could be fixed with which to compare results obtained in similar experiments where, in addition to sugar, alcohol was also given.

The results are best seen in the following graphs.

(Graph III see next page)

To facilitate the interpretation of these results several points require emphasis.

(1) The maximum sugar level occurs on an average (taken from a larger number of experiments than charted) four hours after the giving of the sugar, i.e. the absorption is slow.

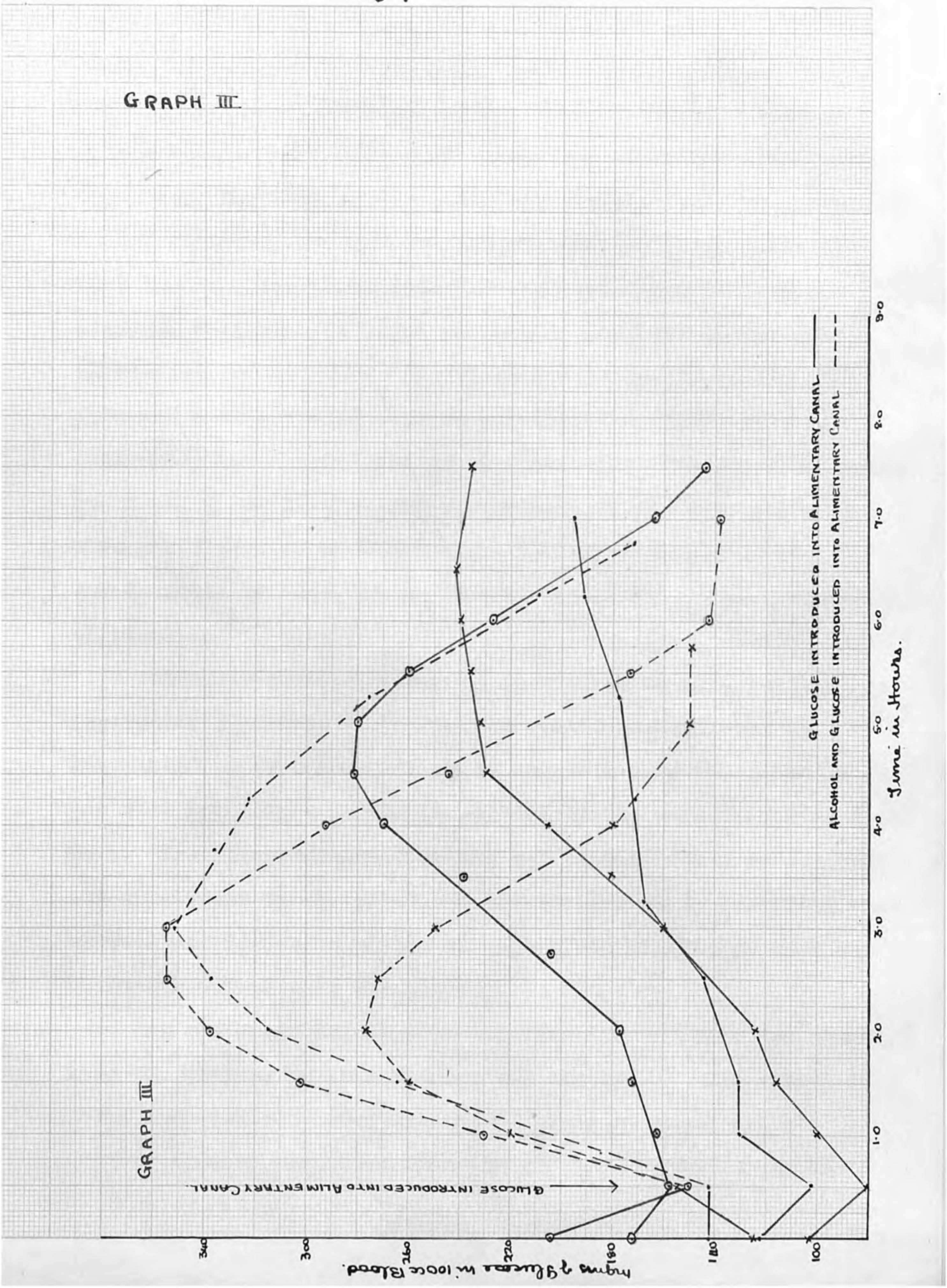
(2) The average maximum figure for all experiments with glucose in the absence of alcohol is 232 mgms per 100 cc.

(3) The fall in the blood sugar level is very slow, so slow that in most cases it was not possible in the experiments to follow the fall.

No doubt the reason of this maintenance of the hyperglycaemia is due to the lowered metabolic rate which is a characteristic effect of amytal and also possibly to a decrease of the glycogenic function of the liver under this drug. That amytal does diminish the activity of the glycogenic function of the liver has been shown by Hindes, Boyd and Leese.[22]

The experiments to be compared with these were carried out under exactly the same conditions. Proportionally the same amount of glucose was given and also half the volume of the glucose solution of 30% alcohol, resulting in a concentration of 10% alcohol.

GRAPH III


GRAPH III
GLUCOSE INTRODUCED INTO ALIMENTARY CANAL.
GLUCOSE INTRODUCED INTO ALIMENTARY CANAL
ALCOHOL AND GLUCOSE INTRODUCED INTO ALIMENTARY CANAL
Time in Hours.
mgms of Glucose in 100cc Blood.
100
140
180
220
260
300
340
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0

Again the results are presented graphically (See Graph III.)

Emphasising the same points as before we have (1) the maximum sugar level occurs on an average two hours after giving sugar together with alcohol, (2) the average maximum sugar level is 311 mgm. per 100 cc., (3) the fall of the sugar level is more rapid. The explanation of the more rapid fall is not altogether clear. It might be that alcohol stimulated the metabolism and so led to a utilisation of the sugar or, that glycogen became formed. These possibilities could only be determined by observations of the metabolic rate and respiratory quotients. But leaving for the present the explanation of this more rapid fall, we see that there is clear evidence of the augmentation of sugar absorption by the simultaneous administration of alcohol.

Whatever criticisms can be applied to results relating to absorption experiments obtained by estimating the rate of disappearance of the substance in question from the lumen of the gut such criticisms cannot be applied to the experiments recorded here. The disappearance from the gut is definitely related to the appearance in the blood, and the conclusion is justified that alcohol accelerates the rate of absorption of glucose from the alimentary canal into the blood.

At the beginning of each experiment a catheter was inserted into the bladder and the bladder was emptied. The volume of urine secreted each hour was noted. This averaged 1·1 cc. whether alcohol was given with the glucose or not. Thus the conditions of the experiments had not affected the secretory activity of the kidneys, 1 cc. per hour being about the average rate of secretion of urine in the cat. Since the secretion of urine did not seem to be affected by the presence of alcohol in the blood, it is probable that the more rapid return of the blood sugar level to normal when alcohol is introduced with glucose is probably not due to its greater excretion in the urine. This point cannot be settled, of course, without analysing the urine.

Summary.

1. If glucose is introduced into the alimentary canal of an animal under amytal anaesthesia the blood sugar rises and reaches a maximum in about 4 hours, after which it very slowly falls.

2. If alcohol is introduced with the glucose the maximum sugar level is reached in about 2 hours.

3. The average maximum level without alcohol is 232 mgms. per 100 ccs. of blood; with alcohol it is 311 mgms. per 100 ccs. of blood.

4. The blood sugar falls much more slowly to the normal value when alcohol is not given.

5. The influence of alcohol alone on the blood sugar level is shown to cause a slight rise.

6. Introduction of alcohol after the maximum level of alimentary hyperglycaemia with glucose alone has been reached, causes a further rise in the sugar level.

7. From these observations it is concluded that the effect of alcohol is not greatly to mobilise liver glycogen but to influence directly the rate of absorption of glucose from the gut.

GENERAL SUMMARY OF THESIS.

When a gas mixture containing N_2 and O_2 is introduced into the stomach and restricted to that cavity, a change in composition occurs which appears to be the result of simple physical process of diffusion from the mucous membrane. The tension of CO_2 is higher during secretory activity than at rest being 40-46 mm.Hg. at rest and 51·5 - 56·5 mm.Hg. in activity.

There was no evidence of absorption of saline solution by the stomach but it provokes a small secretion of HCl.

Alcohol is absorbed with greater rapidity and to a greater extent in the presence of CO_2. In the presence of alcohol, CO_2 disappears rapidly and completely from the stomach. Thus alcohol profoundly alters the gastric mucosa in regard to CO_2.

CO_2 also increases the absorption of alcohol from the small intestine but the effect is less marked.

Glucose is absorbed by the gastric mucosa to the extent of about ·3 gms. per hour. In the presence of alcohol twice this amount disappears.

Alcohol has a similar but less marked effect on the absorption of glucose from the small intestine.

Glucose introduced into the alimentary canal of an animal under amytal anaesthesia causes a rise in blood sugar which reaches a maximum in about 4 hours. If alcohol is introduced with glucose the maximum sugar level is reached in about 2 hours.

The average maximum level without alcohol is 232 mgms. per 100 cc. blood; with alcohol it is 311 mgms.

Blood sugar falls much more slowly to normal value when alcohol is not given.

The influence of alcohol alone on the blood sugar level is shewn to cause a slight rise.

Introduction of alcohol, after the maximum level of alimentary hyperglycaemia with glucose alone has been reached, causes a further rise in the sugar level.

REFERENCES.

1. Planer, Sitzungsb. d. k. Akad. d. Wissensch. Wien. 1860. XLII. 307.

2. Schierbeck, Skand. Arch. f. Physiol. 1891. 3. 437.

3. Ylppo, Munch. Med. Wockschr. 1916. p. 1650.

4. McIver, Redfield and Benedict, A.J. of P. 1926. 76. 94.

5. Argyll Campbell, Proc. of J. of Physiol. 1928. 65.

6. Edkins, J.S., J. of Physiol. 1892. 13. 445.

7. Mendel, A.J. of Physiol. 1898. 1.

8. Cannan and Sulzer, Heart. 1924. 11. 148.

9. Tappeiner, Zeitsch. f. Biol. 1880. 16. 497.

10. v. Anrep., Archiv. Physiol. Abth. 1881. 504.

11. Segall, In aug. Diss. Münch. 1888. Maly's Jahresb. 1889. 281.

12. v. Mering, Verhand. d. XII. Cong. f. Innere Med. z Wiesbaden 1893.

13. Brandl, Zeitsch. f. Biol. 1892. 29. 277.

14. Ryan, J. Pharm. u Exp. Therap. 1912-13. 4. 43.

15. Brequet, Zentralb. f. Biol. 1912. 14. 601.

16. Tschckounow, C.R. Soc. Biol. 1914. 77. 120.

17. Scanzoni, Zeitsch. f. Biol. 1895. 33. 462.

18. Nakamura, Yohoku. J. Exp. Med. 1924. 5. 29.

19. Mellanby, J., J. of Physiol. 1920. 53. 1.

20. Page, J. of Clin. Lab. Med. 1923. 9. 194.

21. Denel, Chambers & Melhorat, J. of Biol. Chem. 1926. 29. 249.

22. Hindes, Boyd and Leese, A.J. of Physiol. 1926. 76. 293.

23. Mellanby. E, Rept. Med. Res. Comm. 1919. No. 31.