VARIATIONS IN ALVEOLAR CARBON DIOXIDE PRESSURE IN RELATION TO MEALS; A FURTHER STUDY.

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In a previous number of this *Journal* (1) one of us (E. C. D.) drew attention to the changes in alveolar carbon dioxide pressure which follow the ingestion of a meal, showing that in the first half or three-quarters of an hour following the meal a rise of from 2 to 6 mm. occurs, with a subsequent fall below the original level and a return to that level during later stages in digestion. In a later paper (2), written in collaboration, we drew attention to the correlation which exists between the curves of gastric acidity and alveolar carbon dioxide pressure following meals, in normal individuals of varying type as regards their gastric secretion. The present series of experiments was designed to throw further light on the later portion of the curve of alveolar carbon dioxide pressure, *i.e.* that portion of the curve during which the pressure drops below the fasting level.

The effect of the direct introduction of substances into the duodenum.

Our subjects, who were healthy men working in our departments, were examined in the morning before any food had been taken. Ryle's modification of the Einhorn duodenal tube (3) was employed for the introduction of substances direct into the duodenum. The subject swallows the tube at about 9.30 a.m. After an hour and a half, or two hours, the withdrawal of a small quantity of alkaline bile-stained fluid is evidence that the tip of the tube has traversed the pylorus. Samples of alveolar air are now taken by the Haldane-Priestley method, and analysed with the Haldane apparatus; an inspiratory and an expiratory sample are taken at each reading, and the mean of the two readings expressed in terms of tension in mm. Hg. It having been ascertained that the subject's alveolar CO_2 pressure is at a constant level, substances are now introduced through the tube directly into the duodenum, by means of a "Record" syringe, and the variations in alveolar CO_2 pressure recorded. The food

substance used has, in the majority of cases, been oatmeal gruel prepared by the formula used in the preparation of gruel for fractional gastric analyses (4). In all cases the food thus introduced produced an immediate fall in alveolar CO_2 pressure with a subsequent return to the fasting level. In fact, the effect has been precisely similar to that seen in the latter half of the curve of alveolar CO_2 pressure following a meal taken in the ordinary way. A typical example of this experiment is seen in Fig. 1, details of which were as follows:

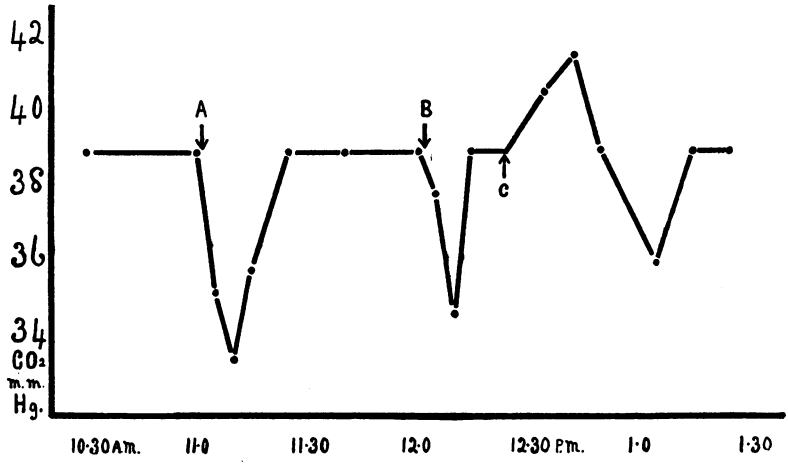

Fig. 1. Variations in alveolar CO_2 pressure produced by the direct introduction of substances into the duodenum.

In this and succeeding figures, abscissæ = time, ordinates = alveolar CO_2 pressure in mm. Hg.

Subject E. C. D. 7.30 a.m. Very light breakfast. 9.45. Duodenal tube swallowed. 10.20. Aspiration from tube yields a little alkaline bile-stained fluid. 11.2. 20 c.c. cold faintly alkaline gruel introduced into duodenum (A). 12.2 p.m. 20 c.c. faintly acid gruel introduced into duodenum (B). 1.26. Tube withdrawn 6 inches so that bulb now rests within stomach. 20 c.c. acid gruel introduced into stomach (C).

A series of experiments similar to the above has been performed, the result in all cases being to show (*a*) that the direct introduction of food substances into the duodenum leads to an immediate *fall* in alveolar CO_2 pressure with a subsequent return to the fasting level; (*b*) that variations in the acidity of the substance introduced do not produce appreciable difference in the response. In some cases a slightly greater response has been given by alkaline than by acid gruel; in other experiments the reverse has been true. Familiarity with the range of acidity of the gastric contents in man enables us to judge with fair precision what may be considered a safe limit in this respect. Food substances which are

definitely alkaline, on the other hand, are so rare that we have judged it unwise to introduce into the duodenum anything which is more than faintly alkaline to phenolphthalein. In Fig. 2 will be seen the result of the introduction of water of varying reaction into the duodenum; the response appears to be equally great in degree to that given by gruel.

In our previous paper (2) we produced evidence from a large number of human subjects to show that the increase in CO_2 pressure which follows the introduction of a meal into the stomach varies in degree

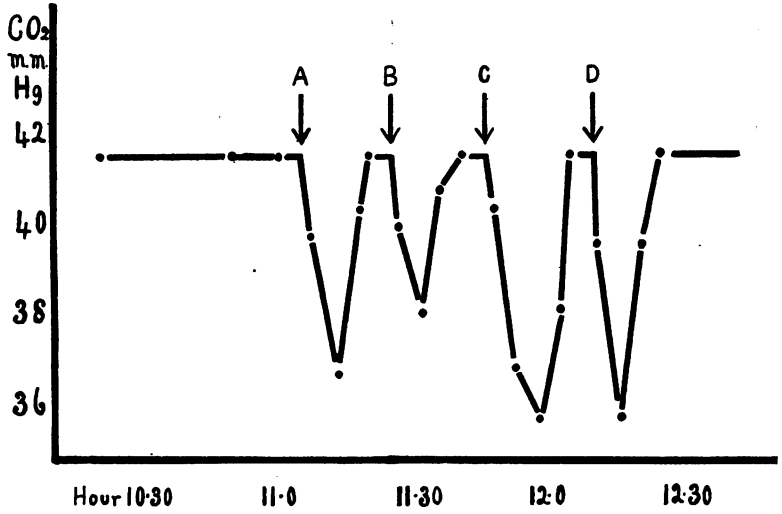

Fig. 2. Variations in alveolar CO_2 pressure produced by the direct introduction of water of varying reaction into the duodenum.

Subject J. W. B. 9.20 a.m. Subject, fasting, swallows duodenal tube. 10.20. Alkaline, bile-stained fluid aspirated. 11.5. 20 c.c. cold tap-water, acidified with HCl to a strength of 16 c.c. *N*/10, introduced into duodenum (A). 11.25. 20 c.c. water, just alkaline to phenolphthalein, introduced into duodenum (B). 11.46. 20 c.c. water, acidified with HCl to a strength of 40 c.c. *N*/10, introduced into duodenum (C). 12.10. 20 c.c. neutral tap-water introduced into duodenum (D).

directly with the amount of gastric HCl secreted by the particular individual; normal subjects, of average type as regards their gastric secretion, giving an alveolar CO_2 response of about 4 mm., those with marked hypersecretion as proved by repeated aspiration of abnormally large quantities of gastric juice, giving an alveolar CO_2 response sometimes as great as 12 mm., whilst those subjects, apparently normal in health, from whose stomachs HCl can never be obtained show no rise in alveolar CO_2 pressure whatever. These three types are reproduced in Fig. 3.

The rise in alveolar CO_2 pressure after a meal of fixed composition, gives an index of the amount of HCl secreted by the stomach of the individual concerned; moreover changes in the amount of HCl secreted, produced by varying the composition of the meal, are equally accurately indicated by alveolar CO_2 pressure observations; thus we have found that in normal human subjects of the usual type, substances such as meat extracts, known to excite an abundant gastric secretion, will produce a much greater rise in CO_2 pressure than is obtained by the administration of less active substances such as dextrose.

The immediate fall in alveolar CO_2 pressure shown in the present

Fig. 3. Curves of alveolar CO_2 pressure following a fixed test-meal in healthy men proved to be of different types as regards their gastric secretion. A. From a subject of the usual average type. B. From a healthy subject with complete achlorhydria. C. From a healthy subject with marked gastric hypersecretion.

experiments to follow the direct introduction of food substances into the duodenum must, we believe, be the consequence of the secretion of alkali into that portion of the alimentary canal. Such alkaline secretion is at least threefold in origin, its sources being from (*a*) the duodenal mucosa, (*b*) the liver, (*c*) the pancreas.

The secretion of bile is believed to be continuous, if so it will have no periodic effect upon the reaction of the blood, and so will not influence the alveolar CO_2 pressure; of the remaining sources, it is indicated by the experimental work of Boldyreff(5) that pancreatic secretion is by far the more important. That such is indeed the case is supported by

an observation which we have been able to obtain from a patient suffering from chronic disease of the pancreas; for many years this subject has been unable to digest more than the smallest quantities of fat; the fæces contain unsplit fat and meat fibres in relative large amounts; the urinary diastase index is high; there is no jaundice nor sign of diabetes. An exploratory laparotomy some years ago revealed a fibrotic condition of the pancreas. In Fig. 4 will be seen the curve of alveolar CO_2 pressure following a test-meal in this subject as contrasted with the picture given by a normal individual of the more usual type. We hold that this observation lends further strong support to our belief that the fall of alveolar CO_2 pressure below its original fasting level, seen during the later stages of digestion of a test-meal, or in the experiments illustrated in this paper, is due to the secretion of alkali into the duodenum, and that this alkali

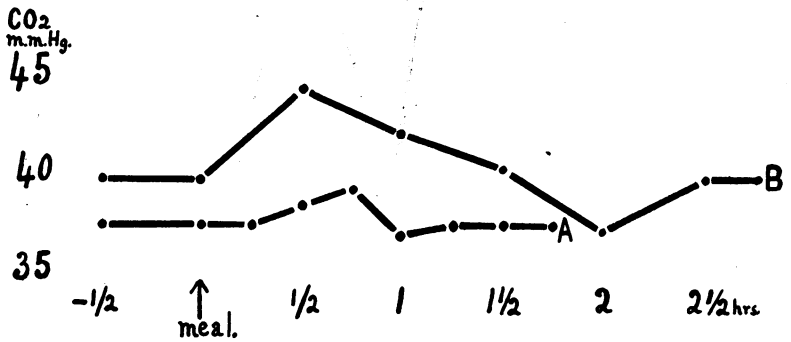

Fig. 4. Curves of alveolar CO_2 pressure following a test-meal in a subject with pancreatic deficiency (A). The curve from a healthy subject of the usual average type is reproduced for contrast (B).

is chiefly pancreatic in origin. If this belief be correct, then our observations, that the alveolar CO_2 response does not materially differ with substances of varying reaction, suggest that the formation of secretin by acid played no appreciable part in the production of pancreatic secretion in these cases. Further, since it is well established that perfect health can be maintained in cases of complete achlorhydria, we think that the formation of secretin by acid can only be regarded as an accessory, and relatively unimportant factor in pancreatic secretion.

THE EFFECT OF THE DIRECT APPLICATION OF ATROPINE TO THE STOMACH AND DUODENUM.

By means of the duodenal tube either in the stomach or in the duodenum, atropine was applied locally, the response of the alveolar

CO_2 pressure to food substances introduced before and after the atropine application being recorded by alveolar air analysis. In Fig. 5 will be seen the effect of the local application of atropine to the gastric mucosa.

A further experiment illustrated in Fig. 6 shows the effect of direct application of atropine to the duodenal mucosa.

We interpret these two last experiments in the following manner:

In each case it is clear that the application of atropine has prevented the change in alveolar CO_2 pressure which normally follows the intro-

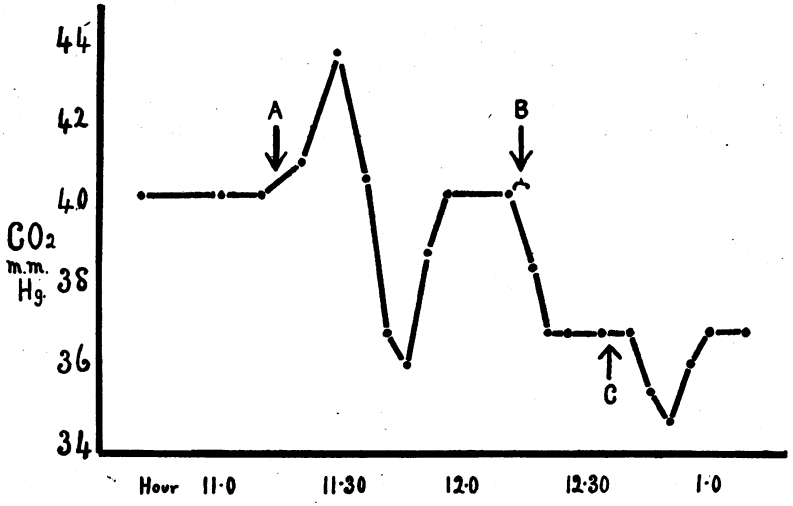

Fig. 5. Effect on alveolar CO_2 response to food, produced by local application of atropine to the stomach.

Subject T. I. B. 9.30 a.m. Tube swallowed into stomach. 10.4. Aspiration yields clear watery gastric juice in small quantities. 11.14. 20 c.c. neutral gruel introduced into stomach through tube (A). 12.13 to 12.16 p.m. Stomach gently washed with atropine solution consisting of $\frac{1}{100}$th grain atropine sulphate dissolved in 100 c.c. distilled water. It was introduced through tube 20 c.c. at a time, stomach being aspirated a moment later. In this way 100 c.c. atropine solution were introduced and about 105 c.c. subsequently withdrawn (B). 12.36. 20 c.c. neutral gruel introduced through tube into stomach (C).

duction of food into the viscus concerned; we believe this to be due to the inhibition of gastric secretions (in Exp. 3) and of the secretion of alkali into the duodenum (in Exp. 4).

More obscure is the interpretation of the change in "fasting level" of alveolar CO_2 pressure produced in these experiments. We believe that here the explanation is that continuous secretions have been inhibited by the local application. The continuous nature of salivary secretion is a matter of universal and everyday observation; Carlson has shown (6)

that in man, the gastric secretion, between meals, is of a similarly continuous nature; it would not therefore be remarkable if the alkaline secretion below the pylorus were of like nature, a slow continuous secretion giving way to a more rapid flow in response to the entry of food into the duodenum. Belief in such a conception is supported by these experiments, for it will explain how the local application of

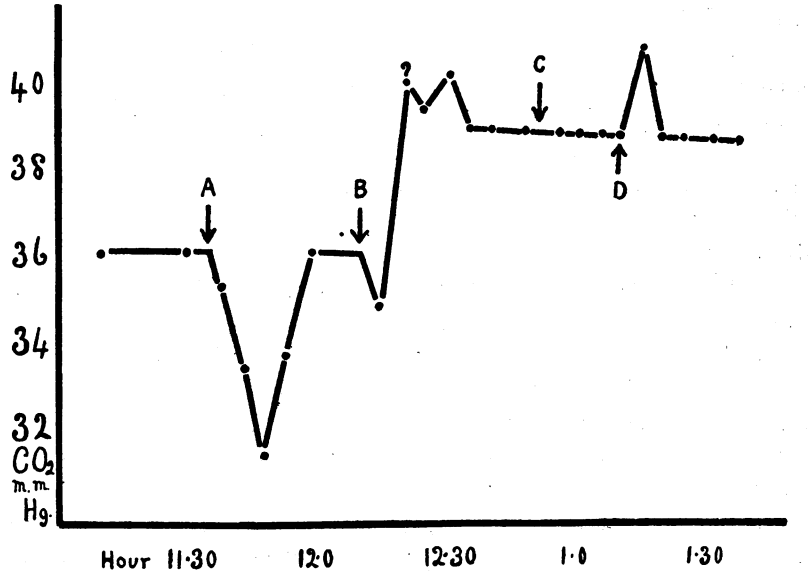

Fig. 6. Alveolar CO_2 response to direct injection of food into the duodenum before and after the local application of atropine to duodenal mucosa.

At the point marked ? on the chart the difference between the expiratory and inspiratory samples was too great to allow the mean to be fairly calculated.

Subject S. M. A. 9.45 a.m. The subject, fasting, swallows duodenal tube to its full extent. 11.10. Faintly alkaline bile-stained fluid aspirated. 11.35. 20 c.c. neutral gruel introduced direct into duodenum (A). 12.10. $\frac{1}{100}$th grain atropine sulphate in 20 c.c. water slowly introduced into duodenum. It is not possible to wash out the duodenum in a manner similar to the stomach. For this reason a rather stronger solution of atropine was employed and only about 3 c.c. of it were recovered by aspiration (B). 12.51, 20 c.c. gruel introduced direct into duodenum (C). 1.10. Tube withdrawn until bulb lies within stomach, 20 c.c. of gruel then introduced direct into stomach (D).

atropine to the gastric mucosa will not only inhibit the response to a meal, but will also, by stopping the continuous secretion of acid, cause an immediate decrease in the production of acid from the blood and a consequent fall in the alveolar CO_2 pressure; similarly we would explain the rise in the "fasting level" seen in Exp. 4 as being the result of the arrest of a continuous secretion of alkali into the duodenum.

SUMMARY.

1. The direct introduction of oatmeal gruel into the duodenum, by injection through a duodenal tube, is followed by an immediate fall in alveolar CO_2 pressure.

2. The degree of this fall in pressure, which can be produced by water alone, appears to be independent of the reaction, acid or alkaline, of the substance injected.

3. Gastric lavage with a weak solution of atropine causes an arrest of continuous gastric secretion, and an immediate fall of the fasting level of alveolar CO_2 pressure.

4. Subsequent to gastric lavage with atropine no rise in alveolar CO_2 pressure occurs in response to the entry of food into the stomach, but the fall in pressure which follows the passage of food into the duodenum still occurs.

5. Local application of atropine to the duodenal mucosa causes an immediate rise in the fasting level of alveolar CO_2 pressure.

6. Subsequent to such local application of atropine to the duodenum, no fall of alveolar CO_2 pressure occurs in response to the direct introduction of food substances into the duodenum; but introduction of food into the stomach evokes the usual rise in pressure with no fall below the fasting level when the food passes beyond the pylorus.

7. In the light of data obtained from a case known to have pancreatic deficiency, the fall in CO_2 pressure observed under the circumstances described above is believed to be due to the secretion of alkali below the pylorus.

8. The respiratory centre allows changes of alveolar CO_2 pressure to occur whose tendency is to maintain the reaction of the blood at a constant level.

9. We conclude from our results that the formation of secretin by acid is not necessarily an important factor in producing pancreatic secretion.

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