Observations

ON

SECRETION INTO THE STOMACH AND
DUODENUM:

WITH SPECIAL REFERENCE TO DIABETES MELLITUS.

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THIS communication is not meant to be of more than a preliminary character, the data on which it is based are insufficient for conclusions of any final nature to be drawn from them; but our results point in a direction so different from that of the majority of existing views concerning diabetes mellitus, and at the same time are so readily brought into line with existing data concerning the disease that we feel it advisable to bring them to the immediate notice of the profession.

Some time ago one of us (E. C. D.) drew attention¹ to the inconstancy of the alveolar CO_2 tension in any individual in the course of the day. Samples of alveolar CO_2 being collected by the Haldane-Priestley method and analysed by

the Haldane apparatus at successive intervals, the mean tension of an expiratory and an inspiratory sample was calculated; the result of these observations may be summarized as follows:

FIG. 1.—Curve of alveolar CO_2 tension to show the continuous level when fasting, interrupted by a rise, followed by a fall, on taking a meal.

2. If such a fasting subject be given a meal the CO_2 tension is found to rise, the tension increasing usually about 3 to 5 mm., reaching its highest point during the first hour; it then regains the original level and proceeds to fall below it to a depth of about 3 to 5 mm., finally rising once more to the fasting level, which it regains about two to two and a half hours after the meal; it then remains at this level until the next meal be taken (vide Fig. 1).

FIG. 2.—Curve of alveolar CO_2 tension following a meal, from a patient whose stomach had been almost completely excised.

that these secretions must be derived from the blood supplying the glands of the alimentary canal, it becomes clear that the outpouring of HCl by the stomach must tend to shift the reaction of the blood to the alkaline side. Now the tendency of the body as a whole is to maintain the reaction of the blood at a constant level, and a rapid method of doing this is to retain in the blood stream the volatile acid CO_2 in proportion as HCl is lost; such retention of CO_2 will result in an increased tension of the gas in the blood and hence a rise in the tension of alveolar CO_2 .

Similarly the evolution of alkali during later stages of digestion will occur at the expense of the blood stream, where less CO_2 will now be necessary for the maintenance of neutrality, and hence there will be a lowered tension of CO_2 both in blood and in alveolar air.

That the rise of CO_2 tension following a meal does correspond very exactly to the extent of gastric secretion of acid

we were able to establish by a series of observations on healthy men, it being shown² that those with marked gastric hypersecretion showed an enormous rise of CO_2 tension, whilst those with no secretion of HCl at any time gave no rise in CO_2 tension whatsoever; the contrast between a case with complete achlorhydria and one with secretion slightly above the average is seen in Fig. 3.

It has been more difficult to establish the exact significance of the drop in CO_2 tension in the later stages of digestion, but by introducing a modified Einhorn's tube into the duodenum we have been able to demonstrate that the direct introduction of food in this situation is, in the normal man, immediately followed by a sharp fall in alveolar CO_2 tension.

Such an experiment is illustrated in Fig. 4, which shows the immediate drop in CO_2 tension produced whenever food is injected into the duodenum (A and B); when, however, the tube was drawn

FIG. 4.—Curve of alveolar CO_2 tension to show the effect of direct introduction of food into duodenum: at points A and B food was injected through duodenal tube; at point C the same process was repeated after tube had been pulled up into stomach.

up into the stomach and the food introduced into that organ (C), a rise followed by a fall, such as is seen after an ordinary meal, was produced.

These experiments, a full account of which will be found in the forthcoming number of the *Journal of Physiology*, have, when examined in conjunction with the curves obtained from normal subjects and those with achlorhydria, confirmed our belief that the fall in CO_2 tension which occurs in the later stages of digestion corresponds with the outpouring of alkali when food has traversed the pylorus.

The alkali secreted into the small intestine is of threefold origin, coming from:

1. The liver.
2. The mucous membrane of the intestine.
3. The pancreas.

The secretion of bile is considered to be a continuous process, and, such being the case, cannot periodically affect the CO_2 tension; of the other two factors the work of Boldyreff³ shows that the pancreatic secretion is by far the more important as a source of alkali. That such is the case is indicated by an observation which was obtained from a patient proved by exploratory laparotomy to have chronic pancreatitis (a fuller account of this case will appear in our paper in the *Journal of Physiology*); the curve of alveolar CO_2 tension is shown in Fig. 5, and it will be seen that the

FIG. 5.—Curve of alveolar CO_2 tension from subject suffering from chronic pancreatitis (A), to show small extent of fall in tension when contrasted with average normal subject (B).

drop in tension is notably diminished when compared either with an average man, or with a case of achlorhydria.

Working with normal human subjects, we have found that the respiratory response to food can be affected by the local application of atropine solution to the gastric or duodenal mucous membrane. Thus if the gastric mucosa be washed with a weak solution of atropine the secretion of HCl, as shown by aspiration of samples of the gastric contents, can be abolished, and we have found that, when a test meal is given after such lavage, the rise in CO_2 tension does not occur, although the later fall in tension still takes place. By means of the duodenal tube we have been able to apply a similar solution of atropine to the mucosa of the duodenum, and in this experiment we found that we had succeeded in abolishing the response which normally follows the entry of food in this situation.

The experiment is illustrated in Fig. 6. The duodenal tube having traversed the pylorus and the fasting subject having a constant tension of O_2 , food was injected through the tube at the point marked A, the result being a typical fall in tension. At the point B the duodenum was washed with atropine solution and the

FIG. 6.—Curve of alveolar CO_2 tension to show effect of atropine when applied to duodenal mucosa. A Food injected direct into duodenum with normal response. B Weak solution of atropine injected into duodenum through tube, producing a rise in the fasting level of O_2 (at point marked "B" difference between samples of alveolar air was too great to allow of accurate measurement). C Food injected into duodenum with no response. D Food injected into stomach causing gastric response without subsequent fall.

CO_2 tension, after fluctuations, assumed a constant, though higher, level once more. At the point C food was again injected into the duodenum, but this time it produced no response whatever; when, however, the tube was pulled up into the stomach and food injected into that viscus at the point D, a gastric rise of tension at once occurred without any fall at a later period.

This, with other experiments with atropine, to be published shortly, bears out and amplifies the local effects of that drug which one of us has referred to in a previous paper.¹ These effects may be summarized as follows:

1. Gastric lavage with atropine solution diminishes or abolishes the secretion of acid by the stomach.
2. Gastric lavage with atropine solution can abolish the rise of alveolar CO_2 tension which normally occurs when food enters the stomach, it does not affect the fall of CO_2 tension which occurs after the food has traversed the pylorus.
3. Gastric lavage with atropine solution causes the fasting level of alveolar CO_2 tension to fall to a lower level.
4. Duodenal lavage with atropine solution can abolish the fall of alveolar CO_2 tension which occurs when food is injected into the duodenum, it does not affect the rise of CO_2 tension which occurs on the entry of food into the stomach.
5. Duodenal lavage with atropine solution causes the fasting level of alveolar CO_2 tension to rise to a higher level.

It here becomes necessary to discuss the meaning of the change in the fasting level of CO_2 tension summarized under headings 3 and 5.

Carlson, in his admirable study, *Hunger in Health and Disease*, has drawn attention⁵ to the continuous nature of gastric secretion; aspiration of the fasting stomach will frequently yield appreciable quantities of juice containing HCl; this is a product of that continuous gastric secretion which goes on in the healthy man at all times, being interrupted at intervals by a much greater flow in response to the approach or entry of a meal. As such a secretion of acid must be made at the expense of the blood stream, it will entail the constant retention in the blood of a corresponding amount of CO_2 ; if, then, by means of atropine, it be temporarily checked, its arrest will be shown by a lessened retention of CO_2 , and hence by a lowering in the fasting level of alveolar CO_2 tension.

Our experiment, illustrated in Fig. 6, shows that a converse phenomenon occurs when atropine is applied to the duodenal mucosa; there is an immediate rise in the fasting level of alveolar CO_2 tension. We would suggest the following explanation of these experimental facts:

1. Gastric secretion is known to occur continuously, even when the stomach contains no food; arrest of this continuous secretion will very naturally lessen the continuous loss of acid from the blood stream, and so will lower the fasting level of alveolar CO_2 tension.
2. It is known that salivary and gastric secretion continue even between meals; it is probable that pancreatic secretion continues in a similar manner.
3. The rise of alveolar CO_2 pressure to a new and higher fasting level which follows atropinization of the duodenum is the result of the arrest of such continuous secretion of alkali into the duodenum.
4. Further, it may be logically deduced from the above that the fasting level of alveolar CO_2 tension in any subject represents a balance between the continuous loss of acid via the stomach, and the continuous loss of alkali via the duodenum. That some such explanation would be arrived at we had suggested in our previous paper, wherein we drew attention to our observation that cases with an excessive secretion of gastric HCl have a high fasting level of alveolar CO_2 tension, whilst in those with achylia gastrica the CO_2 tension is at a low level.

It was this deduction that led us to make further investigation into the problem of diabetes mellitus.

The clinical application of alveolar air analysis in diabetes is due chiefly to the work of Beddard, Pembrey, and Spriggs, who showed that the onset of ketosis and coma might be diagnosed at an early stage by the lowering of the percentage, or tension, of CO_2 in the alveolar air; this effect has been explained by the presence of aceto-acetic acid in the blood stream, which replaces a certain amount of CO_2 in such cases, a view with which we are in entire agreement; at the same time we have been impressed by the fact that many diabetics, even when exhibiting no sign of ketosis, have an unusually low level of alveolar CO_2 tension. Gastric analysis on such cases has not, in our experience, shown an abnormally low secretion of gastric HCl, and the question was raised in our minds as to whether this lowering of alveolar CO_2 tension might not possibly be due to a hypersecretion of alkali by the pancreas.

We have now had the opportunity of examining six cases of severe diabetes mellitus, and we have found that in all of them the curve of alveolar CO_2 tension following a meal is of a type not seen in any other disease which we have investigated. The following is a typical example:

Case 1.—Male, aged 50. Admitted to the Middlesex Hospital in June, 1921, under the care of Dr. A. F. Voelcker. Wasting, thirst, and polyuria. Glucose present in large quantities in the urine, aceto-acetic acid also positive. Reduction of the diet gave slight improvement only. Gastric analysis on July 4th, 1921, showed a secretion of HCl by the stomach slightly lower than the average normal picture (Fig. 7; alveolar CO_2 estimation following a test

FIG. 7.—Curves of alveolar CO_2 tension and of gastric HCl from a severe case of diabetes mellitus. The gastric HCl is rather below the average normal amount; the CO_2 curve shows a small preliminary rise followed by a fall far greater than that seen in the normal subject.

meal on July 5th showed a slight gastric rise followed by a fall of 7 mm. Hg, the tension not returning to the fasting level for more than an hour and a half. In spite of careful dieting this case showed only a moderate degree of improvement on discharge four weeks later.

The results of alveolar CO_2 estimation in this and subsequent cases of diabetes are shown plotted together in Fig. 8, a typical curve from an average healthy subject being plotted in the same figure for comparison. All were diabetics of the severe type, brief clinical notes of their condition being as follows:

Case 2.—Male, aged 55. One month's history of thirst, weakness, and polyuria. Admitted under care of T. I. B., August, 1921. On admission had pyrexia and signs of early diabetic coma,

Urine contained much glucose, acetone, and aceto-acetic acid. Condition improved slightly, but pyrexia continued; signs at bases of both lungs. Ten days later patient became comatose and died. *Post mortem* examination showed purulent prostatitis, septic bronchopneumonia, and slight macroscopic changes in pancreas, sections of which are being cut.

Case 3.—Male, aged 25. Admitted under Dr. R. A. Young, September, 1921, for thirst and loss of weight. Much sugar, acetone, and aceto-acetic acid in urine. Patient refused strict diet and was eventually discharged unimproved.

FIG. 8.—Curves of alveolar CO_2 tension from a series of cases of severe diabetes mellitus: an average normal curve is shown for comparison. In this figure the readings recorded at the moment of the meal are, in Case 2 and Case 3, assumed: several readings were taken in each case before the meal, but not actually at the last moment before giving it. The normal curve is the average of a series of observations.

Case 4.—Female, aged 25. Severe diabetes for four years. Has been sugar-free on diet of less than 1,000 calories per diem for over a year; during last three months tolerance has fallen lower, and she now passes small amounts of sugar on lowest diet compatible with N-equilibrium. No acetone or diacetic acid in urine. Blood sugar curve typical of diabetes mellitus.

A few milder diabetics rendered sugar-free by dieting and having now a fair sugar tolerance, whom we have been able to investigate, have shown curves of alveolar CO_2 not differing from the normal picture seen in health.

If the interpretation which we have given above of the normal curve of alveolar CO_2 tension following a meal be correct, the extreme and protracted drop in tension seen in severe cases of diabetes indicates that in this disease there is hypersecretion of the pancreas. Now, it has been pointed out by Allen and others that the internal secretion of the pancreas is inversely proportional to its external secretion, and, on that hypothesis, the success which has attended the treatment of the disease by the principle of "alimentary rest" is explained. We would suggest that, in severe cases of diabetes, the external secretion of the pancreas is of an extreme degree, analogous to the hypersecretion of the stomach seen in patients suffering from Reichmann's disease. Alimentary hypersecretion is a phenomenon which is exceedingly difficult to demonstrate by any direct method; in the case of the stomach it can be done by accurate measurement both of the amount of juice aspirated at varying periods, and the degree of concentration of this juice; there being no convenient sphincter below the pylorus, it is impossible to collect more than small samples of the pancreatic juice in man, but we are at present devising means of confirming our findings by some such direct method. We wish in the meantime to draw attention to our observations, and to note that our belief that they indicate a condition of pancreatic hypersecretion is not in discordance with existing clinical and laboratory data, even though the conception itself be a novel one.

The parallelism between these curves of CO_2 tension and the curve of blood sugar commonly seen in a diabetic is a fact which must strike anyone familiar with the latter, and we hope in a later paper to bring forward further evidence as to this. The comparative rarity of macroscopic or microscopic evidence of gross pancreatic disease in cases of diabetes seen *post mortem* has long troubled students of this disorder,

and has made it almost impossible to harmonize theory with Minkowski's experimental production of the disease by pancreatectomy; we feel that the present observations supply valuable evidence towards the elucidation of this problem.

As to treatment our experiments with atropine suggest that a considerable degree of control over pancreatic activity may be acquired by the direct application of the drug to the duodenal mucosa; we are not yet in a position to produce clinical evidence in support of this suggestion, but hope to do so at a later date.

We would, in conclusion, express our thanks to our colleagues and co-workers at the Middlesex Hospital for their valuable help and permission to investigate cases under their care. The respiratory observations here recorded form part of a report to the Medical Research Council; the expenses of one of us incurred in this research have been partly defrayed by a Government grant made through the Royal Society.

SUMMARY.

1. The variations in alveolar CO_2 tension after a meal depend, in a subject at rest, on the secretions of acid and alkali into the stomach and duodenum.
2. Confirmation of this is given by the curves of alveolar CO_2 pressure from subjects with varying degrees of gastric secretion, or with pancreatic insufficiency.
3. Further confirmation is supplied by the results of experimental introduction of food direct into the duodenum.
4. The application of atropine to the mucosa of the stomach or duodenum appears to arrest the secretion of acid or alkali into the organ to which the drug is applied.
5. The writers believe that, like salivary and gastric secretion, pancreatic secretion must be a slow, continuous process interrupted by a more vigorous flow whenever food traverses the pylorus.
6. The fasting level of alveolar CO_2 tension in any subject represents a balance between the continuous loss from the blood stream of acid via the stomach, and alkali via the pancreas and duodenum.
7. Cases of severe diabetes frequently show a low fasting level of alveolar CO_2 tension even when no ketosis is present.
8. Cases of severe diabetes investigated by the writers have, after a test meal, shown a fall of alveolar CO_2 tension greater than that seen in any other condition so far examined.
9. It is suggested that this is due to a condition of hypersecretion of the pancreas, analogous to the gastric hypersecretion seen in cases of Reichmann's disease.

REFERENCES.

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HEMIPLEGIA IN A YOUNG CHILD, FOLLOWED LATER BY LOCOMOTOR ATAXIA.

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THE explanation of the rather complicated signs in the following case is probably as follows. The patient inherited syphilis, and developed a vascular lesion at the base of the brain when 3 years old, probably a syphilitic thrombosis in an artery at the left internal capsule. This gave rise to the right hemiplegia and aphasia at the time, and to the slight diminution of size and strength of the right side, which is the more marked where there is the greater differentiation of function—that is to say, most in the hand, least in the trunk—and to the right Babinski, and to the increased jerks in the right arm. A couple of years ago locomotor ataxia set in, and she developed the droop and the diplopia; we have no proof that the Argyll Robertson pupil, the inequality of the pupils, and the loss of knee-jerks developed at the same time, but we surmise it.

A girl, aged 17 years, was admitted to the Royal Victoria Hospital, Belfast, on August 19th, 1921, under Dr. Calwell. Her father had died, aged 48, from angina pectoris. She is the only child alive; four sisters and one brother died before two years of age; two were premature, one died aged 7 weeks and the other aged 8 months. Her personal history, as given by the mother, is that she had a sudden attack of right-sided paralysis with aphasia when 3 years old; she recovered her speech in two weeks and the use of the arm and leg was regained in a year. Ever since she has had a "halt" in her gait, and no spring in the right foot; she says the right side is weaker than the left.