symptoms to subside, we have to wait also for the recovery of the damaged cardiac muscle and adaptation of the heart to the valvular lesions which are almost invariable in the rheumatic form of pericarditis. Six months spent in nursing the heart back to efficiency is a very small part of a lifetime, and you cannot go far wrong if you make each forward step a test, guided by the pulse, the apex beat, the cardiac outline, the temperature, and, above all, the general condition of the child.

In conclusion, though I realize you already know much that I have commented upon, this lecture may help to recall to you that in the treatment of pericarditis in childhood we must be prepared to display all our clinical knowledge and that balance of judgement which it is so difficult to keep when pressed by urgent illness, complicated conditions, anxious parents, and possibly divergent opinions

A Study

OF

SOME FACTORS CONTROLLING THE NORMAL SUGAR CONTENT OF THE BLOOD.

BY

P. J. CAMMIDGE, J. A. CAIRNS FORSYTH,
M.D.LOND., F.R.C.S.ENG.

AND

H. A. H. HOWARD, B.Sc.LOND.

ACCURATE knowledge of the mechanism by which the sugar content of the blood is normally maintained and controlled is obviously an indispensable preliminary for a correct interpretation of the means by which hyperglycaemia and glycosuria may be produced. When, therefore, we found it impossible to explain satisfactorily on current theories many of the phenomena we observed in the course of an experimental investigation of diabetes mellitus to which we had been led by previous work upon the changes in carbohydrate content of the blood associated with pancreatic disease, it became necessary to study the subject afresh. The experimental part of the work was commenced in 1919, and reference has been made to some of the results in a previous paper,¹ but we now propose to discuss the subject in greater detail.

Before doing so it will be advisable to deal briefly with the methods of analysis adopted, for the discrepancies between the figures quoted by different observers are no doubt to be explained to some extent by the various processes for estimating the carbohydrate content of the blood employed. Many of the older findings were obtained with methods which do not completely remove all traces of protein, and are therefore of little value, but even in some of the more modern processes, such as Benedict's picric acid method, where this is successfully accomplished reducing substances other than sugar are included in the determination. After much preliminary experiment to discover a method of analysis which would give a reliable estimate of the reducing sugar, and that alone, we adopted in the first place a modification of the process described by one of us in 1917.²

In this the proteins are removed by filtration after they have been precipitated by heating with sodium chloride and dilute acetic acid. The reducing power of an aliquot part of the filtrate is then determined by boiling with a solution containing copper sulphate, sodium carbonate, and potassium citrate, converting the cuprous oxide formed into cuprous chloride by adding hydrochloric acid and then estimating the cuprous chloride with standard iodine and sodium thiosulphate solutions, using starch as the indicator.

Later, we more frequently employed a modification of the process described by Folin and Wu,³ as a considerable saving of time is effected when a large number of estimations have to be made, as was often necessary.

In the Folin and Wu method the proteins are precipitated with a solution of sodium tungstate and dilute sulphuric acid; an aliquot part of the filtrate is heated with an alkaline copper solution and the reduced copper dissolved in an acid mixture containing sodium molybdate and sodium tungstate. This solution is then made alkaline with sodium carbonate, diluted to a fixed volume, and the depth of the resulting blue colour compared in a colorimeter with that given by a standard solution of pure dextrose treated in the same way.

Although these methods differ in principle, numerous control experiments with sugars, and many simultaneous estimations of the sugar content of normal and pathological bloods, have shown that they give results which correspond within the limits of experimental error, the variation being not more than 0.002 per cent. either way in experienced hands. It is therefore probable that they give as accurate a determination as is possible of the proportion of reducing carbohydrate. Since our investigations of the blood were carried out at hourly, or in some instances at half-hourly, intervals for several hours, and sometimes throughout the whole day, it was necessary that we should work with as small an amount of material as possible and obtain it with a minimum of discomfort, to avoid the effects of nervous disturbance and fatigue; we therefore employed as a rule 0.3 c.cm., taken from the root of the nail in the human subject and from the marginal vein of the ear in animals. This amount was drawn into an accurately calibrated narrow pipette, direct from the puncture made by a sharp needle, without the use of oxalates or other anti-coagulating substances.

It is now recognized that the percentage of sugar present in the blood is not a fixed quantity, even in health, but varies within limits which are, however, confined to a comparatively narrow range. As the most important factor influencing the proportion of sugar in the blood at any particular time is the ingestion of food, it follows that, to obtain comparable results, the blood must be taken after a fast of sufficient duration to eliminate the direct action of food, or that the effects of test diets of known composition should be studied.

To consider first the figures obtained after fasting. We have found that in fifty human beings from whom samples of blood were taken in the morning, twelve to sixteen hours after the last meal, the sugar content of the blood averaged 0.085 per cent., with extremes of 0.070 per cent. and 0.102 per cent., but that nearly half (41 per cent.) gave a fasting level of 0.080 per cent. or 0.082 per cent. This agrees with the results obtained by Rona and Döblin,⁴ who found an average of 0.080 per cent. in ten individuals, with extremes of 0.048 per cent. and 0.128 per cent. by the polariscopic method. In the carnivorous dog our average fasting level for eight animals was 0.083 per cent., with extremes of 0.074 per cent. and 0.090 per cent., which corresponds closely to Oppler and Rona's polariscopic average of 0.085 per cent. for four animals, their extremes being 0.073 per cent. and 0.102 per cent. The average fasting value for twenty-five rabbits, which we took as examples of herbivorous animals, worked out at 0.083 per cent., the extremes being 0.080 per cent. and 0.096 per cent. These figures are lower than were obtained by Oppler and Rona and most other observers, but agree with the more recent values quoted by Jones, working with MacLean's micro-method,⁵ who found an average of 0.085 per cent. in sixteen rabbits, the highest being 0.116 per cent. and the lowest 0.068 per cent. The great difference in the blood sugar values found in rabbits by many experimenters is probably due to the fact that they are peculiarly liable to emotional disturbances which raise the percentage of sugar in the blood. The fasting value for cats is usually stated to be very high. Lyttgens and Sandgren⁶ give 0.291 per cent., and Oppler and Rona an average of 0.280 per cent. for four estimations, with extremes of 0.154 per cent. and 0.354 per cent., but a sample of blood we obtained from a small accidental cut on the paw of a fasting cat showed a blood sugar content of 0.094 per cent., a figure which corresponds more nearly to the average values for other mammals, and agrees fairly closely with the value of 0.088 per cent. quoted by Pavy⁷ as given by the heart blood of a cat killed by pithing. The higher figures for cats, like those quoted for rabbits, are probably to be attributed to emotional excitement.

Although we have found that the same person, or animal, does not invariably give exactly the same fasting value, the length of the fast does not appear to exert any material influence on the proportion of sugar in the peripheral blood, judging from our experience with rabbits which we have examined after twelve to seventy-two hours' abstinence from food. Allen⁸ has come to the same conclusion, and states that "approximately the normal percentage is stubbornly maintained through prolonged starvation, almost up to death." It would therefore seem that, when the digestive apparatus is functionally inactive, the sugar content of the blood is kept at an almost constant level for the same individual, and only varies within very narrow limits for different mammals, irrespective of their usual diet.

Turning now to the effects of food on the sugar content of the blood, we find that the rise in the percentage of sugar associated with functional activity of the digestive apparatus follows a curve which ranges within well-defined limits that appear to be practically identical for all

mammals under similar conditions; the shape of the curve is also of a similar type for omnivorous, carnivorous, and herbivorous animals. Since Jacobson⁹ published his observations on the normal sugar values of the blood and their physiological variations, in 1914, it has been known that the effects produced by food vary to some extent with its composition. According to Jacobson, sugar taken by the mouth causes the most rapid rise in the percentage of sugar in the blood, with starch a comparable though slower increase occurs, but with proteins and fat there is no appreciable change. Our observations confirm his conclusions as regards sugar and starch, but we cannot agree with the statement that protein foods have no appreciable effect on the sugar content of the blood.

As the charts (Figs. 1 and 2) show, dextrose and laevulose taken by the mouth produced in both human beings and dogs a rapid rise in the blood sugar, which reached its maximum at the end of an hour, and during the next hour there was an equally rapid fall, so that the normal fasting level was regained. Starch, whether in the form of bread taken by man or a dog, or of oats given to rabbits, produced a slower increase, which did not reach its maximum until the second or third hour, and was equally slow in subsiding (Figs. 3, 4, 5). Although our observations show that a purely protein meal, in the shape of 6 ounces of boiled haddock containing 40 grams of protein, did not raise the sugar content of the blood as rapidly or to as high a level as 100 grams of bread containing 54 grams of carbohydrate, there was an unmistakable rise, which reached its maximum at the fourth hour in man (Fig. 3), while 4 ounces of lean meat taken by a dog gave the same maximum percentage of sugar as a mixed meal of bread, dog biscuit, meat, bones, and an ounce of marmalade, but the increase did not take place as rapidly as with the mixed diet (Fig. 4).

In order to study the effects of fat, an ounce of olive oil was taken fasting by one of us, and on the two following days test meals of bread-and-butter and of sardines were given to the same subject. The meal of plain oil was followed by a very slight rise in the sugar content of the blood at the first hour (Fig. 3), then by a slow and steady fall in the next two hours, after which it returned to the fasting level again. The addition of fat, in the shape of butter, to bread was found to retard the rise and prolong the fall in the percentage of sugar in the blood, so that the maximum level was not reached until the third hour, instead of at the second, as when the same amount of bread was taken alone and the maximum was also a little lower. Similar results were obtained with normal dogs. A meal of protein and fat in the form of sardines gave results which differed in much the same way from those obtained when a fat-free protein was taken (Fig. 3).

It is therefore clear that sugars, starches, and proteins all increase the sugar content of the blood in animals and man, but that the rate at which the increase takes place, and the extent of the rise above the fasting level, vary with the nature of the material, pure sugars producing the most rapid rise and fall, then starch, and then pure protein; fat, on the other hand, tends to depress the level of the blood sugar when taken alone or with another food, either carbohydrate or protein. On comparing the effects of mixed meals consisting of oatmeal porridge, eggs, bread-and-butter, marmalade, sugar, milk, and tea in man (Fig. 3), and bread, dog biscuit, meat, bones, and marmalade in the case of a dog (Fig. 4), with oats, cabbage, carrot, for a rabbit (Fig. 5), it will be seen that the form and range of the blood sugar curves are remarkably constant, reaching their maximum point at the third hour, and returning to the fasting level again about the fifth or sixth hour. The slightly higher level attained in man than in the dog, and in the rabbit than in man, is possibly related to the amount of fat contained in their respective diets, although there may be a constant difference of this degree in the upper blood sugar limit characteristic of the species, for in each case the maximum on a mixed diet and on simple foods was approximately the same.

From these results it is evident that (1) the fasting level of the blood sugar is remarkably constant, and is not related to the habitual diet; (2) the time and space relations of the variations in the sugar content following the ingestion of food are also strikingly similar in herbivorous, carnivorous, and omnivorous animals; (3) while carbohydrate foods induce the greatest excursion above the fasting level, the effect of a purely protein meal is little if any less, but that fat causes a very slight increase, and has a delaying action and depressing effect on the rise which would otherwise occur with carbohydrates and proteins; (4) the upper limit attained by the blood sugar after a meal is apparently not directly dependent upon the amount of food taken after a certain minimum has been consumed.

Any theory, therefore, regarding the mechanism by which the sugar content of the blood is controlled must account for all of these facts, and also be capable of explaining how hyperglycaemia may occur under pathological conditions. It has been very generally assumed that the increase in the percentage of sugar in the blood following a meal is due to the direct passage into the

peripheral circulation of sugar derived from the food. If it were true that such an increase only follows the ingestion of sugar or starch, this might be accepted as a possible explanation, although even then it would be difficult to account for the remarkably constant maximum level produced by different carbohydrates and varying quantities of the same starch or sugar; but as a purely protein meal causes a similar rise, which may attain the same maximum as after a carbohydrate meal (Fig. 4), the true explanation is probably not so simple.

It may, of course, be contended that sugar can be formed from protein in the body; but it seems unlikely that it would appear in the circulation almost as rapidly as the sugar produced by the digestion of starches, and one would expect the rise in the sugar and urea of the blood after a protein meal to correspond more closely in point of time than the experiments of Jacobsen and Edwards¹⁰ have shown is the case. Another fact which cannot be explained by the current theory is the distinct reduction of the sugar content of the blood following the ingestion of oil. The delay in the sugar curve produced by the addition of fat to either carbohydrate or protein might be accounted for by more prolonged gastric digestion, but this would not explain the effect of fat taken alone.

When we were investigating the blood changes produced by solutions of various amounts of sugar we carried out a series of controls in which the same fluid without the sugar was taken, and found that a distinct, although much less pronounced, increase in the sugar content of the blood could be produced (Fig. 1). This result led us to investigate the blood changes following "sham feeding," and we found that when a patient was given a meal of "thrice-boiled" vegetables (that is, vegetables of low carbohydrate value which had been boiled in three changes of water to remove practically all the starch and sugar) a blood sugar curve of the same type, but of diminished range, as that induced by a carbohydrate meal was produced.

A pronounced example of this is seen in the diagram (Fig. 6), where the effects of a meal of oatmeal porridge and another of thrice-boiled vegetables are contrasted. It will be noticed that in this case the maximum height of the sugar curve was attained at the end of the first hour in both experiments, instead of at the second or third hour as is usual. Since the patient complained of symptoms suggesting hyperchlorhydria, and analysis of a specimen of stomach contents recovered after an Ewald test meal showed an excess of hydrochloric acid, it seemed possible that the unusually rapid rise in the sugar content of the blood might depend upon this. We accordingly investigated the blood sugar changes in healthy persons following the additions of varying amounts of hydrochloric acid to a similar meal taken on successive days, and found that as the quantity of acid was increased the maximum level of the blood sugar curve was reached more quickly, so that with the addition of 60 minims of dilute hydrochloric acid (B.P.) a first-hour instead of a third-hour curve was produced (Fig. 7). At the same time the curve became steeper in its ascent and descent, and also reached a higher level, 60 minims of the acid being followed by a maximum of 0.17 per cent. of sugar and 30 minims by 0.164 per cent., compared with a maximum of 0.152 per cent. when no acid had been taken by the mouth. The converse experiment of taking an alkali with the meal produced the opposite effect, depressing the maximum and prolonging the fall of the curve; 10 grams of bicarbonate of soda, for instance, taken with a meal of the same composition as in the preceding experiments, resulted in a maximum blood sugar of 0.140 per cent.

From these findings it is evident that the space and time relations of the blood sugar curve induced by food, or even the introduction into the stomach of any substance stimulating its physiological activities, are intimately related to the acidity of the gastric contents. The fact that the ingestion of olive oil induces practically no change in the sugar content of the blood, and that fat taken with carbohydrate or protein delays and depresses the rise which would otherwise occur, is in conformity with this conclusion, for it is well known that fat inhibits the flow of acid in the stomach and induces neutralization of the gastric contents by regurgitation of the alkaline duodenal secretions into the stomach.

The question which now arises is, How does the acid produce its effect? The first answer that suggests itself

is that since the speed at which the stomach empties is related to the acidity of its contents, the rapidity with which the sugar derived from the food enters the circulation may also be dependent upon the acidity of the gastric contents. Although this theory would explain the results obtained with starch and sugar, it would not account for the effects produced by sham feeding or of tea without milk or sugar. It seems probable, therefore, that the presence in the duodenum of the acid is itself in some way responsible for the rise in the blood sugar. There are three ways in which this effect might be brought about—(1) by

the direct action of the acid upon the liver cells, with consequent glycogenolysis; (2) through the formation of salts, which activate a glycogenolytic ferment in the liver; (3) by the inhibiting of some controlling factor which interferes with the conversion of glycogen into sugar in the fasting state.

Murlin and Sweet¹¹ have endeavoured to explain the rapid onset of diabetes in depancreatized dogs on the first hypothesis. They maintain that since the hydrochloric acid of the gastric juice cannot in such a condition be completely neutralized owing to the absence of the alkaline

FIG. 1.

FIG. 2.

FIG. 3.

FIG. 4.

FIG. 5.

FIG. 6.

FIG. 7.

FIG. 8.

FIG. 9.

FIG. 10.

FIG. 11.

FIG. 12.

FIG. 1.—Blood sugar content following dextrose (D) 100 grams by mouth, and weak tea (T) without milk or sugar, taken fasting.

FIG. 2.—Blood sugar in normal dog following 1.5 grams per kilo of dextrose (D), and 1.5 grams p.r. kilo of laevulose (L) by the mouth, taken fasting.

FIG. 3.—Blood sugar content in man following M, mixed meal; P, protein (haddock); C, starch (bread); O, fat (olive oil); Cf, starch and fat (bread-and-butter); Pf, protein and fat (sardines); F, fasting level.

FIG. 4.—Blood sugar content in a dog following M, mixed meal; P, protein (lean meat); C, starch (bread); Cf, starch and fat (bread and margarine); F, fasting level.

FIG. 5.—Blood sugar content in a rabbit following M, mixed meal; O, dry oats; Op, oatmeal porridge; F, fasting level.

FIG. 6.—Blood sugar content in man following O, oatmeal porridge; S, sham feeding with "thrice-boiled" vegetables.

FIG. 7.—Blood sugar content in normal man following M, mixed meal; Ac, a similar meal with 30 minims acid, hydrochl.; Ac', a similar meal with 60 minims acid, hydrochl.; Alk, a similar meal with 150 grains sod. bicarb.; F, fasting level.

FIG. 8.—Effects of intravenous injections of pancreas extract on the blood sugar of a fasting rabbit: P, pancreas taken from a fasting rabbit; D, taken three hours after a mixed meal; B, boiled extract.

FIG. 9.—Blood sugar content of rabbit after mixed meal (M) following the injection of 0.05 gram hydrazone phosphate; 2 D, two days after injection; 4 D, four days after injection; 7 D, seven days after injection; N, normal values before injection; F, fasting level.

FIG. 10.—Effects of intravenous injections of secretin (5 c.cm. and 1 c.cm.), and dilute HCl (5 c.cm. of 0.2 per cent. solution) on the blood sugar of a fasting rabbit.

FIG. 11.—Variations in the sugar content of the blood in a normal person through the day: F, fasting; B, breakfast; L, lunch; T, tea; S, sugar.

FIG. 12.—Scheme of the more important factors controlling the sugar content of the blood.

pancreatic secretion, it is absorbed into the portal circulation, and, reaching the liver, causes injury of the cells, which result in the liberation of glycogen and its rapid transformation into sugar. Subsequent experiments by Hendrix and Crouter¹² have not supported these conclusions, and, in any case, injury of the hepatic cells such as Murlin and Sweet assume cannot be the explanation of the rise in the blood sugar after a meal under normal conditions. It is conceivable, however, that the sugar-producing mechanism of the liver may be sensitive to very slight variations in the hydrogen ion concentration of the blood, such as would be produced by acid phosphates, and that, like the respiratory centre, it may respond to a much smaller change in reaction than the equivalent of the difference between tap water and distilled water. Experiments by Pavlov and his pupils have shown that the amount of alkali secreted by the pancreas is apparently proportional to the production of acid in the stomach, and that secretion by the pancreas begins as soon as the production of acid commences in the stomach; but as it is well recognized that the urine becomes less acid, and may indeed become alkaline to litmus, during gastric digestion (the so-called alkaline tide), it is evident that a proportion of the hydroxyl ions entering the circulation as the gastric glands secrete acid into the stomach are not appropriated by the pancreas for the formation of its secretion and are lost to the body in the urine, thus bringing about for a time a slight, but possibly sufficient, variation in the hydrogen ion concentration of the blood from the fasting level to induce a temporary formation of sugar from glycogen by the liver.

That very slight variations in the reaction of the blood do influence its sugar content is suggested, on the one hand, by the hyperglycaemias of asphyxia and muscular exercise, on the other: by the drop below the fasting level we have found to occur in normal persons during the first half-hour or so after a meal, which is the period where the alkaline tide in the urine is apt to occur and there is probably a relative excess of sodium ions passing into the circulation from the stomach.

In one case, for example, specimens of blood were taken at intervals of a quarter of an hour following breakfast, starting three-quarters of an hour after the meal had been commenced. From a fasting level of 0.084 per cent. the sugar fell in the first quarter of an hour to 0.080 per cent., fifteen minutes later it still stood at the same figure, then it began to rise, and in another quarter of an hour stood at 0.080 per cent.; at the end of the hour 0.120 per cent. of sugar was found.

As the result of experiments carried out with a glycerol extract of minced and dried calf liver, at body temperature, with phosphate solutions of different hydrogen ion concentrations and added glycogen, Langfeldt¹³ came to the conclusion that, since only inconsiderable hydrolysis occurred at a reaction corresponding to that of the blood and the optimum conversion of glycogen into sugar took place at a hydrogen ion concentration so far on the acid side as to be practically impossible, the regulation of the blood sugar content cannot be exerted through such an influence alone under physiological conditions. When, however, corresponding experiments were carried out with similar mixtures to which 0.6 per cent. sodium chloride had been added, glycogenolysis was found to be much accelerated, more complete hydrolysis of the glycogen occurring at the normal hydrogen ion concentration of the blood, and the optimum being reached at a point representing neutrality. He therefore inferred that, although the liver diastase forms complexes with both phosphates and chlorides which vary in their activity with the hydrogen ion concentration, the chloride diastase compound is the more important. Normally, the reaction of the liver is removed some way on the alkaline side from the neutral point at which chloride-diastase exerts its maximum effect, but when the hydrogen ion concentration is changed through the absorption, or formation, of acids or acid salts, so that the reaction more nearly approaches neutrality, an increasing hydrolysis of glycogen will occur and the sugar content of the blood will be raised accordingly. In this way the practically constant fasting level of the sugar in the blood could be explained and the effects of the passage of hydrochloric acid from the stomach into the duodenum can be accounted for.

The fact that pure liver diastase is inactive has been pointed out by several observers, but Bang¹⁴ was the first to show that contact with sodium chloride is necessary for

the development of its glycogenolytic powers in the liver. As the normal resting cell is impermeable to sodium chloride, he came to the conclusion that secretion of bile by the liver cells is a necessary preliminary for its absorption. It is believed that bile is constantly being secreted by the liver, but there is undoubtedly a rapid rise in the output when the stomach contents enter the duodenum; and it is clear from the experiments of Starling and others that this is due to the same cause as the simultaneous flow of pancreatic juice, to which it runs parallel—namely, stimulation of the cells by the secretin formed by the mucous membrane of the intestine. According to Starling,¹⁵ the injection of secretin may double or treble the output of bile. If, as Bang maintains, activation of the liver diastase is dependent upon the cells being rendered permeable to sodium chloride through the secretion of bile, it would seem probable that the entrance of secretin into the portal blood may increase sugar formation by the liver cells, and since the production of secretin appears to be proportional to the acidity of the gastric contents, the quantity of sugar passing into the blood would also vary with the amount of acid entering the duodenum. That secretin hastens glycogenolytic changes in the liver is indicated by the effect of perfusing the surviving liver of a rabbit with a neutralized preparation suspended in Locke's solution, and comparing the results with those obtained on perfusion with Locke's solution alone.

In one such experiment, for example, we found that whereas with Locke's solution alone 70 per cent. of the glycogen originally present had been broken down, with the production of 64 per cent. of sugar in sixty minutes, perfusion with neutralized secretin was followed in the same interval of time by the disappearance of 81.5 per cent. of the glycogen and the formation of 73 per cent. of sugar.

Further confirmation of the direct participation of the liver in the maintenance of the normal sugar content of the blood is furnished by the absence of the usual rise in the ferment value of the blood and the lower maximum level of the blood sugar curve, after a meal, met with in rabbits whose livers have been damaged by subcutaneous injections of hydrazine phosphate, a drug which has a specific toxic action on the hepatic parenchyma¹⁶ (Fig. 9).

We have also investigated the effect of intravenous injections of secretin on the sugar content of the blood in rabbits, and found that there is a gradual rise for about an hour after the injections in all cases, followed by a fall which took place more slowly the larger the dose given. The maximum percentage of sugar reached also varied with the dose, an injection of 5 c.cm., for example, inducing a rise of 0.050 per cent. above the fasting level, whereas 1 c.cm. of the same preparation only increased the blood sugar 0.018 per cent. (Fig. 10). In order to exclude the effect of the acid used in preparing the secretion a control experiment was carried out, in which 5 c.cm. of dilute hydrochloric acid (0.2 per cent.) was injected intravenously; the result was a rise of only 0.004 per cent. in the sugar—a figure within the limits of experimental error. It is therefore evident that secretin raises the sugar content of the blood, and that a sufficient dose will cause as great a rise as the ingestion of food—a meal of dextrinized oatmeal, for example (Fig. 5). Since this effect cannot arise from a change in the hydrogen ion content of the blood, it must be due to the action of the hormone itself.

It is possible, as we have suggested previously, that the action of secretin may be produced through an increased permeability of the liver cells for sodium chloride as a result of an augmented flow of bile, but it seems unlikely that alone would account for such a striking increase in the blood sugar, and it appears probable that some other mechanism must also be set at work by the injection. One naturally thinks of the pancreas, for it is well known to play an important part in carbohydrate metabolism, and its external secretion is controlled by secretin.

Our experiments upon dogs¹⁷ have shown that after pancreatectomy the fasting level of the blood sugar rises as increasing proportions of the pancreas are removed, although as long as about a quarter of the gland is left the increase is comparatively small.

Thus a dog with a normal fasting level of 0.090 per cent. gave a fasting value of 0.120 per cent. two weeks after one-third of the pancreas had been excised, another with the same fasting level showed 0.130 per cent. of sugar a fortnight after a two-thirds pancreatectomy, while a third dog, having a normal

fasting value of 0.084 per cent., gave a fasting value of 0.190 per cent. a couple of weeks subsequent to total pancreatectomy. At the same time the amylolytic ferment of the blood showed a corresponding increase, rising from a normal level of 2 or 3 units to 5 units in the one-third depancreatized animal, 15 units in the dog from which two-thirds of the pancreas had been removed, and 50 units after total pancreatectomy.

These results suggest that the diastase of the liver is, partly at least, under the control of the pancreas, and that as the inhibitory powers of the gland are decreased by the removal of larger proportions, the glycogenolytic powers of the enzyme become more active, so that increasing amounts of sugar pass into circulation, even in the fasting state. If this inference is correct we should expect a corresponding fall in the blood sugar to be produced by additions of pancreas, and this in fact appears to be the case. We have found that intravenous injections into fasting animals of the clear liquid produced by centrifugalizing the extract prepared by grinding fresh pancreas in Locke's solution with sand give rise to a rapid fall in the sugar content of the blood, which reaches its maximum about one hour after the injection has been made (Fig. 8). Since boiling the liquid previous to injection prevents the effect, and there was no evidence of shock or reaction, it is probable that it is not due to a toxic action of the injected protein, but arises from the presence of a substance destroyed by heat, which is most likely, therefore, an enzyme. Experiments described by Kleiner¹⁸ prove that in depancreatized dogs intravenous injections of a watery extract of fresh pancreas cause a more pronounced temporary decrease in the blood sugar than we found in normal rabbits. He further showed that injections of submaxillary gland, spleen, or voluntary muscle induced either an increase or only a very slight drop.

Numerous determinations of the diastase content of the blood before and after a variety of test meals have shown that in both normal individuals and animals it increases and decreases in proportion to the sugar; and since our experiments with depancreatized dogs have suggested that such variations are related to the functional efficiency of the pancreas, it is not unlikely that the rise which occurs during digestion may be the result of a temporary diminution in the internal secretion of the gland induced by the stimulating effect of secretin on the external secretion. Support is lent to this view by a comparison of the effects on the sugar content of the blood of a fasting animal produced by injecting extracts of the resting pancreas and of the pancreas taken at the height of digestion.

In the former case the level of the blood sugar was reduced from 0.092 per cent. to 0.076 per cent., whereas the injection of a preparation of the gland taken three hours after a heavy meal only brought down the sugar to 0.084 per cent. at the end of an hour (Fig. 8). A comparable effect is seen in normal individuals as the result of a series of meals when estimations of the sugar content of the blood are made at hourly intervals throughout the day. We have found that the curves become steeper, and the maximum percentage attained is slightly higher, after each successive meal (Fig. 11), so that a person with a maximum of 0.14 per cent. at the third hour after breakfast may reach a maximum of 0.15 per cent. two hours after lunch, and of 0.16 per cent. one hour after tea.

These changes can hardly be explained by differences in the food taken, or in the hydrogen ion content of the blood and liver, but suggest rather fatigue, and can be accounted for by diminishing control of the pancreas over the glycogenolytic activities of the liver arising from its inability to produce a sufficiency of its internal secretion.

As a study of the factors controlling the sugar content of the blood confined to glycogenolysis would be incomplete, it is necessary also to consider the question of glycogen formation. In 1903 Grube¹⁹ showed by a series of experiments upon surviving liver-pancreas preparations that perfusion with glucose leads to the deposition of glycogen in the liver, and the following year Dovon and Morel²⁰ reported similar results with glucose injected into the mesenteric veins of dogs; subsequently other observers confirmed their observations. Martz,²¹ on the other hand, experimented on isolated livers, without pancreas, and failed to observe glycogen formation after glucose injections. It is therefore evident that the presence of the pancreas is necessary for the deposition of glycogen in the liver, and that this is so is further suggested by the observations of Barrenscheen,²² who found that when the liver of a dog which has undergone total pancreatectomy some days previously was transfused with dextrose

no glycogen was formed, but that after partial pancreatectomy glycogen formation still took place. It is generally agreed that the pancreas influences the formation of glycogen in the liver through an internal secretion, but it is not necessary to assume, as some authors have, that it acts through a special ferment which is directly concerned in the building up of glycogen. It is probable that liver diastase, like other enzymes, is reversible in its action, so that glycogenolysis and glycogenesis go on side by side. When the ferment acts unchecked the disruption of glycogen into sugar predominates, and the fasting level of the blood sugar is raised, but when its glycogenolytic activities are inhibited glycogenesis predominates, and the fasting level of the blood sinks in proportion to the control exerted. The experiments we have quoted suggest that the pancreas exerts such an inhibitory power over liver diastase, possibly by means of an antiferment. This would agree with the changes in the total carbohydrate content of the blood associated with disease of the pancreas we have described elsewhere,²³ and also account for the fact that the liver is never quite free from glycogen, even after total pancreatectomy. It would further explain the lack of any direct relation between the percentage of sugar in the blood and the amount of carbohydrate in the food as long as the latter lies within certain limits, representing on the one hand a maximal stimulating effect on the mechanism of sugar production, and on the other the capacity for glycogen formation existing in the liver at the time the food is absorbed.

The more carefully one considers the normal sugar content of the blood the more certain it becomes that, both in the fasting condition and after a meal, the level is determined by the interplay of a number of influences, some of which accelerate the production of sugar, while others inhibit the process and promote the formation of glycogen, but that under average conditions the food itself takes no direct part in the process. We have considered individually each of the most likely factors taking part; it now remains to discuss them collectively and suggest a scheme which will represent their combined effect.

Summary.

The theory we at present hold is shown diagrammatically in the figure (Fig. 12), and may be summarized as follows:

1. The liver contains a diastatic ferment, the action of which is reversible.
2. In the fasting state the glycogenolytic activities of this ferment are very largely inhibited by (a) an antiferment formed by the pancreas, (b) the impermeability of the resting liver cells to sodium chloride, (c) the reaction of the fasting blood and liver cells.
3. As long as the pancreas and liver are functionally intact and a flow of blood with a normal reaction is maintained, glycogenolysis will be constant therefor and the sugar content of the blood vary within very narrow limits. This is true of all animals of similar constitution, no matter what their habitual diet may be.
4. The entrance of food into the stomach causes a flow of acid, and when this acid reaches the duodenum a formation of secretin results.
5. The secretin (a) stimulates the liver cells to produce bile, thus permitting the entrance of sodium chloride, which activates the diastatic ferment; (b) causes the pancreas to pour out its alkaline secretin into the intestine to combine with the acid gastric contents, forming acid salts and sodium chloride, which pass to the liver and increase the activity of the diastatic ferment; (c) interferes with the formation of the internal secretin of the pancreas, thus diminishing its inhibitory effect on glycogenolysis in the liver.
6. Carbohydrates reaching the liver from the intestine or formed from proteins in the liver are converted into glycogen by the diastatic ferment, the efficiency of the process depending upon the extent to which the glycogenolytic action of the enzyme is inhibited by the internal secretin of the pancreas. Unless the power of glycogen formation possessed by the liver is exceeded, sugar as such, or formed from starch in the intestine, does not pass into general circulation or play any direct part in the rise of blood sugar following feeding.

This theory appears to account for the constant level of the normal sugar content of the blood in a fasting condition and to explain the variations produced by the ingestion of food. It also permits of a reasonable explanation

of the changes occurring in disease. There are no doubt other factors, such as emotional excitement, nervous disturbances, changes of temperature, etc., which affect the percentage of sugar in the blood, but these are probably of comparatively minor importance under normal conditions, and a discussion of their mode of action would not have a material bearing on the subject we are considering, or affect the general principles of the scheme we have outlined.

In conclusion, we wish to express our thanks to Professor Starling for permission to carry out the animal experiments described in his department at University College.

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ANAESTHESIA FOR NOSE, THROAT, AND ABDOMINAL SURGERY BY THE NITROUS OXIDE-OXYGEN-C.E. COMBINATION.*

BY

H. EDMUND G. BOYLE, O.B.E., M.R.C.S., L.R.C.P.,
ANAESTHETIST AND LECTURER ON ANAESTHETICS,
ST. BARTHOLOMEW'S HOSPITAL.

In the study of anaesthesia there can be no better or surer way of improving our knowledge than by conferences such as this. Here are gathered together anaesthetists from every quarter of this great continent, all ready and willing to share their knowledge with their fellows for the benefit of mankind in general and anaesthetics in particular.

As regards the administration of nitrous oxide-oxygen-chloroform ether combination for nose, throat, and abdominal surgery, let me begin by saying that I think the two great essentials for an anaesthetist to keep in his mind are (1) the safety and comfort of the patient, and (2) the comfort and convenience of the operator. If we take the first, and most important, I think that in a great many cases safety depends on the knowledge the anaesthetist has of some given method. By this I mean that it is safer for a man to use a method he knows rather than to use another method which in itself is safer but of which he has no knowledge.

When considering this question of safety and comfort of the patient we must include the pre-operative, operative, and post-operative periods. Take the pre-operative time; this includes the preparation before operation, etc. In my opinion there is no need for the drastic treatment that used to be meted out prior to operation; there is no need for that starvation and severe purgation that were in vogue years ago. The patient should be on a light diet and should be given an ordinary laxative. We must remember that any operation entails a certain amount of strain on the patient; it calls for an effort on his part, and he should not be enfeebled by starvation, purgation, and enemata. Of course there are a certain number of cases when it is essential to have the bowel clear, and naturally one does not include these in the above statement.

Pre-operative medication has done much to rob operations of their terrors, and if the patient is given hypodermically some morphine and atropine, or morphine, atropine, and scopolamine, before the operation, he usually comes to the table in a drowsy state with his mind somewhat dulled—a great gain on the condition of years ago, apart entirely from the fact that less anaesthetic is usually needed.

During the last four years I have been endeavouring to find some anaesthetic or mixture of anaesthetics which could be used in combination with gas and oxygen as an adjuvant to produce relaxation when necessary, and in

nose and throat work to assist in the maintenance of anaesthesia. I have tried a great many mixtures, and until the introduction of ethanestal recently by Dr. Mackenzie Wallis and Dr. Hewer, I was using as my adjuvant a mixture of chloroform and ether of equal parts. Now I have substituted ethanestal for ether, and I find that the chloroform is only needed for nose and throat work and in some of the abdominal cases. The aim of all who have been working on this matter has been to produce a form of anaesthesia not only safe and pleasant for the patient and adequate for the surgeon's needs, but also as little toxic as possible.

The after-condition of a patient who has been operated on under gas and oxygen anaesthesia ought to be, and is in practice, far better than when ether or chloroform has been given, for since the nitrous oxide and oxygen is non-toxic and quickly eliminated, the patient returns to a normal state far more readily than after the more potent and toxic drugs. After an ether or chloroform administration it takes some time for the drug to be eliminated from the system, and this process of elimination must add to the strain on the patient. The actual technique of the administration is quite simple and the necessary skill is readily acquired.

In 1917, when I read a paper on gas and oxygen with regulated rebreathing in military surgery, I had not then had much opportunity for using this anaesthetic in civil work, but since then I have been using it for a great variety of cases. In 1917 I thought that gas and oxygen was not well suited to abdominal work; I have been trying to form a combination of anaesthetics which would give me adequate relaxation and yet would use the minimum of toxic substances. At the moment I am using as my relaxant a mixture of chloroform and ethanestal of equal parts, so that the anaesthetic becomes a combination of nitrous oxide-oxygen-ethanestal-chloroform, and with this I have been producing a type of anaesthesia which entails but little strain on the patient, and is wholly adequate for the surgeon's needs. The actual technique I employ now is as follows:

The patient is given morphine, atropine, and scopolamine half an hour before the operation. Gas and oxygen is then given in the proportion of about 1 of oxygen to 10 of gas, and as soon as the breathing begins to get deep and regular the gases are allowed to pass over the surface of a mixture of chloroform and ethanestal (equal parts), so that they pick up a small amount of mixture. In a few minutes the breathing becomes automatic, with slight soft stertor, thus showing that anaesthesia has been obtained. The tap on the mixture bottle is then turned back, so that the patient is only having gas and oxygen, and the operation is started. The amounts of gas and oxygen must now be regulated to what the administrator thinks will be the correct amount, and this for the majority of cases is about 1 to 4 (or 1 of oxygen to 4 of gas). For a great number of operations it is quite unnecessary to give any more mixture, and the remainder of the operation is conducted under gas and oxygen.

Given in this way, the anaesthesia is excellent both for patient and operator, whilst the after-condition is extremely satisfactory. The patients readily regain consciousness and are not usually inconvenienced by nausea or vomiting. In addition to this is the fact that they are hardly, if ever, conscious that they have had anything save gas and oxygen, for they do not, as a rule, have any taste or smell of ethanestal or chloroform. This lack of smell and taste of ethanestal and chloroform carries another point worth bearing in mind: Those working in the theatre—surgeons, anaesthetist, nurses, etc.—do not become impregnated with the smell and odour of ether or chloroform—an important point for their own comfort.

I find nowadays in using this method that after a long afternoon in a theatre I can leave feeling quite fresh and well, and the atmosphere of the theatre never becomes laden with the vapour of ether and chloroform as it often did formerly. The small amount of ethanestal or mixture that one needs with this method is sometimes astonishing to those who are unfamiliar with it, for it is quite usual for only a drachm to a drachm and a half to be used during a long operation like, say, the removal of a breast.

Operations such as amputation of the breast, hernias, varicoceles, and the like, are quite easily done under gas and oxygen, and a very small quantity of either ethanestal or mixture; it is when one comes to the abdominal and nose and throat work that the difficulty begins. For some time now many of us have been trying to get some combination to act as a really good relaxant for abdominal

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