desired effect is obtained. The amount of insulin used will depend not only on the carbohydrate tolerance of the patient, but on the height and fixity of the blood sugar level.

Whether we shall in the future permit patients to have higher blood sugar levels than at present seems advisable is a point on which there is conflicting evidence. At present we are inclined to the belief that more successful results are obtained with regard to the general well-being of the patient, clearing up of minor and even major infections, etc., if a normal blood sugar level is aimed at. Owing to the short duration of the effect of insulin it might seem desirable to ingest the carbohydrates at one particular meal and give the extract in relation to this meal, thus avoiding the number of injections—two to three daily sometimes necessary in the severer cases. This, however, is not the case, as the carbohydrate is apparently stored and burned under the influence of the insulin, and during this period the patient feels like a healthy, normal person, and later, when only fat and some protein is available for burning, he gets a mild ketosis and experiences lassitude or fatigue. In our view a prolongation of the period of action is most desirable, and whether this is to be obtained by slowing the rate of absorption or by more frequent injection is a matter for further study.

After these patients are freed from glycosuria and ketosis and are permitted to use an adequate basal ration they usually feel so well that they demand increased food to satisfy their desire for exercise. In this case we are less particular about spreading the carbohydrate intake throughout the day and usually prescribe an increased amount of carbohydrate with three to four times as much fat at one or possibly two meals, and a corresponding amount of insulin. The same thing may be accomplished by raising the diet instead of decreasing the initial dose of insulin. As the protein is not as efficient as carbohydrate in preventing disordered fat metabolism, the amount of fat which can be given with protein is much less than with carbohydrate. Owing to the high caloric value of fat it seems desirable to raise first the carbohydrate in the diet. When increase in calories is not so urgently required, then protein may be used and fat added in the proportion of 10 grams of fat to each 8 grams of additional protein.

In severe diabetics and comatose patients the alterations in metabolism under the influence of insulin are most interesting. They furnish material for a considerable amount of investigation which we hope to report upon later. The study of the respiratory quotient reveals positive evidence of the utilization of carbohydrates. Patients with any considerable carbohydrate tolerance may be expected to produce a certain amount of insulin themselves. This may be mobilized under suitable stimuli, and the initial rise in the respiratory quotient sometimes seen is probably due to this factor. The specific effect following the administration of insulin is almost coincident with the attainment of normal blood sugar levels. Demonstration of the effect of pancreatic extracts in raising the respiratory quotient can best be made on the most severe cases of diabetes mellitus.

Other factors which we must decide in the patient's interests are his most suitable weight and condition of nutrition and the means which shall be employed to attain them, and also to what extent work shall be allowed. Following the principle of low maintenance diets in treatment it seems unwise to allow increases in weight in stout patients, or even marked increases in the emaciated. In the former, reduction of the patient's weight by using insufficient fat in the diet is recommended; in the latter it is felt that some increase in the weight is desirable on account of the associated improvement in the general condition of the patient, his resistance to infection, etc., even though an increased amount of insulin is required. Work, involving as it does the increased use of foods and consequent drain on the supply of insulin, is not to be regarded as desirable when pushed to excess, and patients are accordingly advised to moderate their usual activities.

Diabetics are perhaps more subject to infections and gangrene than any other class of patients. In such cases a distressingly high mortality has been observed. Without doubt the more recent dietetic treatment has removed many of the terrors of operation, such as coma, and has even aided in the more rapid clearing up of infections for the less severe degrees of the disease. However, many patients lose a great deal of their carbohydrate tolerance when infection is added to their diabetic condition. And further, the infections are more prone to occur in the more severe cases who do not respond favourably to dietetic treatment. For both types of patients insulin furnishes most valuable assistance in treatment in that it keeps the blood sugar normal—an important consideration in the treatment of infection—enables the patient to utilize carbohydrates, and, in consequence, prevents acidosis and removes the danger of post-operative coma. It seems clear that necessary surgical procedures may be undertaken in properly treated cases with practically no more risk than in the normal.

Attention must be paid to various other influences in the treatment of diabetic patients. Symptomatic treatment for minor complications, such as constipation, insomnia, etc., must be carried out. Psychic factors, such as fear, anxiety, and worry, are well known to produce hyperglycaemia and glycosuria. The effect of insulin is so specific that these need not be considered as influencing the results of treatment, but in this, as in all other diseases, the best results in treatment can be obtained with happy, contented patients.

SUMMARY.

The following is a summary of the results of our investigation:

1. Under treatment with insulin in patients who are not otherwise amenable to treatment:
   (a) Glycosuria is abolished;
   (b) Ketones disappear from the urine and the blood;
   (c) Blood sugar is markedly reduced and maintained at normal levels;
   (d) The alkali reserve and alveolar carbon dioxide of patients in acidosis and coma return to normal;
   (e) The respiratory quotient shows evidence of increased utilization of carbohydrates;
   (f) The cardinal symptoms of diabetes mellitus are relieved and the patients show well-marked clinical improvement.
2. Insulin is a specific in the treatment of diabetic coma.
3. Certain procedures are suggested as a guide in the administration of insulin.
4. Hypoglycaemic reactions in man have been studied and described.
5. Hypoglycaemic reactions following insulin are relieved by the administration of carbohydrates and also by the injection of epinephrin.

To Dr. Duncan Graham, professor of medicine, we desire to express our sincere thanks for his interest in directing and supervising the investigation throughout its course.

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ON A POSSIBLE MODE OF CAUSATION OF DIABETES MELLITUS.

BY

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IN a paper, now in the press,[1] we show that the normal blood sugar in man and animals has a lower rotatory power than would be given by the α–β equilibrium form of glucose as deduced from the copper reduction value. The sugar gives an osazone with the same crystalline form and melting point as that of glucosazone. The instability of the sugar is shown by its transient rotatory power, the curve of polarimeter readings reaching the copper reduction value in three to four days in acid solution. The sugar at first decolorizes potassium permanganate more rapidly than a solution of α–β glucose in similar concentration. This distinction no longer obtains when the polarimeter reading corresponds with that of α–β glucose. These facts, in conjunction with the work of Hewitt and Pryde[3] on sugar solutions introduced into the intestine, suggest that normal blood sugar is γ glucose. That ingested glucose or fructose is rapidly converted into normal blood sugar was shown by feeding experiments on normal persons. After 100 to 150 grams of glucose or fructose no alteration in the nature of the blood sugar could be detected.

In cases of diabetes mellitus we show that this sugar is not present in amounts capable of detection by the method employed. The polarimeter reading in these cases is initially greater than the copper reduction value, and the curve gradually falls until the copper value is reached. This suggests that besides α–β glucose, disaccharides or other substances with a polarimeter : copper reduction ratio greater than that of α–β glucose are present in the blood of diabetic persons. We suggest that α–β glucose cannot be directly stored or utilized, but that an enzyme is responsible for the conversion of α–β glucose into γ glucose. We picture the change:

$$\text{Glycogen} \longrightarrow \alpha\text{–}\beta \text{ Glucose} \longrightarrow \gamma \text{ Glucose.}$$

The absence or inactivation of this enzyme is suggested as the direct cause of diabetes mellitus.

Macleod and his co-workers[2] have recently shown that injection of "insulin" into depancreatized dogs causes a decrease in the blood sugar. Determinations of the respiratory quotient showed that sugar was being utilized as long as the administration of insulin was maintained. Similar results were obtained by the injection of insulin into persons suffering from diabetes mellitus. We suggest that the effect of the insulin is to activate the enzyme responsible for the conversion of α–β glucose $\longrightarrow$ γ glucose. If this view be correct, examination of the blood sugar of diabetics after injection of insulin should show that the nature of the sugar approximates to that of normal persons.

We have investigated the action of tissue extracts on the rotatory powers of glucose and fructose. We have confirmed the observations of Hewitt and Pryde[3] that extracts of the intestinal mucous membrane are inactive. The liver would appear to contain the enzyme. That another factor is concerned is shown by the fact that the enzyme is almost inactive in the absence of an extract of pancreas. The extracts of pancreas which we have recently used are preparations of "insulin" obtained by Collip's method.[4] Similar activation of the enzyme is obtained.

Solutions of glucose or fructose when incubated at 37° C. with very small amounts of insulin and liver extract in a jacketed polarimeter tube have their rotations altered in a downward and upward direction respectively. In view of the fact that our insulin preparations invariably contain phosphorus, it is noteworthy that addition of phosphate accelerates the reaction to a degree not obtained by the use of other salts. Phosphate buffers have therefore been employed. Boiled liver extract is inactive, whereas insulin would appear to be thermostable in this respect. Our insulin preparations were tested for activity on rabbits.

The degree of alteration in rotatory power may be seen from the following examples:

Glucose.		*Fructose.*	
First reading ...	1.70° R.	First reading ...	177.92°
Lowest reading ...	1.47° R.	Highest reading ...	178.30°

The solutions contained 15 c.cm. of an arbitrary glucose or fructose solution, 2 c.cm. phosphate buffer, 1 c.cm. 0.1 M. KCl, 1 c.cm. weak insulin solution, 0.3 c.cm. liver extract.

Without phosphate—

Glucose.		*Fructose.*	
First reading ...	1.32° R.	First reading ...	178.60°
Lowest reading ...	1.30° R.	Highest reading ...	178.61°

The enzyme would appear to be slowly inactivated under these conditions. The unstable nature of the sugar formed is shown by the fact that after the maximum change has occurred the rotation tends to revert to the original value. Our experiments with the enzyme *in vitro* do not show a ratio copper reducing : polarimeter value equal to those observed in the case of blood sugar. It is difficult to convert any considerable amount of the sugar in our solutions into the reactive form, as this is not removed from the sphere of action. A stage would appear to be soon reached at which the reverse process attains a velocity equal to that of the original one.

The copper reducing power of the sugar solution at the beginning and end of the reaction is unaltered. The reaction is therefore different from that described by Levene and Mayer[5] in connexion with muscle and pancreas extracts, in which the copper reducing power was lowered.

This method would seem to lend itself to the further purification of insulin. We have already found that the final product obtained by Collip's method is capable of being divided into two fractions, which differ markedly in their nature and activity as tested by the above method and on rabbits.

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THE VITAMIN CONTENT OF CERTAIN PROPRIETARY PREPARATIONS.

BY

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AT the request of the BRITISH MEDICAL JOURNAL the writers have examined the vitamin content of certain of the best known of those proprietary preparations which are advertised in the medical press as containing vitamins. The following preparations were tested:

Metagen (Messrs. Parke, Davis, and Co.). The advertisements state that this is guaranteed to contain the three principal vitamins, and that it is "a concentrated product for therapeutic administration."

Maltoline (the Maltine Manufacturing Co., Ltd.). The advertisements state: "Maltoline is therefore rich in three well-known vitamins, and is recommended as a nutritive to those who are unable to take or digest cod-liver oil"; and also that "Maltoline . . . satisfactorily takes the place of cod-liver oil."

Roboleine (Messrs. Oppenheimer, Son, and Co., Ltd.). The advertisements state: "The 'A.B.C.' of Diet. Because it is *very rich in the vitamins* 'A,' 'B,' and 'C' there is no tonic food more serviceable in wasting diseases"; and the statement is also made that it "supersedes cod-liver oil."

Virol (Virol, Ltd.). The advertisements state that one of the "essential points in the diet of growth" is that "the food must contain those food accessory substances known as vitamines, but the presence of vitamines is not sufficient in itself," and that "Virol as it reaches the public contains the vitamines."

Vitmar (Messrs. Callard and Co.). The advertisements state: "Biological tests prove that vitmar contains vitamins in abundance."

Mellin's Food (Mellin's Food, Ltd.). The advertisements state: "Vitamins. Those elusive principles of food which are essential to nutrition are present in Mellin's food when mixed for use as directed according to the age of the infant."

The specimens of these foods tested were all bought in the open market. Most of them claim to contain all three vitamins. Vitamins A and B are rapidly destroyed by certain chemical processes, and therefore their concentration or purification is a matter of extreme difficulty, but it is not difficult to prepare them in an unconcentrated form, in which they will keep for a prolonged period. Vitamin C is much more unstable; so far as we can ascertain it has not been concentrated, and it is difficult even to preserve it in a crude form. Dried orange and lemon juice are indeed the only known preparations in which this vitamin can be preserved for prolonged periods.

We have therefore only tested the above preparations for the presence of vitamins A and B, and have not tested for the presence of vitamin C, for it is reasonable to assume that any methods for the concentration or preservation of vitamins which fail in the case of vitamins A and B will be even less successful in the case of vitamin C.

The presence of vitamin A was determined as follows: Young rats (weight about 50 grams) were fed upon a diet which was free from vitamin A, but otherwise adequate. The rats consumed from 16 to 20 grams of food (moist weight) daily. On this diet they soon ceased to grow, and then a known amount of the substance to be tested was given to the rat before its basal diet each morning, or added to a small amount of the diet which was consumed before the rest of the basal diet was given. The minimal amount of the substance which contained sufficient vitamin A to produce growth in young rats was thus determined.

The presence of vitamin B was also determined by experiments upon rats. In this case young rats were fed upon a diet free from vitamin B but otherwise adequate. This diet soon caused arrest of growth, and the vitamin B content of the proprietary preparations was determined by finding the minimal quantity of the various preparations required to produce growth.