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THE purpose of this paper is to give the physician a brief outline of the principles underlying the action and use of insulin. I have purposely avoided a review of the voluminous literature because time is wanting. I therefore give you the conception of diabetes built upon the innumerable researches of associates past and present, not least among whom was Lepine, of France, whose grandson represents France at this conference.

In the normal healthy individual, carbohydrates such as starch and sugar, when taken in the food, are converted into glucose by digestion. In this form it is absorbed into the blood stream. It is then carried to the liver, where it is converted into and stored as *glycogen*. As the tissues of the body require glucose, the glycogen stores of the liver are drawn upon. If the supply of carbohydrates greatly exceeds the demand of the tissues, carbohydrates may be converted into *fat* and stored as such. Very small amounts are excreted in the normal urine.

When glucose is absorbed into the blood stream there is an increased percentage of sugar in the blood, which stimulates the islands of Langerhans to pour out their secretion. Normal islet cells have a tremendous reserve and may cause very large amounts of glucose to be metabolized. *When, as in diabetes mellitus,* the functional ability of the islet cell is impaired by nerve strain, infection, changes in blood supply, or over-activity, the extra reserves are found wanting, and sugar, if given in large amounts, remains circulating in the blood stream, in a *higher percentage,* and for *longer periods of time* than normal. This increased percentage of sugar in the blood is recognized by the kidney, and sugar is excreted in the urine. The

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hyperglycæmia thus produced gives rise to excessive *thirst.* The large amount of fluid taken to combat the thirst gives rise to *polyuria.* Since the tissues are undernourished from failure to burn sugar, there is an increased demand for food, as evidenced by excessive *hunger.* The increased amount of food throws still greater strain upon the insulin-producing mechanism which is required for its metabolism, and a vicious circle is established which results in rapid emaciation and loss of strength despite the ingestion of large quantities of food.

Thus the classical symptoms of diabetes mellitus are explained. Fats only burn in the fire of carbohydrates. If the progress of such a case is not interrupted by treatment, acidosis occurs. When the rate of production of acetone bodies exceeds the rate of excretion, they accumulate in the system, giving rise to diabetic coma. This cycle is observed in all cases of untreated pancreatic diabetes. In children and young adults the progress is *usually rapidly fatal.* In middle life and old age, the development of the disease is slower.

The fundamental principle underlying dietetic treatment in diabetes depends upon the administration of the minimum amount of carbohydrate necessary for the maintenance of life, and at the same time administering it in such a form that absorption would be so slow that the pancreas could pour forth its secretion in adequate amounts for the normal metabolism of the *given* carbohydrate. Thus Allen elaborated a system of treatment which consisted of rendering the patients' blood sugar normal by starvation and then feeding them upon vegetables and fruit in which the percentage of carbohydrate was very low, protein and fat being added sparingly. Woodyatt, Wilder and others finally evolved a diet in which there was a definite ratio between the carbohydrate, protein and fat.

In order to live, the body requires a certain number of calories. This caloric requirement varies in different individuals approximately with the *surface area* of their bodies, their *age, sex* and *weight,* and can be calculated by the Dubois chart and the Aub-Dubois table. Roughly speaking, this basal requirement is about twenty-five calories per kilo of body-weight per day. If this requirement is not supplied by the food, it is drawn *from* the tissues of the *individual.* Protein and carbohydrate when burned in the body provide four calories of heat per gram, while each gram of fat supplies nine calories of heat. The utmost use should therefore be made of the fat, but its use is limited by the fact that without carbohydrate it cannot be *completely* oxidized. In the same way the use of protein as a carbohydrate substitute is limited since 46 per cent. of it may produce ketone bodies, and 56 per cent. of it *may* be converted into carbohydrate. It has been estimated that the body requires two-thirds of a gram of protein per kilo of body-weight per day. The remaining calories must be supplied by carbohydrate and fat in a ratio that will prevent the production of ketone bodies. In order to ascertain the number of grams of the various food substances many formulæ have been compiled. For example, the simplest is that of Doctor Hipwell, which is as follows:

M = caloric requirement, ⅔ of the body-weight in kilos, gives the protein requirements in grams = P. The carbohydrate C, and fat F requirements are derived from the following formulæ:

$$F = \frac{M}{10} - \frac{P}{2} \qquad C = \frac{M - 10P}{30}$$

M = total number of calories required by individual.
(1) 75 per cent. of M = calories derived from fat.
(2) 13 per cent. of M = calories that must be derived from carbohydrate.
(3) 12 per cent. of M = calories that must be derived from protein.

By dividing the protein and carbohydrate calories by four, and the fat calories by nine, the respective grams of each are obtained. For example, patient weighs sixty-four kilos:

Minimum caloric requirement was calculated 64 x 25—1600 calories. The diet prescription was as follows:

$$\text{Fat}\ \frac{75\%\ \text{of}\ 1600}{9} = \frac{1600 \times 0.75}{9} = 133\ \text{grams}$$

$$\text{Carbohydrate}\ \frac{13\%\ \text{of}\ 1600}{4} = \frac{1600 \times 0.13}{4} = 52\ \text{grams}$$

$$\text{Protein}\ \frac{12\%\ \text{of}\ 1600}{4} = \frac{1600 \times 0.12}{4} = 48\ \text{grams}$$

Having ascertained the number of grams of carbohydrate, protein and fat, the patient's diet is compiled by the use of food tables.

There is no disease which requires such an intimate *coöperation* between the physician and patient as diabetes mellitus. Patients should be thoroughly instructed in the cause, course and complications of their diseases and should be taught *urinalysis,* the calculation and preparation of a diabetic *diet*, and how to administer their own insulin and to calculate its dose. They should be particularly warned of the prodromal symptoms and treatment of *overdosage*. It is impossible and impracticable for a physician to treat and teach the patient except in a hospital where, in addition to an accurately dispensed diet prescription, daily urinalysis of the 24-hour specimen for volume, specific gravity, reaction, albumin, acetone, and qualitative and quantitative sugar, may be done. The estimation of blood sugar is desirable but not absolutely imperative if the urinary sugar is closely followed.

When the patient presents himself for treatment a careful *history* is taken and a *complete physical examination* is made. Special attention is directed to the finding of a possible *focus of infection*—tonsils, teeth, sinuses, chest, and digestive system are examined clinically as well as by X-ray. Special consideration is given to biliary tract infection, constipation, and chronic appendicitis. If any source of septic absorption is located, it is *appropriately* treated, since such condition may lower and unstabilize carbohydrate tolerance.

The patient is placed upon a diet, the caloric value of which is calculated on his basal requirement, and is maintained on it for three or four days or until the urine is sugar-free. The quantity of sugar excreted is estimated daily, and this amount subtracted from the available carbohydrate ingested, gives *approximately* the utilization. The available carbohydrate includes 56 per cent. of the protein, 10 per cent. of the fat, and the total carbohydrate in the diet. It may be noted that when a patient is placed upon a diet in which the protein, fat and carbohydrates are *balanced,* the amount of sugar excreted daily soon approaches a fairly constant amount; whereas, if the diet is not well adjusted to the patient's requirements, there is wide variation in the amounts of sugar excreted.

If a patient becomes sugar-free and blood sugar normal on a basal requirement diet, the *caloric intake* is *gradually* increased until sugar appears in the urine. The tolerance is thus ascertained. If a patient remains sugar-free and has a normal blood sugar when *on* a diet containing 700 calories above his basal requirement, the case is not considered sufficiently severe for insulin treatment, since 700 calories over and above his basal requirement are sufficient for the needs of his daily activities. If, however, he is unable to metabolize this amount, insulin treatment is commenced.

Diabetes mellitus is due to a deficiency of the internal secretion of the pancreas. The main principle of treatment is, therefore, to correct this deficiency. If it is found that the patient is unable to keep sugar-free on a diet that is compatible with an active, useful life, sufficient insulin is administered to meet this requirement.

The initial dose of insulin should not be more than five units twice a day. This amount can be gradually increased until the patient becomes sugar-free, the diet being kept constant. It may be roughly estimated that each unit of insulin causes from 1½ to 2½ grams of carbohydrate to be utilized. The amount of utilization per unit of insulin is less in severe cases with high blood sugar and during the course of infection, and is greater in mild cases. The *time* of administration of insulin is an important factor. It is best given from twenty minutes to half an hour before the morning and evening meals so that the curve of hypoglycæmia produced by the insulin is just *superimposed upon, and counter-balances* the curve of *hyper*glycæmia produced by the meal. A larger dose is usually given before breakfast so that the noon meal is also cared for. For example, if a patient is receiving twenty-five units of insulin per day, fifteen units would be administered in the morning dose, and ten units in the evening. When the *dose of insulin* and *diet* are balanced so that the patient's blood sugar is normal, they are concurrently increased until the required amount of food is reached. Insulin is given hypodermically, since other means of administration have been found unsatisfactory.

When a patient is given too large a dose of insulin the blood sugar falls below its normal level, producing marked reaction, which begins in from *one and a half* to *six hours* after the patient receives the overdose. The average time is *three to four hours.* The interval varies with the individual, the dosage, and the food ingested. The first warning of this hypoglycæmia reaction is an *unaccountable anxiety* and a feeling of impending trouble associated with *restlessness.* This is frequently followed by *profuse perspiration.* The development of this symptom is not affected by atmospheric conditions and is independent of physical or mental activity. At this time there is usually a great desire for food. Very soon the patient will notice a certain sensation as of *clonic tremor* in the muscles of the extremities. This can be controlled at first. Coördination, however, is impaired for the more delicate movements. Coincident with this, there is a marked *pallor* of the skin with a rise in *pulse-rate* to one hundred or *one hundred and twenty* beats per minute. Pupils become dilated. The blood-pressure falls about fifteen to twenty-five millimetres of mercury, and the patient feels faint. The ability to do physical or mental work is greatly impaired. In a severe reaction there may be a considerable degree of *aphasia*, the patient having to grope for words. The *memory* of names and figures may be quite faulty. As the blood sugar falls to a still lower level, the blood-pressure and body temperature also fall and *collapse, unconsciousness, convulsions, and finally death, may occur.*

The *onset* of hypoglycæmic symptoms depends not only on the *extent* but also on the *rapidity* of fall in blood sugar. The level at which symptoms occur is higher in the diabetic with marked hypoglycæmia than in a patient whose blood sugar is normal. A hypoglycæmic reaction when once experienced by a patient is rapidly recognized on following occasions. Consequently it is safer for every patient before leaving hospital to have experienced the sensations of an overdose.

The ingestion of carbohydrate in the form of orange juice (four to eight ounces), glucose or candy, relieves these symptoms in from five to ten minutes. If untreated, and coma or convulsions have occurred, ten to fifteen minims of *epinephrin* will usually restore consciousness within three minutes.

The ability of the severe diabetic to burn glucose is markedly impaired, therefore the excess of fat is incompletely oxidized, giving rise to ketone bodies. These appear in the blood and urine as acetone, diacetic and beta-oxybutyric acids. Insulin causes increased carbohydrate metabolism, and consequently fats are completely burned. This is substantiated by the fact that acetone and sugar disappear from the urine almost simultaneously following adequate amounts of insulin.

When the *production* of acetone bodies is more rapid than the *excretion*, they accumulate in the blood, giving rise to air hunger, drowsiness, and coma. The need of insulin is then imperative. After its administration the utilization of carbohydrate by the body gives complete combustion of the fats.

When a patient is admitted to hospital in diabetic coma the blood and urinary sugar and acetone estimations are done as soon as possible. (The urine is obtained by catherization if necessary.) While these tests are being carried out the large bowel is evacuated with copious *enemata.* If sugar and acetone are present in large amounts in the urine, from thirty to fifty units of insulin are given subcutaneously immediately. Blood and urinary sugar should be frequently estimated because of the danger of hypoglycæmia. To prevent this from 30 to 50 grams of glucose in 10 per cent. solution may be given intravenously or by rectum. If the patient is profoundly comatose the insulin may be administered intravenously with the glucose.

The patient usually regains consciousness in from three to six hours. From this time on fluids and glucose may be administered by mouth *if retained.* The patient should be urged to take at least *200 cubic centimetres* of fluid per hour. In from eight to ten hours the ketone bodies are markedly reduced.

On the following day protein may be given every four hours, as the white of one egg in 200 cubic centimetres of orange juice. In two or three days, when ketone bodies have disappeared from the urine, fat is cautiously added, and the patient is slowly raised to a basal requirement diet. He is then treated as an ordinary diabetic. During the period of coma the patient is kept warm and toxic materials eliminated from the bowel by purgation and repeated enemata. A large amount of fluid is given to dilute the toxic bodies and promote their elimination. This may be administered intravenously, subcutaneously, or *per rectum.* If signs of circulatory failure develop, these are treated by appropriate stimulation.

Striking results have been obtained with the above procedure. However, it has been found that the longer the period of untreated coma the more *grave* is the prognosis and the slower the recovery if it occurs. Cases complicated by severe infection, gangrene, pneumonia, or intestinal intoxication may recover from acidosis and coma but succumb to the complication.

In the diabetic with *tuberculosis* insulin enables the use of proper nourishment to combat the tubercle infection. Patients formerly considered *bad surgical risks,* if given proper dietetic treatment with insulin may be protected from the acidosis, hypoglycæmia, and glycosuria which otherwise usually results from the anæsthetic. Diabetic infections such as boils, carbuncles, and gangrene, and also intercurrent infections such as bronchitis, influenza, and fevers, are favorably influenced by the normal blood sugar and increased metabolism which the administration of insulin permits.

Regardless of the severity of the disease, it has been found that by carefully adjusting the *diet and the dose of insulin, all patients may be maintained sugar-free.* Since this is possible, it is to be strongly advocated, because we have abundant evidence for the belief that there is *regeneration of the islet cells of the pancreas* when the strain thrown upon them by a high blood sugar is relieved. The *increase in tolerance* is evidenced by the *decreasing dosage of artificially administered insulin. In fact, in some moderately severe cases,* the tolerance has increased sufficiently that they no longer require insulin.

Diabetes mellitus may be considered fundamentally as a *disordered metabolism, primarily of carbohydrates,* and *secondarily of protein and fat.* It is indisputably proven that for normal metabolism of carbohydrate in the body, adequate amounts of insulin are essential. It follows, therefore, that the treatment consists in giving just sufficient insulin to make up for the deficiency in the patient's pancreas.

Insulin enables the severe diabetic to burn carbohydrate as shown by the rise in the respiratory quotient following the administration of glucose and insulin. It permits glucose to be stored as glycogen in the liver for future use. The burning of carbohydrate enables the complete oxidation of fats, and acidosis disappears. The normality of blood sugar relieves the depressing thirst and consequently there is a diminished intake and output of fluid. Since the tissue cells are properly nourished by the increased diet, there is no longer the constant calling for food, hence *hunger pain* of the severe diabetic is replaced by *normal appetite.* On the increased caloric intake, the patients *gain rapidly in strength and weight.* With the relief of the symptoms of his disease, and with the increased strength and vigor resulting from the increased diet, *the pessimistic, melancholy diabetic becomes optimistic and cheerful.*

Insulin is not a cure for diabetes; it is a treatment. It enables the diabetic to burn sufficient carbohydrates, so that proteins and fats may be added to the diet in sufficient quantities to provide energy for the economic burdens of life.