Theory and practice of modern therapy in diabetes mellitus

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on

THE THEORY AND PRACTICE OF MODERN THERAPY IN DIABETES MELLITUS.

by

Cecil F. Simmons
Introduction.— Dogmas are slow of abandonment even in the face of facts. In the practice of medicine of to-day we have a few who cling tenaciously to methods of the past even though the experimentation of the present has pointed out inadequacies in these methods and has revealed improved and more effective procedures. In general, however, the progressive and courageous spirit of our profession is mirrored by the modern practice of the healing art, the steady advance of which is assured by those of laboratory and clinic who are constantly seeking new solutions of old problems and who zealously hold aloft the torch of progress. In the last decade we have advanced in mighty strides and have thrown to the wayside older theories and methods which have been repudiated by the constructive findings of research and which have failed to be effective when applied to the human subject.

In presenting a subject of this nature, we should consider briefly the vast work of research which underlies the recent progress in the treatment and management of the many thousands who have the disease, diabetes. Historical side-lights will illuminate the basic principles of our modern methods of therapy. For many years the eye of research has been piercing the cell in order to solve its many mysteries and understand its physico-chemical activities, both in regard to the physiologically normal cell and the pathological cell. Just as the endeavors of the past have pioneered the way for the victories of the present, our work of to-day is directed toward the laying of foundation stones for the edifice of future victories.

Definition.— Osler defines diabetes mellitus as being "a disease of metabolism, especially of the carbohydrates, in which the normal utilization of carbohydrates is impaired with an increase in the sugar content of the blood and consequent glycosuria." (Bib. I)
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... or completely lost its capacity for the utilization of sugar. The pancreatic hormone, insulin, which is essential for the oxidation of sugar in the body, is deficient or lacking. This metabolic derangement produces disturbances in fat metabolism which result in ketosis. Certain toxic fatty acids accumulate as a result of destruction of protein and fat with the liberation of still more carbohydrate, which is a compensatory mechanism in the presence of a vitiated cellular ability to utilize sugar and produce a most important source of energy. The urine excretes the unutilized sugar which accumulates in the blood.

**History of Diabetes.**—Diabetes was known to Celsus. (Bib. I) The term, diabetes, was first employed by Aretaeus, who called it a mysterious affection "melting down the flesh and limbs into urine," and who suggested that the disease received its name from the Greek word meaning a syphon.

In 1682 Conrad Brunner inconclusively demonstrated that complete pancreatectomy in dogs resulted in severe and fatal diabetes. (Bib. II). In the seventeenth century Willis gave an admirable description of diabetes and told of the sweetness of the urine "as if there has been sugar and honey in it." The presence of sugar in the urine was demonstrated by Dobson in 1776. Rollo gave an excellent description in 1797 and advised the use of a meat diet. Osler states that Claude Bernard's demonstration of the hepatic glycogenic function in 1857 marks the birth of the modern study of the disease.

The pancreatic Islands of Langerhans were first described by Paul Langcrhans in his Inaugural Dissertation in Berlin in 1869. In 1889 von Mering and Minkowski definitely showed that diabetes with a fatal issue can be experimentally produced in a dog by doing a pancreatectomy. Before this, in 1884 Arnozant and Vaillard had noted that ligation of the pancreatic duct in rabbits resulted in atrophy of the pancreas without...
producing glycosuria. Inasmuch as Murray in 1891 discovered that thyroid gland extract administered hypodermically would cure myxedema, the contemporaries of von Mering and Minkowski entertained the hope that diabetes might be similarly cured. In 1903 Rennie observed a "principal islet" in the pancreas of teleostean fishes which was distinct from the tissue of the pancreatic acini. Rennie believed that this "principal islet" secreted an endocrine substance which effected the body utilization of dextrose, and, accordingly, with Fraser in 1907, fed this islet tissue, both in the raw and boiled state, to patients with diabetes; however, the results were inconclusive. In 1902 Ssobolew was the first to demonstrate that, following ligation of the pancreatic duct, the atrophy was confined only to the acinous tissue and that glycosuria developed after an interim of one hundred and twenty days or more at the end of which time the atrophy had involved also the pancreatic island tissue.

The real search for a curative pancreatic ferment received its impetus by the declarations of Opie in 1901 and Ssobolew in 1902 that the islands of Langerhans were the glandular tissues involved in diabetes mellitus. Previously, in 1893, Laguesse believed that the pancreatic islands were the source of an internal secretion, but he suggested no relationship of this internal secretion to diabetes. Laguesse demonstrated the greater development of the pancreatic island tissue in fetal and new-born animals than in adult animals. The significance of Ssobolew's observation of pancreatic atrophy and suggestion of glycosuria developing subsequently to atrophy of the island tissue was overlooked until 1912 when Scott recognized the importance of the islands of Langerhans in his experiments. Allen was probably discouraged by Rennie's results in 1903 because he did not carry out in experiment the suggestion
of his writing in 1913: "Apparently no one has ever tried the interesting possibility of feeding the glands of new-born or fetal animals, in which the islands have a relatively high development and little external secretion." (Bib. II). Wegele's single report of a case in a man fifty-two years of age in whom the pancreas had supposedly atrophied and in whom glycosuria had completely disappeared when pancreas was fed is certainly not convincing. The experiments of Pratt and Spooner, cited by Allen in his summary of the literature as demonstrating the most conclusive results in the feeding of pancreas to dogs, consisted of feeding pancreas to dogs in which the pancreas had been separated from the duodenum and had subsequently atrophied. The feeding of fresh pancreas for a period of six weeks caused the sugar tolerance to rise gradually until it was above normal, but the tolerance did not drop until more than a month after cessation of pancreas administration. Lepine was another who explained that diabetes following depancreatization was due to the absence of an internal pancreatic secretion essential to the proper oxidation of glucose in the body.

In 1916 Sir E. A. Schafer gave the name of "insulin" to the internal secretion of the pancreas. In 1917 Kamimura confirmed the work of Sobolew by showing the degenerative changes in the parenchyma of the pancreas following ligation of the pancreatic ducts in rabbits and by demonstrating that glycosuria did not develop as long as the island tissue remained uninvolved.

The presence of the proteolytic ferment, trypsinogen, caused the great difficulties which attended the attempts of several years to isolate a pure extract of the island tissue. In 1907 and 1909, Zuelzer performed some epoch-marking work. He realized the antagonism between adrenalin and the then unnamed anti-diabetic hormone of the pancreas. By alcoholic extraction he so freed the extract from protein that a biuret test gave
an almost imperceptible reaction, and then preserved the hormone in a four per cent solution of sodium chloride. By experimenting on rabbits with intravenous injections, he demonstrated an anti-diabetic principle in his extract. Zuelzer designated as a unit that amount of extract which would prevent the glycosuria produced by the injection of one mg. of adrenalin. His work was thorough and conclusive. He demonstrated clinically the total suppression of ketosis and glycosuria in two de-pancreatized dogs and in eight human diabetic individuals! The extract caused one patient in diabetic coma to revive and live five days. The toxic effects of the extract were so severe that the resulting fever and chills warned against the further application of this treatment. Zuelzer's findings were confirmed by Forschbach in 1909 who worked with diabetic dogs and humans, but the effects were similarly too toxic to warrant further experimentation. It was Forschbach who anastomosed the blood circulatory systems of two dogs and then depancreatized one of the animals. He interpreted his discovery that neither dog developed diabetes as being due to the activity of the hormonal secretion of the pancreas of the unoperated dog which was adequate to regulate the carbohydrate metabolism of both animals.

It seems quite certain that if our modern methods of testing blood-sugar percentages had been then available, these and other earlier pioneers would have enjoyed a much higher degree of success in their endeavors to find a more effective therapy in diabetes.

De Meyer is given the credit for discovering the solubility in alcohol of the active pancreatic substance. The respiratory quotient, as a measure of glucose combustion, was first used by Murlin and Kramer in 1913 who used largely the extracts of the pancreas of the dog. (Bib. III). They used a few extracts made from the pancreas of the cow which was acidu-
lated with hydrochloric acid until after the boiling point was reached and which was then filtered and neutralized with sodium carbonate. They used, also, a mixture of duodenal extract and pancreatic extract, prepared as described. Their report showed that the respiratory quotient of a depancreatized dog increased after the injection of duodenal and pancreatic extracts from 0.69 to 0.73. Duodenal extract was included on the presumption that its secretin content activated the anti-diabetic hormone of the pancreas. We have evidence to believe that Murlin's and Kramer's boiled extract was potent although the more favorable effects obtained by Zuelzer, Forschbach, Kleiner, Paulesco, and Banting and Best followed the use of unboiled extracts. Murlin's work in Rochester demonstrated that at a pH of 6.7 to 7.2 boiling does not inactivate insulin whereas a pH of 4.4 to 5.7 destroys the hormone. Kramer, Marker and Murlin have shown that acids and alkalies act antagonistically in accelerating or retarding the processes of glycogenolysis and glycogen in normal animals. Sodium bicarbonate lessens glycosuria, probably, by favoring the retention of pre-formed glycogen and by changing available glucose into glycogen. (Bib.III)

The latest of those who pioneered the way for Banting and Best was Paulesco who, in 1921, demonstrated the reducing effect of intravenous injection of the pancreas of a dog upon glucose, acetone and urea.

It was F. G. Banting, a young orthopedic surgeon who discovered insulin. C. H. Best, who was then only a second-year medical student well trained in research work, gave invaluable assistance to Banting. Banting states his conception of a method for extracting the pure secretion of the islets of Langerhans as follows: "The hypothesis underlying this series of experiments was first formulated by one of us in November, 1920, while reading an article dealing with the relation of the isles of Langerhans to diabetes. From the passage in this article, which gives a resume of the degenerative changes in the acini of the pancreas, following ligation
of the ducts, the idea presented itself that since the acinous but not the islet tissue degenerates after this operation, advantage might be taken of the fact to prepare an active extract of islet tissue. The subsidiary hypothesis was that trypsinogen or its derivatives was antagonistic to the internal secretion of the gland. The failures of other investigators in this much-worked field were thus accounted for."

(Bib. II).

Brevity does not permit a description of the many details of their work. Only the salient features may be mentioned. In November, 1921, they made the discovery that fetal calf pancreas of under five months' development was lacking in digestive pancreatic juice but not in an internal secretion. This led to a new era in investigation. Accordingly, Banting and Best prepared an extract of fetal calf pancreas by macerating the glands in Ringer's solution and filtering until the solution became clear. The blood sugar of a ten kilogram dog was reduced by this solution from 0.4 per cent. to 0.15 per cent. in three hours. Subsequent experiments yielded much better results. In this manner they were able to prepare large quantities of the hormone without admixture with the destructive trypsinogen. Subcutaneous administration of this extract was found to work more slowly but just as effectively as the intravenous method. Then, two important discoveries followed; namely, that addition of the antiseptic 0.7 per cent. tricresol did not impair potency, whereas passing it through a Berkfeldt filter did lessen potency and that the active principle could be extracted with ninety-five per cent. ethyl alcohol. The protein was largely removed by fractional precipitation of the extract with alcohol. Collip was instrumental in discovering the purification of insulin by means of fractional precipitation. The lipoids were later removed with ether, and the filtrate was distilled in vacuo to a pasty consistency. Addition of eighty per cent. alcohol and centri-
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Fugation then resulted in the formation of four layers; namely, a bottom layer of salt crystals; above this a saturated aqueous solution of salt; in the region above a flocculent layer of protein; and, on top, a clear layer of alcohol, containing the whole active principle in solution. Extracts, which were practically free from proteins, salts and alcohol-soluble substances, were prepared. These extracts were rendered isotonic and injected subcutaneously without producing local reactions.

The advent of the discovery of insulin marks a new era in the therapy of diabetes which has supplanted the handicapped attempts of the past to control this disease by means of a purely dietetic and hygienic regime.

Many zealous workers in research have experimented with this invaluable hormone. Doisy, Somogyi and Shaffer proposed a modification of Collip's method of preparing insulin in the pure state. This later procedure effected a further purification of insulin by precipitation at the isoelectric point, which is approximately pH 5.0. It is an interesting fact that the preparation of insulin from clams and other invertebrates, in which the insulin is apparently associated with glycogen, was accomplished by Collip. Collip prepared, also, an insulin-like substance, which he called glucokinin, from plant tissues. This substance, prepared from vegetative tissues of several angiospermous plants as well as yeast, produces a marked hypoglycemia in normal rabbits and in depancreatized dogs. Glucokinin probably controls starch formation in the plant. This principle, extracted from the onion, kept a depancreatized dog alive for sixty-six days. Only three injections of the substance were made. One day to several weeks may lapse before glucokinin reduces the blood-sugar. (Bib. IV).

As we trace the history underlying the ultimate isolation of insulin, we appreciate the value of a theory which finally found expression in practical terms.
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**The Metabolism of Glucose.** A brief survey of glucose, as a metabolite, is indispensable to a presentation of the theory and practice of the modern treatment of diabetes. Glucose undergoes many chemical changes following absorption. The dietary carbohydrates do not serve as the only source of glucose, for glycerol and certain amino-acids yield glucose and glycogen during metabolism. Approximately fifty-eight grams of glucose are yielded by the sugar-forming amino-acids present in one hundred grams of protein. Dogs that have been rendered diabetic by injecting phlorhizin excrete large amounts of sugar in the urine even after the liver and other tissues have been depleted of glucose. In such animals, the tissue proteins are partially converted into glucose; in the most severe conditions, 3.65 grams of glucose are excreted to each gram of urinary nitrogen. Approximately 6.25 grams of protein are represented by every gram of nitrogen in the urine. In phlorhizinized dogs there is nearly a complete conversion of glycerol to glucose, as shown by Chambers and Deuel, whereas glycerol is normally oxidized to carbon-dioxide and water. This work reveals an important source of glucose from glycerol in the diabetic state. As first shown by Claude Bernard, the glucose in the portal circulation is carried to the liver and to other tissues, especially muscle, for storage. The normal liver stores about three hundred grams of glycogen. Glycogenesis or glycogen synthesis conserves food for oxidation and regulates the blood-sugar level. When the blood-glucose concentration exceeds 0.10 to 0.11 per cent. in the normal individual, the liver and other tissues quickly remove the excess glucose for storage. Insulin controls the blood-sugar concentration and the oxidation of glucose. (Bib. V.)

The renal regulatory function prevents the accumulation of sugar
above a certain level in the blood. The sugar in the urine does not exceed 0.02 to 0.04 per cent. normally. When the blood-sugar concentration reaches 0.16 to 0.18 per cent., the so-called "renal threshold," the sugar spills over into the urine. In diabetes mellitus the renal threshold is often in excess of 0.18 per cent.

The glucose tolerance test has been very valuable as an aid in the diagnosis of diabetes. This test aids, also, in determining the severity of the disease. The disappearance of glucose from the blood is taken as the basis for determining the carbohydrate tolerance. The blood-sugar level is determined before, and at intervals after, giving a definite amount of glucose, usually one hundred grams. In the normal individual the blood-sugar concentration reaches a maximum during the first half hour or hour after the ingestion of glucose and returns to normal levels by the end of the second hour. In diabetes the maximum height of the curve exceeds the normal, often reaching 0.22 to 0.24 per cent. and does not return to normal until three hours or more have passed. However, carbohydrate tolerance may be reduced in conditions of hepatic injury, as in phosphorus and chloroform poisoning and in cases of interference of the blood supply of the large muscles, as by applying a tourniquet or by elevating the legs. (Bib. V and VI).

**Insulin.** Insulin has a wide distribution in both vertebrates and invertebrates. The pancreas of cattle serves as the main source of insulin. Active preparations of insulin are extracted from fetal pancreases which lack functional acinous tissue. Trypsin from the acini readily destroys insulin. This fact probably accounts for the ineffectiveness of insulin when given by mouth. In 1923 Dudley discovered that pepsin is also destructive to insulin. (Bib. VII). As already mentioned, there is an insulin-like substance in oatmeal, onions and other plant substances.
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Plant insulin differs in its action from animal insulin in that the former lowers the blood-sugar concentration not immediately but after a delay of twelve hours or more. A similar action is manifested by the insulin-like substance of yeast. Collip has named this plant principle "glucokinin" to distinguish it from animal insulin. (Bib. IV, VIII and IX).

When administered orally, insulin has no effect. Subcutaneous injection is very effective, and intravenous injection yields a maximum effect. In diabetic animals, the introduction of insulin into the duodenum, when gastric digestion is not going on, is reported to decrease hyperglycemia and glycosuria. Intravenous administration of insulin results in a rapid fall in the blood-sugar. Hypoglycemia follows injection of sufficient insulin. The rabbit develops hypoglycemic convulsions at a blood-sugar concentration of 0.04 to 0.045. The animal dies if glucose is not administered. (Bib. V, pages 235-239). Convulsions do not develop as quickly in animals with a large reserve glycogen as in under-nourished animals. Injection of glucose relieves insulin convulsions. Noble and Macleod have shown that, in smaller measure, mannose, galactose, levulose and maltose will relieve these convulsions. Increase of the blood-sugar level does not follow the injection of the pentoses xylose and arabinose nor of the disaccharides, sucrose and lactose. (Bib. X).

In the diabetic, insulin quickly relieves the symptoms of hyperglycemia, glycosuria, acetonuria and acidosis. Insulin improves markedly the utilization of carbohydrates and increases the glycogen content of the liver. Secondarily, the fat metabolism is rendered more complete, and the tissue proteins are conserved more fully.

We are still uncertain as to the mechanism underlying the action of insulin. Some biochemists believe that insulin converts $\alpha$- and $\beta$-glucose
into an active form. Insulin acts antagonistically to adrenalin and pituitrin. Sahyun and Luck advance the theory that epinephrine promotes hepatic glycogenolysis and decreases the peripheral utilization of blood-sugar whereas insulin is pictured as an inhibitor of hepatic glycogenolysis and a promoter of the utilization of blood-sugar by muscle tissue. The administration of insulin to epinephrinized animals inhibits hepatic glycogenolysis and results in an increase in the quantity of liver glycogen. Yet, this relative increase was observed only during those periods in which the liver glycogen of the control epinephrinized animal was decreasing. At other times, the quantity of liver glycogen remained unchanged or exhibited a tendency to decrease. (Bib. XI). In 1922 Banting, Best, Collip, Macleod and Noble demonstrated that insulin will prevent the hyperglycemia produced by epinephrine. (Bib. XII). Burn demonstrated that the hypoglycemia following insulin administration is prevented or lessened in severity by the administration of pituitrin.

Shonle and Waldo believe that insulin gives more the reaction of a proteose than that of a protein. (Bib. XIV). Ammonium sulphate, uranium acetate, picric acid and other reagents precipitate insulin. Insulin does not dialyze through collodion membranes, is insoluble in organic solvents and is adsorbed by kaolin and charcoal. Bodansky believes that insulin is either a protein or is on some manner associated with protein. In studying the nitrogen content of insulin, Scott declared that arginine, lysine, histidine, cystine, tyrosine and tryptophane were present. (Bib. XV and XVI). Insulin seems to be composed of a multiplicity of amino-acids and may be termed a polypeptide. It also contains sulphur, and, according to an article appearing in the Practitioner in October, 1929, its sulphur content determines the activity of any given solution of insulin. The interpretation follows that insulin is a substance
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similar to the ptomaines. Some rare instances of haematuria following the administration of large doses of insulin and clearing up completely in two days or less have been reported. This author believes the rare instances of haematuria to be toxic phenomena, due to the ptomaine-like nature of insulin. (Bib. XVII).

The testing of the strength of insulin by studying its effect upon rabbits was essential for its practical application. The original unit was determined as that amount of insulin required to reduce the blood-sugar of a one-kilogram rabbit, starved for twenty hours, to 0.045 per cent or to produce convulsions in three hours. Later, the Health Section of the League of Nations adopted as the unit one-third the amount of insulin required to lower the blood-sugar of a two-kilogram rabbit to 0.045 per cent., which is the convulsive level in the rabbit. A more recent standard unit of insulin was prepared by the Insulin Committee of Toronto in 1923. (Bib. II). Campbell writes that the present standard unit of a standard preparation of insulin, which has been defined by the Permanent Standards Committee of the League of Nations as being equivalent to one-eighth of a milligram of a certain preparation of dry insulin hydrochloride, is not pure insulin. Crystalline insulin is approximately three times as active as the standard powder. (Bib. XVIII).

It has been commonly believed that one unit of insulin will metabolize 1.5 to 2 grams of glucose. However, Williams, who has co-operated for six years with the Eli Lilly Company in the clinical testing of insulin, recently made the surprising report that one unit of insulin causes the utilization of approximately four grams of glucose. Other investigators have not accepted this report. (Bib. XIX).
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The Objects and General Rules of Treatment. The advent of the discovery of insulin, it is true, marks a new era in the therapy of diabetes which has supplanted the attempts of the past to control this disease by means of a purely dietetic and hygienic regime. The value of this discovery is incomprehensible. Yet, we still must admit: "Once a diabetic always a diabetic," although no one one knows how much further we may advance in the treatment of this condition. In the light of modern knowledge, we must admit that diabetes is not permanently curable. But diabetes can now be controlled under proper conditions and under well-directed management and intelligent co-operation on the part of the patient. (Bib. XX)

Until recent years untold numbers of diabetic patients died despite the most zealous efforts of the most capable clinicians whereas diabetic individuals suffering from equally severe conditions of the disease may be saved for a happy, useful existence. Thousands, to-day, are snatched from the clutches of diabetic coma which was greatly dreaded only a few years ago. Diabetics may now be given surgical treatment with very little risk so far as the diabetes is concerned. Many are being kept in a state of health which is not conducive to the appearance of complications. To-day we see many aged diabetics whereas, a few years ago, these patients made an exitus during the earlier years of life, due to the development of complications, uncontrolled hyperglycemia and other secondary effects.

The objects of therapy are to preserve a good state of nutrition, to keep the patient sugar-free and to keep the blood-sugar level as nearly normal as possible. Under such ideal conditions complications are prevented. Treatment resolves itself into the proper solution of a problem in metabolism in terms of diet and the adjunct of insulin administration when the latter is necessary. (Bib. XX)
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Woodyatt's simile accords with modern views on diabetes. (Bib. XXI). He compares the human body to a gasoline engine in which the glucose serves as fuel, the secretions of the islands of Langerhans as the spark. In the engine combustion is impaired when the spark-plug is dirty, and, from the exhaust, the black smoke and carbon and unignited gasoline make exit. In diabetes the sugar in the urine compares, in the analogy, to the unignited fuel and black smoke and carbon. A condition of hyperglycemia overstimulates the pancreatic islands until this tissue becomes exhausted and unable to "spark." Reduction to the normal blood-sugar level rests the pancreas, restores the "spark" and re-establishes a normal combustion of glucose in the body. Therefore, sugar tolerance increases when the patient is rendered persistently sugar-free. But, also, the blood-sugar level must be kept normal or nearly normal; otherwise the pancreatic island tissue will "spark" defectively. According to such a viewpoint, it is unwise management to permit dietary indiscretions with excessive insulin administration, for there will result periods of undetermined hyperglycemia which will impair the function of the isles of Langerhans.

The following data are essential to the intelligent management of diabetes: (1) the patient's weight, (2) the daily amount of sugar in the urine, (3) the glucose tolerance, and (4) the degree of acidosis. Under certain conditions it is necessary to know the percentage of blood-sugar, as in diabetic coma, but in periods of normal progress such knowledge is not indispensable. Yet, there are times when failure to know the existing blood-sugar level will result in neglect which will prove fatal to the patient. (Bib. XX).

The presence and degree of acidosis may be determined by testing the urine for acetone and diacetic acid and by testing the carbon-dioxide content of the alveolar air. The determination of the urinary ammonia and the hydrogen-ion concentration are more complicated tests of much less common
use in practice. Gerhardt's Test for the presence of diacetic acid in
the urine is convenient and reliable for this test. (Bib. XXII).

The Education of the Patient. The character and intelligence of the
patient are factors of greater importance in successful treatment than
the severity of the diabetic condition. Every diabetic patient should be
taught to weigh his own food on a set of scales. Most general practitioners are
appallingly lacking in this very necessary knowledge. Manuals, which
are published for the instruction of the patient, have great value
and render the patient more appreciative and co-operative.

The patient should be taught the essential differences between carbo-
hydrates, proteins and fats. That the weight of the food is just as im-
portant as the kind of food should be impressed upon the patient. Dr. Con-
lin of the University of Nebraska, College of Medicine, has well demon-
strated the value of this necessary intelligent co-operation on the part
of the patient. His simply and clearly illustrated charts which he ex-
plains to his patients secure the patients' appreciative co-operation.

An ideal method in therapy consists of the group instruction of diabetic
patients. These patients would suffer the results of fewer "carbohydrate
spree" if all clinicians showed more patience and if all patients showed
a more intelligent co-operation.

Too frequently the patient does not understand how to take the correct
dosages of insulin. Graphic charts of the insulin syringes, which illus-
trate the correct dosages of insulin to be taken morning, noon and evening
and which record the strength of insulin prescribed, should be given to
the patient by the physician. This method obviates errors in insulin
dosage. For example, the use of U-80 insulin in the same quantity when
the point on the syringe on the graphic chart is marked for U-20 insulin
would result in taking four times the prescribed dosage. (Bib. XXIII).
The successful practitioner always pays attention to details.
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Diabetic patients should be taught to test the urine for sugar. Exceptionally, harmful results may follow this method if the patient should be of a neurotic temperament and have a low sugar tolerance and frequent periods of glycosuria.

A manual, such as has been prepared by Wildor and by Joslin and others, should be made available for every individual who has diabetes.

**Caloric Requirements in Diabetes.** Joslin advocates that the diabetic diet should yield, except for brief intervals, the minimum number of calories required by a normal individual under similar conditions. It is generally agreed that a normal man weighing seventy kilograms at moderate work requires approximately 2900 calories in twenty-four hours or about forty calories per kilogram. These figures should be proportionately reduced for individuals with a smaller body weight or with less strenuous occupations. In such cases, the number of calories per kilogram is proportionately decreased from forty to thirty. The caloric requirements decrease with increase in age; e.g., 1800 calories will suffice at age seventy if the requirement is 2000 calories at age thirty; also, approximately 1600 calories would be required at age eighty. According to Joslin, in the normal diet yielding 2900 calories, about 400 grams of carbohydrate, 100 grams of protein and 100 grams of fat should be given. (Bib. II).

In the standard normal diet, fifty-five per cent. of the calories should be derived from carbohydrates, fourteen per cent from protein and thirty-one per cent from fats. (Bib. II).

Most clinicians restrict the total carbohydrate in the diabetic diet to seldom more than 100 grams. (Bib. II, page 254). This constitutes a reduction to approximately one-fourth of the normal carbohydrate allowance. Yet, many modern therapists allow more carbohydrate content of the diet. Joslin believes that this radical change in carbohydrate allowance
induces symptoms of disturbed digestion.

Tables are published for convenience in determining the amount of carbohydrate in the various vegetables and fruits ingested during the twenty-four hours. These are listed under four headings; namely, those containing approximately five per cent., ten per cent., fifteen per cent. and twenty per cent., respectively. In regard to the vegetables of the five per cent. and ten per cent. groups, a deduction should be made in the percentage of carbohydrate because cellulose, which is not assimilable, comprises a portion of the carbohydrate content. Consequently, three per cent. and six per cent., respectively, is the more accurate amount of available carbohydrate in the five per cent. and ten per cent. vegetables.

The carbohydrate content of foodstuffs given in different tables are often so divergent and contradictory that the variations frequently amount to several hundred per cent. Lawrence and McCance have used methods of analysis which separated and determined only those carbohydrates physiologically available for metabolism. Some of the new figures differ greatly from the older ones, as the following comparison indicates:—

<table>
<thead>
<tr>
<th>FOOD</th>
<th>OLD</th>
<th>NEW</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cabbage</td>
<td>2.3</td>
<td>1.0</td>
</tr>
<tr>
<td>Celery</td>
<td>3.5</td>
<td>1.0</td>
</tr>
<tr>
<td>Lettuce</td>
<td>2.5</td>
<td>0.7</td>
</tr>
<tr>
<td>Olives</td>
<td>9.0</td>
<td>0.7</td>
</tr>
<tr>
<td>Rhubarb</td>
<td>2.5</td>
<td>0.6</td>
</tr>
<tr>
<td>Strawberries</td>
<td>9.0</td>
<td>4.4</td>
</tr>
<tr>
<td>Tomatoes</td>
<td>4.0</td>
<td>2.4</td>
</tr>
<tr>
<td>Beetroot</td>
<td>7.0</td>
<td>3.0</td>
</tr>
<tr>
<td>Potatoes</td>
<td>20.0</td>
<td>19.2</td>
</tr>
<tr>
<td>Bread</td>
<td>50 - 55</td>
<td>50 - 55</td>
</tr>
</tbody>
</table>

The above older figures were taken from tables prepared by Harrison and Lawrence in 1923 from the sources then available. It is readily seen that the large changes appear in most vegetables and fruits, in which
much of the total carbohydrate has been found to be " unavailable. " Unavailable carbohydrates are cellulose, pentosans, inulin, etc., the exact nutritious value of which is not definitely known.

Therefore, in practice, diabetic patients may be allowed large amounts of green vegetables, sufficient to satisfy the largest appetite. Furthermore, it is unnecessary to boil vegetables three times, as has been commonly advised in the past, inasmuch as they contain very little carbohydrate after the ordinary methods of cooking. As the carbohydrate content of diabetic diets becomes more and more accurately known, treatment becomes more and more accurate, as a consequence, and especially therapeutic investigations. (Bib. XXIV).

Carbohydrate values for such vegetables as lettuce, asparagus and rhubarb have been found to be so small that they are permissible as "extras." These new carbohydrate values, recently determined in England, increase the total carbohydrate values as given by Joslin, the American standard of values, from fifty grams to nine-four grams. It is interesting to note that Joslin now advocates giving eighty to one hundred grams of carbohydrate a day to even severe cases of diabetes, which are amounts equivalent to the new values placed by Lawrence and McCance on Joslin's dietary tables. This recent discovery of existing errors in carbohydrate values may account for the appearance of acetonuria previously as an accompaniment of dietary regimes in which the ratio of carbohydrate to fat was intended to be one to three. Acetonuria and imperfect oxidation were occurring because the patient was receiving less carbohydrate than was supposed. (Bib. XXIV).

The amount of protein required by diabetic patients varies with the weight, age and occupation of the individual as well as with the renal function. Joslin believes it is a safe rule to increase the protein con-
tented gradually to that amount needed by a normal individual. As Chitten-
den pointed out, sixty grams of protein, which is only one-half the former
protein standard, is adequate to meet all of the physiological demands of
the body under ordinary circumstances. A still smaller quantity will
suffice, according to Joslin, in the case of an individual not experiencing
an active out-of-door life.

The Carbohydrate Balance. The difference between the total quantity of
carbohydrate ingested and the sugar excreted in the urine during the same
period represents the so-called carbohydrate balance. When the quantity of
sugar in the urine is exceeded by the quantity of carbohydrate in the
diet, a positive carbohydrate balance is said to exist. When the amount
of carbohydrate in the diet is less than the amount of sugar in the urine,
a negative or minus carbohydrate balance is said to exist. In the latter
case it is evident that the sugar in the urine is derived either from the
glycogen stores of the body or from the body proteins and fats. (Bib. II,
page 275).

Modern Dietary Regimes with Insulin and without Insulin. Since Düring's
"rice cure" in 1852, Europe has advanced various dietary regimes. Von
Noorden's "oatmeal" cure was favored in Europe and America until Joslin
did his work in America. Joslin made practical application of Allen's ex-
periments and advanced his popular "starvation diet." Joslin is respon-
sible for the plan of starting on thrice-washed green vegetables, follow-
ing the starvation period. This procedure, as advocated by Joslin, seems
unnecessary when viewed in the light of the recent work of Lawrence and
McCance. Allen recommended that patients with mild diabetes should re-
ceive 1.5 grams of protein per kilogram of body weight. Results with the
undernutrition methods of treating severe cases of diabetes have certainly
not been ideal. The extreme emaciation which often resulted seemed to be
harmful in its effect. Glycosuria cannot be completely controlled on a high protein diet.

Then came the "High fat diet" of Newburgh and Marsh. (Bib. XXV). Newburgh and Marsh allowed two-thirds gram of protein for each kilogram of body weight. They believed that acidosis would not result if sufficient carbohydrate were given to burn the fat.

Many, later, used Woodyatt's "balanced maintenance diet." Woodyatt issued a set of formulas for the purpose of calculating the diet in grams for any given case. Woodyatt showed that it is impossible to put the diabetic patient completely to rest so far as the metabolism is concerned, inasmuch as the body will catabolize its own tissues if sufficient food is not supplied. (Bib. XXI).

Woodyatt allows one gram of protein for every kilogram of weight, which is higher than the Newburgh and Marsh allowance but lower than the Allen allowance. A knowledge of the patient's glucose tolerance is valuable. This is figured by determining the number of grams of glucose passed in twenty-four hours and subtracting this figure from the total amount of glucose assimilated from the patient's food. The total carbohydrate intake is calculated by taking 100 per cent. of the carbohydrate in the food, fifty-eight per cent. of the protein and ten per cent. of the fat. Woodyatt based his calculations upon the assumption that the fatty acids will be burned completely provided the ratio of fatty acids formed in metabolism and the glucose formed in metabolism is 1.5 or less.

The ketogenic-antiketogenic ratio is expressed as follows:

\[
\frac{G + 0.58 P + 0.1 F}{0.46 P + 0.9 F} = 1.5, \text{ when the ratio of fatty acids to glucose is at its maximum without developing ketonuria.}
\]

Simplifying this we obtain \( F = 2G + P/2 \). Assuming that 100 grams of
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glucose is the maximum derived from all sources that the patient can utilize, as determined by the glucose tolerance test,

100 grams = C + 0.58 P + 0.1 F.

In order to secure the largest number of calories, the diet must contain every gram of fat (at 9 calories per gram) that the value of G and the ratio expressed in, $F = 2G + F/2$, will permit, and consequently the lowest possible carbohydrate-protein fraction (at four calories per gram).

Furthermore, as regards carbohydrate and protein, the protein must be reduced as much as possible and the carbohydrate increased as much as possible, because one gram of carbohydrate yielding one gram of glucose and four calories provides for the normal oxidation of 1.5 grams of higher fatty acid. One gram of protein having the same caloric value as carbohydrate yields less glucose to support fat combustion and, also, forms acetone. Assuming the body weight of the patient to be fifty kg., and one gram of protein per kg. is adopted as a conservative minimum, then $F$ becomes 50 gm., and $F = 2G + F/2$ becomes $F = 2C + 25$. We have already assumed that $G = 100$ gm. The glucose supplied by the 50 gm. protein will be $0.48 \times 50$, or 29 gm., leaving 100 - 29, or 71 gm., to be distributed between carbohydrate and fat. Expressed by ratio, $C + 0.1F = 71$. From this we get, $F = 710 - 10C$. We also have that, $F = 2C + 25$. Therefore, $2C + 25 = 710 - 10C$. Solving this we get, $C = 57$ gm. Substituting this value for $C$ in, $F = 2C + 25$, we find, $F = 139$ gm. Therefore, the optimal food combination that will fulfill these conditions and specified relations is: Carbohydrate, 57 gm.; protein, 50 gm.; fat, 139 gm. Total number of calories = 1680. (Bib. XX and XXI).
The advent of insulin introduced marked changes and advances in the therapy of diabetes and thoroughly overshadowed all dietary procedures. Soon, it was learned that proper dietetic control was advisable in all cases, with or without insulin, and many dietary regimes have since then been offered.

Falta discredits any departure from a normal diet. He advises the use of adequate doses of insulin without periods of dietary restriction. He recommends a diet of cereals and vegetables, taken for a short time, for the control of gastro-intestinal disturbances. Falta does not approve of Petren's diet, which permits large amounts of fat with limited protein and carbohydrate intake. Falta points out that any ill-balanced diet disturbs metabolism and proves harmful.

The treatment of Professor Jansen of Bonn is as follows: There are two initial starvation days during which 220 grams of meat broth and 50 cc. of brandy are given. The patient may drink as much as is desired. Although the sugar leaves the urine quickly, acetonuria may or may not become more mild. Then, Jansen institutes a "fundamental diet" which is maintained for from ten to fourteen days. He gives 0.75 gram of protein and two grams of fat per kilogram of body weight. Jansen's routine is to give to a patient weighing 120 pounds 300 grams of bouillon, 120 grams of cheese, one egg, 200 cc. of red wine and coffee or tea sweetened with saccharin. Some five per cent. carbohydrates are added. Every two or three days twenty grams of bread or forty grams of potato are added if the urine remains free from sugar and acetone. A tolerance of forty to sixty grams of carbohydrates is usually reached. A starvation diet is employed again if glycosuria reappears. Finally, a permanent diet which gives 1.5 grams of protein and thirty-five calories per kilogram of body weight is reached. Jansen employs the Petren system in the event that his own fails.
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Petren offers a high fat diet in which unlimited amounts of six per cent vegetables, 200 to 250 grams of butter or bacon, fifty grams of cream and the required number of calories are given. Following failure of this regime after six weeks to maintain the blood-sugar at 120 milligrams per cent., insulin is advised. The food allowance is gradually increased when the diet alone secures the desired results. It should be mentioned, at this point, that Petren's regime of a high fat diet is an abrupt departure from the general modern therapeutic trend of the high carbohydrate-low fat diet. (Bib. XXV).

An unusual view is presented by Porges in a recent book. (Bib. XXV). Porges states that increased carbohydrate tolerance is secured when the glycogen depots of the liver are well charged. He believes that intense pancreatic activity stimulates increased secretion of insulin. Quite a contrasting teaching and radical departure when viewed in the light of our universally accepted principle of rest as a most valuable and restorative therapeutic procedure! Porges believes that decreased insulin secretion results from rest of the pancreas. Porges' routine consists of eighty grams of protein, 100 to 200 grams of carbohydrate and fifty grams of fat daily with disregard of glycosuria in the early course of treatment and with insulin administration when indicated.

K. von Noorden of Vienna believes in the value of using two foodstuffs. Noorden holds that the sameness of the Petren diet renders this system inadvisable. He believes that Porges' diet is excellent for most cases of diabetes. According to von Noorden, Falta's diet of fruit and vegetables is too low in protein and too high in fats for continued use. Noorden states that carbohydrate tolerance is increased from 80 to 200 per cent. when a low fat diet replaces a high fat diet. He believes that protein restriction is not advisable as was suggested by Porges in 1926. Von Noorden asserts that metabolism is directed toward normalcy and that sugar tol-
erance increases by giving his own diet of vegetables and fat and eggs with forty to fifty grams of protein.

Bauer of Vienna employs a test diet in which forty grams of carbohydrate, 110 grams of fat and sixty grams of protein are given. Alcohol is given to increase the number of calories to 1700. If there is no acetonuria nor glycosuria during one week of such treatment in which the patient is resting in bed, carbohydrates are gradually increased until glycosuria supervenes. According to Bauer, patients with a tolerance of forty grams of carbohydrate require no insulin. By reducing the fat or by alternating the diets, he endeavors to increase the sugar tolerance to forty grams if such amount is not tolerated. In his one to three "vegetable days," he allows four eggs, clear soup, vegetables, a little alcohol, twenty-five grams of protein, 170 grams of fat and black coffee. Then, three "oatmeal days" may be ordered, and the patient is given 150 grams of oatmeal, 50 to 150 grams of fat, clear soup, wine, black coffee and sometimes eggs or vegetables. Then, the "vegetable days" follow. Later, a strict carbohydrate-free diet is ordered. Next, there follows a starvation day in which less than sixty grams of fat, one or two eggs, soup and black coffee are allowed. A day of strict diet or a vegetable day should be adopted each week. Such an alternating diet includes the advantages of two foodstuffs.

Nixon discredits the starvation treatment and the high fat dietary of pre-insulin days as being unnecessarily and unwisely grafted upon the insulin method of treatment. (Bib. XXVII). He believes that much harm and no advantages result from the substitution of an excess of fat or protein for carbohydrate because if a diabetic patient, deprived of carbohydrate, does not convert the fat or protein of his diet into glucose, he cannot live. He states that a diabetic patient need not be burdened with the "task of living cheerfully and working usefully on a sort of knife-edge of starvation. A starved pancreas will not regenerate even though the blood-sugar
is low; new tissues are not built up by such means."

Nixon stresses the fact that a high fat and low carbohydrate diet produces fat deposit and not glycogen deposit in the liver, leaving no room for glycogen. "A respectable glycogen deposit in the liver provides to the diabetic who is receiving insulin a definite safeguard against hypoglycemia." Glycogen storage is assured by a diet rich in carbohydrate and poor in fat. Nixon advises placing the patient on an adequate maintenance diet, replacing the fats so far as possible with their equivalent of carbohydrate; that is, 2.25 ounces of carbohydrate for every ounce of fat. High fat and protein administration are to be given with great caution to a pregnant, diabetic woman. (Bib. XXVII).

Although Nixon does not take the extreme view of Porges that overstimulation of the pancreas results in increased production of insulin, Nixon presents the view that starvation of the pancreas lessens the capacity of this viscus to secrete insulin and, therefore, rest obtained in this way is definitely harmful to pancreatic function.

Hare points out the fact that, although diabetes is a chronic disease, it is not incompatible with a life of physical and mental vigor; nevertheless the diabetic regime is a difficult one. Complete relapse is liable to follow any relaxation of the regime. The practitioner must convince the patient that "feeling well" is not being well" and that the extent of continued health will proportionate itself to the degree of the patient's co-operation.

Despite the utmost care in regulating a diabetic regime, the diabetic patient never acquires a perfectly balanced metabolism. Hare states that this balance is approached in practice when the urine remains sugar-free on a fixed diet, with or without insulin, which is adequate to maintain a normal weight and to supply sufficient energy for all of the body activities. He does not believe that the ideal condition in the diabetic is that
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in which the blood-sugar level never exceeds the normal maximum, since such a normal level can be maintained only by keeping the glycogen stores empty. Such glycogen depletion results in a languorous and depressed patient. Hare points out that a higher blood-sugar level with intermittent glycosuria is compatible with a vigorous life and contentment and sense of well-being in the diabetic patient since an increased blood-sugar concentration when the glycogen reserves accumulate. (Bib. XXVII). This teaching is certainly not in harmony with the time-honored belief that the blood-sugar level should be kept around the normal and the sugar persistently sugar-free; nevertheless Hare's reasoning appears quite plausible. Porges also believes, as we have seen, that the glycogen stores should be kept well charged. (Bib. XXV).

We know that diabetic therapy during pre-insulin days consisted of maintenance of permanent under-nutrition with a previous fasting period, prolonged for a sufficient time to render the urine sugar-free. In severe diabetes this method has been abandoned, in the by and large, according to Hare, because under-nutrition induces a period of invalidity. Hare states that, from the beginning, a "maintenance diet" or normal nutrition diet should be prescribed; i.e., a diet calculated to maintain the normal body weight in health. The degree of the patient's activity will determine the caloric value of the diet. After the initial course of treatment, the patient should be given a list of the permissible and forbidden foods and be allowed to select a well-varied diet of approximately correct values.

Hare points out that insulin is administered to metabolize alimentary carbohydrate ingested at a known time; however, an excessive rise of blood-sugar with temporary glycosuria cannot be avoided when there is a mobilization of glycogen reserves, leading to increased tissue glucose. In working out the patient's "balance," changes in both diet and insulin dosages
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should not be made at the same time. Hare outlines a plan to begin insulin therapy in a severe case by starting with a dose of ten units daily until a maximum of fifty units daily is attained. Individual dosages should not exceed twenty-five units. It is well to avoid large evening doses, according to Hare. The effect of insulin in decreasing blood-sugar begins about fifteen to thirty minutes after the dose and becomes maximum two to four hours later. Glycosuria results when the blood-sugar level becomes so increased that the "renal threshold" for sugar is far exceeded by the blood-sugar concentration. The time of urine-sugar leaks can be determined by the examination of separate specimens of the twenty-four hour sample. (Bib. XXVIII).

Beginning hypoglycemia can be recognized by the patient himself by the presence of an "all gone feeling," giddiness, sweating and trembling. When an ordinary dose of insulin is gradually increased, severe hypoglycemia seldom results.

There is no constant insulin-carbohydrate ratio to be applied to treatment of the diabetic. The amount of glucose metabolized by a unit of exogenous insulin depends on the internal pancreatic and hepatic activity of the patient and the rapidity of absorption of the carbohydrate. Therefore, as Hare points out, concentrated carbohydrates; such as, starches and sugars, causes a less efficient control of metabolism in the diabetic by exogenous insulin than when proper dietary restriction is observed. The carbohydrate should be restricted both as to total value and form. In severe cases a high total diet with large doses of insulin causes an excessive gain of weight. (Bib. XXVIII).

Foster and Lowrie bring out the fact that the many charts and schemes which have been issued as guides for collecting proper values for diabetic diets and which are based upon the basal caloric and nitrogen requirements
of the individual through the use of data collected throughout years of careful research in metabolic processes, sometimes carry the calculations to a ridiculous fineness when we consider the possible errors in the actual food analysis and the differences in the actual food values of different specimens of the same food and the unavoidable error made by patients in weighing or estimating the diet. (Bib. XXIX). Probably too many practitioners pay too little attention to these possible sources of error.

Foster and Lowrie state that placing the patient at once on a full maintenance diet with sufficient insulin to keep the urinary sugar-free shortens the hospitalization period, prevents unnecessary incapacitation which might follow a period of severe under-nutrition and prevents the mental depression that accompanies starvation. We have already seen that Hare stresses this fact also. (Bib. XXVIII).

These writers believe that the patient's state of nutrition and not the severity of the diabetes determines the initial diet to be given to an adult diabetic patient who has no complications. (Bib. XXIX). They believe that, since insulin is now available, no diabetic should receive a diet containing less than fifty grams of carbohydrate, even though the diabetes be severe. The carbohydrate allowance is increased as the tolerance becomes greater. In preference to lowering the carbohydrate ration below fifty grams, appropriate doses of insulin are given to bring the blood-sugar down to normal.

They believe that two-thirds of a gram of protein per kilogram will usually maintain a positive nitrogen balance. After the protein, carbohydrate and calories have been determined, Foster and Lowrie determine the number of calories to be supplied by fat by subtracting the total calories derived from the protein and carbohydrate from the total number of calories to be given. This balance divided by nine gives the number of grams of fat needed.
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Consequently, the K/AK ratio will usually lie between one and two which is a very satisfactory safeguard against ketogenic excess, according to Foster and Lowrie.

Malnutrition is often the result of diabetes and may be used as an index of its severity. Diabetic symptoms become more severe in the mal-nourished state. Therefore, therapy must be directed both toward controlling the diabetes and toward improving the physical state. Very low diets are contra-indicated by a state of malnutrition.

Adequate food allowance is essential for a gain in weight. The amount of insulin should be so adjusted, according to Foster, that the blood-sugar level is kept above the normal (125-150) in order to prevent the unusually severe hypoglycemic reactions that are otherwise common in malnourished individuals. The fatigability so characteristic of this group is overcome only by raising the level of nutrition. (Bib. XXIX).

However, in the aged patient no attempt should be made to increase the weight to the estimated normal inasmuch as the mortality rate of the underweight individuals who are above fifty years of age is less than that of individuals of this age of normal weight and is greatly less than that of those who are overweight. (Bib. XXIX).

The best therapeutic results are secured with the overweight diabetic patients. Reduction in weight lowers the basal number of calories required and, consequently, lessens the severity of the diabetes although the pancreatic function be not improved. A diet yielding 1200 calories in the case of the obese diabetic will usually effect a weight loss of about one pound per week. The maintenance protein of two-thirds gram per kilogram, fifty grams or more of carbohydrate and the balance of the calories in fat are prescribed. In the event the weight loss is too rapid, the patient will be clinically worse instead of better. A drop in blood pressure below
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100 systolic indicates a too rapid weight loss, according too Foster. *(Bib. XXIX)*.

The following table showing food allowances for overweight, normal weight and underweight patients has been devised by Foster:

<table>
<thead>
<tr>
<th>Data necessary.</th>
<th>Age</th>
<th>Height</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calories</td>
<td></td>
<td>Protein</td>
<td>Fat</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Grams</td>
<td>Grams</td>
</tr>
<tr>
<td>Overweight.</td>
<td>1200</td>
<td>55</td>
<td>90</td>
</tr>
<tr>
<td>Normal weight.</td>
<td>25 per kilo</td>
<td>2/3 gram per kilo</td>
<td>Sufficient to bring calories to desired level</td>
</tr>
<tr>
<td>Underweight.</td>
<td>3000</td>
<td>1 gram per kilo</td>
<td>Sufficient to bring calories to desired level</td>
</tr>
</tbody>
</table>

According to Spriggs of London, many obese individuals with mild diabetes require no other treatment than a reduction in the amount of food eaten. *(Bib. XXX)*.

Foster has endeavored to give others an appreciation of the fact that insulin enables us to adjust some suitable plan of dietary combination to any case of diabetic deficiency. *(Bib. XXX I)*. Insulin has enabled modern practitioners to depart considerably from the early pre-insulin arrangement of a diabetic diet on a " can take " and " cannot take " principle.
31.

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Foster of New York urges one gram of protein per kilogram of body weight because a wide range of amino-acids is essential to health although an adult can exist on less than one gram per kilogram. (Bib. XXXI).

Foster writes that mathematical precision is possible in the treatment of diabetes and that the patient should be well trained to use scales in measuring his diet. In small communities where a dietitian is not available, some diabetic patient may be secured to teach another with some small compensation for his work.

Foster of New York believes that a maintenance diet should be adopted at once. This basal maintenance formula is determined by Foster as follows: In estimating the theoretical caloric requirements of a patient weighing fifty-five kilograms, a basis of thirty calories per kilogram may be adopted. He requires a total of 1650 calories per day. The protein factor, then, is fifty-five grams daily, which is equivalent to 220 calories, leaving a balance of 1430 calories to be distributed between carbohydrate and fat. The grams of carbohydrate required is determined by dividing 1430 by the number 17 which equals ninety-seven grams of carbohydrate. This amount of carbohydrate equals 388 calories. Therefore, 1430 minus 388 equals 1042 ÷ 9 = 116 grams of fat. The formula, then, is, carbohydrate, 97; protein, 55; fat, 116. An inadequacy of the amount of food given is indicated by a loss of weight and a loss of strength when the patient assumes his usual mode of life. The diet should be accordingly increased and the insulin dosage readjusted.

Rather commonly a patient with rather mild diabetes will not become sugar-free until insulin is administered in large doses, sixty to eighty units a day. Gradually an increase in insulin production results, according to Foster. Each insulin dose may be decreased by ten or fifteen units until none is necessary. It appears that the claims of Foster are somewhat extravagant. He writes that it is seldom necessary to give more than two
doses of insulin, one in the morning and one in the evening. The noon dose is gradually divided between the morning and evening doses.

Foster states that obesity in diabetes indicates a mildness of the disease because weight loss would ensue if the condition were severe. (Bib. XXXI.) A moderate carbohydrate content is urged in giving a reducing diet because acidosis would otherwise supervene due to the patient metabolizing his own excess body weight.

The method of cooking the food must be considered in regulating the diet because vitamins are largely destroyed by heat, especially under full exposure to the air. The pot water containing most of the mineral salts is too often discarded. Since the cooking of canned vegetables is done after the sealing process, some canned vegetables are more beneficial than those cooked in many of the homes. (Bib. XXXI).

The large amounts of fat in the early diabetic diets probably tend toward lipemia and ultimately to vascular hypertension and arteriosclerosis. Aschoff's hypothesis maintains that the early lesion in arteriosclerosis is an infiltration of the endothelium with plasma. In severe diabetic acidosis, cholesterolemia and lipemia are markedly elevated. The pernicious effect of continued cholesterol and lipoid infiltration of the intima is very plausible. Elevated blood lipoids are present in inanition and certain diseases, as nephrosis. It seems likely that arteriosclerosis may result in earlier years from excess dietary fat or insufficient carbohydrate. (Bib. XXXI).

Animal experiments have shown that foods of the acid-ash type; i.e., meats, fish, cereals, bread and eggs, induce chronic interstitial nephritis, hypertension and arteriosclerosis as revealed by autopsy. Probably, diabetic and other patients should eat dominantly those foods of the alkaline-ash type; i.e., vegetables, fruits and milk.
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Diets high in carbohydrate and low in both protein and fat yield better and prompter results in cases of arteriosclerotic complications; such as, retinitis and circumscribed gangrene of the feet. (Bib. XXXI).

Liberal doses of insulin should be given. High carbohydrate diets should give better results as an adjunct of treatment of myocardial and renal degenerations, which are probably due to similar valvular lesions. According to Foster of New York, there is much evidence to show that high carbohydrate diets benefit and hasten whereas high protein diets delay the regeneration of liver cells.

Sansum, Blatherwick and Bowden recommend a diet low in fat and high in carbohydrate. (Bib. XXXII and XXXIII). Their diets contain two or more grams of carbohydrate to each gram of fat. Such a dietary, it is true, is a radical departure from the time-honored dietary management of diabetes; yet these investigators claim excellent results. Their first diet, which is an "acidosis diet," consists of ninety grams of oatmeal (dry weight), 300 cc. of skim milk and 1000 cc. of fruit juice. The oatmeal and skim milk are fractionated into three meals; the fruit juice is given with the meals and between meals. Orange juice proved to be the most suitable. Lemon juice or grapefruit juice was often added to the orange juice, especially if the patient showed tendency toward nausea and vomiting. When the patient has recovered from the acidosis, the remaining diets are ordered in the following sequence until a maintenance level is reached:

**Routine Diet Formulas.**

<table>
<thead>
<tr>
<th>No.</th>
<th>Diet.</th>
<th>Carbohydrate</th>
<th>Protein</th>
<th>Fat</th>
<th>Calories</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Acidosis</td>
<td>257</td>
<td>28</td>
<td>12</td>
<td>1248</td>
</tr>
<tr>
<td>2.</td>
<td>1000 calories</td>
<td>95</td>
<td>48</td>
<td>49</td>
<td>1013</td>
</tr>
<tr>
<td>3.</td>
<td>1500 calories</td>
<td>146</td>
<td>68</td>
<td>71</td>
<td>1499</td>
</tr>
<tr>
<td>5.</td>
<td>2500 calories</td>
<td>217</td>
<td>93</td>
<td>107</td>
<td>2203</td>
</tr>
<tr>
<td>6.</td>
<td>2500 calories</td>
<td>245</td>
<td>100</td>
<td>124</td>
<td>2496</td>
</tr>
<tr>
<td>7.</td>
<td>3000 calories</td>
<td>301</td>
<td>116</td>
<td>150</td>
<td>3018</td>
</tr>
</tbody>
</table>
Considerable amounts of insulin are necessarily given. Diet No. 2 causes the glycosuria to disappear. No attempt is made to clear up the glycosuria on the "acidosis diet." A larger amount of fat is given than in the diets of Porges and Aldersberg. Sansum and his co-workers claim that the high carbohydrate content of the diet gives greater physical and mental vigor. Acidosis can scarcely occur, even with co-existing sugar in the urine, because the high carbohydrate factor introduces a large margin of safety. These investigators claim that later vascular involvement is not so liable to occur on account of overcoming the acid-ash type of acidosis by means of the milk, potato and fruits. The increased carbohydrates lend a greater palatability to the diet. (Bib. XXXII and XXXIII).

Sansum and his co-workers believe that the greatest contribution to the modern therapy of diabetes is the knowledge that reduction in fat increases the carbohydrate tolerance, especially in children. The cause of this, when well understood, may open up new avenues of procedure for the control of diabetes.

Williams states that the dietary of normal individuals contains from 500 to 800 grams of glucose-producing food. (Bib. XXXIV). In normalcy, the pancreas secretes 75 to 200 or more units of insulin daily depending on the daily food intake. As already mentioned, Williams experimental work for six years with the Eli Lilly Company in the clinical testing of insulin revealed that one unit of insulin will metabolize about four grams of glucose. Diabetes results when the pancreas fails to produce enough insulin to metabolize the carbohydrate content and glucose-forming content of the diet. The urine-sugar represents that portion of glucose which is not oxidized and which exceeds the storage capacity of the body. The balance obtained by subtracting the number of grams of glucose excreted in the urine from the number of grams of glucose ingested is termed by Williams the
"glucose utilization" factor. Williams believes that the use of insulin will increase the fairly constant glucose utilization factor in a well-managed case of diabetes. He states that the number of units of insulin secreted by either a normal or diabetic individual is determined by dividing the number of grams of glucose utilized by the number four. The resulting figure, which may be called the "insulin coefficient," is a fairly constant factor in diabetes. The so-called "insulin coefficient" of the diabetic is determined by subtracting the number of units administered from the total number of units required to metabolize the food. (Bib. XXXIV).

Williams states that this coefficient is not materially affected by occasional dietary indiscretions, even with a high glycosuria and high blood-sugar levels. This view is somewhat in accord with Hare's belief that intermittent glycosuria and raised blood-sugar concentration are compatible with a life of physical and mental vigor. (Bib. XXVIII). Insulin administration does not influence the insulin coefficient, according to Williams.

Williams classifies clinically all cases of diabetes as follows: (1) severe diabetes,- insulin coefficient ranging below 20; moderately severe diabetes,- ranging from 20 to 35; mild diabetes,- ranging from 35 to 75.

The insulin coefficient is very valuable to know since it is a more valuable guide to the progress of an infection in diabetes than is the leucocyte count or the febrile curve, since it offers valuable prognostic information, since it measures most efficiently the progress of a case and the results of therapy and since it offers a most valuable check on the integrity of a patient's dietary allowance or insulin dosage. Satisfactory progress, according to Williams, would be indicated by a rise in the insulin coefficient of five to ten units a year. Williams believes that the insulin coefficient method is much more reliable than the glucose-tolerance test in differentiating spurious and renal diabetes from true diabetes. He writes:
"A glucose tolerance test is about as useful and reliable a method of determining the efficiency of the pancreas as is the hundred-yard dash in eleven seconds a measure of the physical ability of an individual to walk five miles at a leisurely gait." (Bib. XXXIV).

One rather promising feature of the insulin coefficient factor is that it will enable clinicians of widely separated communities to accurately contrast and evaluate different therapeutic measures. (Bib. XXXIV).

Nixon presents a summary of the advantages secured by a diet rich in carbohydrate: (1) It offers contentment and satisfaction; (2) The regimen is more easily observed; (3) The serious danger of ketosis is removed; (4) Arteriosclerosis is delayed; (5) The most important advantage is that a fat-poor diet increases carbohydrate tolerance and the prospects of pancreatic regeneration. (Bib. XXXV).

Fain, Edmondson and Nicely of Wisconsin present some dietetic principles which have been regularly taught to all patients at the Spa during the last sixteen years: (1) Green vegetables two or three times daily; (2) Fruits (preferably fresh fruits) twice daily; (3) Fresh meat (preferably animal protein, whether fish, fowl, eggs or cheese); (4) Cream and butter.

They advocate that the diet be adequate, agreeable, well-varied and that the patient must not be required to weigh and calculate his diet. To the above, cereals and vegetables are added if the patient's tolerance for blood-sugar producing foods will permit. Fresh fruits and green vegetables are very essential, according to them, since they supply a high mineral salt and vitamin content. Careful histories taken by these writers showed that mineral salts and vitamins are largely lacking in a large number of diets followed at the time the diabetes developed. The polyuria of diabetes depletes the mineral salts of the body. They declare that high carbohydrate diets necessitate large doses of insulin and frequently result in insulin
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reactions, especially when there are digestive disturbances. ( Bib. XXXVI ).

The Treatment of Diabetic Coma. Bowen and Hekimian write that insulin alone does not produce satisfactory response in cases of diabetic coma. They urge placing the patient in a warm bed and applying heat. They give a hypodermoclysis of 1000 cc. of normal salt solution and give an enema if the bowels have not moved during the day. The use of sodium bicarbonate in the amount of forty grams or less during the twenty-four hours, given by mouth or by proctoclysis if the stomach is irritable, is absolutely harmless and sometimes seems to be decidedly beneficial.

According to Bowen and Hekimian, the average insulin dosage for the first twenty-four hours should be approximately 150 units whereas some patients require three times this dosage and others respond to one-half this amount. This insulin requirement did not seem to depend on the blood-sugar concentration, the carbon-dioxide capacity of the blood, the degree of leucocytosis or the blood nitrogen although extremely hyperglycemic patients usually tolerate more insulin. Carbohydrate is given by them with the insulin when the initial blood-sugar is low. Frequent urine examinations are made in order to determine the progress of the patient and to estimate the insulin-carbohydrate administrations. They state that catheterization should not be done unless the bladder is distended inasmuch as repeated catheterization may result in urinary tract infection in comatose cases. Caffeine sodium benzoate or digitalis preparations hypodermically often appear to be effective in combatting the circulatory insufficiency, acro-cyanosis, hypotonia and tachycardia manifested in some degree by nearly every patient having diabetic coma. These attending conditions are probably due to acid intoxication. Fluids should be forced to overcome the dehydration. ( Bib. XXXVII ). They report favorable results in eighty-one cases by the use of the above outlined treatment.
Joslin, Root, White and Adams do not believe that alkalies are beneficial in diabetic coma. In Joslin's report of 105 cases of diabetic coma, representing ninety patients, there were fourteen deaths, five occurring during coma with complications, two during uncomplicated coma treated during the early insulin period and seven during complications developed after recovering from the coma. But Bowen and Hekimian, as we have seen, believe that the use of alkalies causes a quicker response and a more ready relief from hyperpnea. (Bib. XXXVII and XXXVIII).

John of Cleveland outlines a plan of treating diabetic coma similar to that of Bowen and Hekimian. For vomiting John orders a gastric lavage with warm and slightly alkalinized water, the last bulbful being left in the stomach. He sometimes gives 30 to 40 cc. of castor oil through the lavage tube after completion of the lavage. Then, the patient receives 250 cc. of a ten per cent. solution of dextrose to which from fifty to one hundred units of insulin have been added. The first treatment is often adequate; however, two or three such administrations may be given during the first twenty-four hours. An ampoule of caffeine sodium benzoate, containing 7.5 grains, is added to the dextrose solution and, if the patient is restless, he adds 0.25 grain of morphine to the solution. If the patient has any infection, as a carbuncle or pneumonia, a blood culture is indicated. John usually administers twenty units of insulin every half hour until the blood-sugar level drops to 250 mgms. or less, when insulin is given less often; that is, every one or two hours as determined by repeated blood-sugar examinations. John stresses that there is very little danger of overinsulization inducing insulin shock in diabetic coma. "A patient in coma, especially if he has an infection, soaks up insulin like a sponge; that is, insulin does not seem to produce the same effect per unit as in the ordinary case." He states that he has never seen a case die of hypoglyce-
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Coma is the most acute emergency that arises in diabetes, and insulin should be given in large amounts immediately and persistently. For dehydration in diabetic coma, with vomiting, gastric lavage is necessary. Water should be given in large amounts followed by a hypodermoclysis of 2000 cc. (Bib. XXXIX).

We know that insulin administration is the best assurance against acidosis passing into coma. Campbell of Toronto advocates that glucose or other carbohydrate be given with the insulin in the proportion of one gram of carbohydrate to each unit of insulin in order not to give an excess of the hormone. (Bib. XL). John, on the other hand, believes there is very little danger of overinsulization. (Bib. XXXIX). Insulin is indicated when acetoacetic acid is present in the urine, as determined by the ferric chloride test, and when symptoms and signs of acidosis and dehydration are present, such as, dyspnea or prolonged, painful or difficult breathing; vertigo; nausea, vomiting and abdominal pain; deepening drowsiness; and a fruity odor of the breath. Reduced tension of the eyeball, dry and hard tongue and skin indicate that the patient in acidosis is in imminent danger of coma; at this time, treatment must be immediate and vigorous. Warm drinks of various kinds should be given frequently and generously. Campbell does not believe in giving morphine very often because it produces complications. (Bib. XL). Campbell gives twenty to forty units of insulin repeatedly until the symptoms disappear. A drink of orange juice, grape juice or diluted corn syrup is given with the insulin. Any hypoglycemic tendency is avoided by making repeated urinary examinations to make certain that glycosuria continues. He believes that most patients in acidosis will be prevented from passing into coma by giving forty units of insulin per day in divided doses until the diet and insulin are properly adjusted. Ten grams of sodium bicarbonate given daily per orum probably hastens a recovery from acidosis.
When frank coma develops, Campbell adopts an emergency regime. He believes that most comatose cases which terminate fatally could have been saved by giving an initial dose of sixty units of insulin at once. A delay of only one hour may cause a fatal issue. He states that two or three ounces of corn syrup, in water or coffee, should be given. Also, he combats ketone production by giving adequate caloric requirements in foods other than fats. He reduces metabolism to a minimum by putting the patient to bed and keeping him warm. This procedure is agreed upon by all clinicians. One hundred units of insulin with 1000 cc. of ten per cent. glucose solution are given intravenously at once. The insulin is repeated if necessary but rarely in large doses after the initial administration. Campbell finds that two hundred units in all are adequate to entirely overcome the coma. He prefers to have the glycosuria persist until the patient assumes an interest in outside activities again. Two twenty unit doses of insulin are given to prevent a relapse into acidosis. One-fourth cc. of pituitrin or pitresin may be repeatedly given intravenously in order to support the circulation. Campbell advocates other measures already described under the plans of other clinicians. (Bib. XL).

Foster of New York says that twenty to forty grams of dextrose given every two or three hours with adequate insulin will prevent clinical acidosis preoperatively and postoperatively. He writes that dextrose is best given in twenty-five to fifty per cent. solutions intravenously inasmuch as dextrose by hypodermoclysis does not seem to be rapidly absorbed and sometimes irritates. When the diabetic patient burns largely fat, which is the least essential tissue, acidosis supervenes. Acidosis in surgical cases accompanies high mortalities. Acidosis is the surgeon's greatest hazard. (Bib. XXXI).

Before the advent of insulin, the mortality rate accompanying coma was
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100 per cent. The average mortality rate of cases now reported in the literature is approximately 25 per cent. Although this marks a tremendous gain, the rate will undoubtedly be still further lowered. Joslin's idea of a mortality rate of zero seems very doubtful. John's mortality rate in diabetic coma has been only 5.6 per cent. (Bib. XXXIX). The stomach of a moribund patient in diabetic coma should not be washed out unless it is distended as such a procedure may lead to a fatal issue.

John reports that the use of Fisher's solution by vein yields excellent results in treating the oliguria and evening anuria that occasionally accompanies diabetic coma. The ketosis probably causes renal damage as is shown by the presence of casts with adhering epithelial cells in the urine. (Bib. XXXIX).

Dodds of the Middlesex Hospital, England, relies for the insulin dosage in cases of diabetic coma on the results of blood-sugar analyses. He states that the blood-sugar estimation requires only about fifteen minutes; then, he gives the first dose of insulin, usually about one hundred units. (Bib. XLI).

Joslin, Root and White have worked out a scheme for giving insulin depending upon the hours the comatose patient is expected to live. If the estimated period is twenty-four hours, twenty units are given every hour until there is clinical improvement and a markedly lowered blood-sugar and urinary sugar. If the estimated period is only twelve hours, the dose is forty units per hour. During the post-comatose state insulin is given by them in smaller amounts. It would seem that estimation of the number of hours of life expectancy could not be made with any fair degree of accuracy inasmuch as symptoms of various individuals differ so markedly.

Hare urges a watchfulness for the first hypoglycemic symptoms in giving massive doses of insulin for diabetic coma in order to immediately decrease
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the insulin and increase the glucose. ( Bib. XXVIII ).

Lawrence believes that he caused the recovery of two patients in desperate diabetic coma by giving extremely large quantities of intravenous fluid, hypertonic saline and gum acacia solution. He states that certain clinical observations may be made which will readily differentiate the cases requiring such treatment from less severe cases, which will readily respond to insulin alone. In both types there are typical air hunger and varying degrees of unconsciousness. In the most severe cases the pulse is rapid and feeble, the blood pressure very low, the veins are empty, the tissues are drained of water, and the most striking sign is the low eye tension. The excessive polyuria and the failure to absorb fluid due to the vomiting and unconsciousness produces this extreme dehydration. An increased hemoglobin content indicates a concentrated condition of the blood. The dehydration and low blood pressure causes a very scanty excretion of urine and sometimes actual anuria. Nitrogen accumulates in the blood; blood urea concentrations of 80 to 100 mgm. per 100 cc. or even higher, due to dehydration, are present. The blood chlorides are greatly depleted.

These findings explain the efficacy of the treatment, according to Lawrence. Insulin rectifies the chemical changes in the blood due to the diabetic state. Forced fluids, which in desperate cases should be given in very large amounts and preferably by vein, rectifies the dehydration chemical changes in the blood. Lawrence gives 1.8 per cent. saline solution since the body is depleted of chlorides and the blood chlorides are greatly reduced. Seven per cent. of gum acacia was given after the saline because the former is colloidal and remains in the vessels. Much of the saline leaves the blood and passes into the dehydrated tissues. A pint of gum acacia amplifies and gives body to the pulse more than the earlier larger volume of saline solution. ( Bib. XXVI ).
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Dodds and Robertson believe that the cause of death in uncomplicated diabetic coma is circulatory failure rather than the condition of ketosis or nitrogen retention. In their fatal cases death was preceded by a persistently falling blood pressure. This view supports the important procedure of instituting vigorous measures to support the circulation. (Bib. XLII).

Even under the insulin regime, constant supervision of the doctor and intelligent co-operation are necessary to avert a mortality from diabetic coma. The treatment of coma is the administration of glucose rendered usable by insulin because ketosis results from incomplete oxidation of fats. Carbohydrates are essential to complete oxidation of fats. Under carbohydrate deprivation the body derives its caloric requirements from the fats which are incompletely burned. The urine should be kept continuously free of ketone bodies as indicated by Rothera's sodium-nitroprusside test, according to Nixon. Glucose administration is the only effective method of eliminating ketosis. Carbohydrates must be given freely with the insulin because insulin may exhaust the blood-sugar and yet be insufficient in quantity to burn up all the ketones. Therefore, continued coma with hypoglycemia may eventuate if glucose is withheld. (Bib. XXVII).

The Treatment of Diabetes in Children. Foster of New York believes that two grams of protein per kilogram should be allowed during the growth period of childhood and that the total food allowance should also be increased. (Bib. XXXI). Since bony growth requires lime salts, a quart of milk should be included in the ration of a diabetic child since insulin will metabolize the lactose. Raw fruits and green vegetables must be given to include all mineral and vitamin requirements. Fruit juices, tomato juice, the leafy vegetables, carrots, butter and cod liver oil each furnish some substance requisite either to growth or health. (Bib. XXXI).
Geyelin and Mackie stress the fact that diabetes in children is more severe than in the adult and, consequently, is more difficult of treatment inasmuch as a diet sufficient for proper growth and development must be given. Treatment is rather uncertain because there are no entirely satisfactory standards of height and weight for age and because we do not know the ideal caloric intake for the various ages. Ladd has concluded that the normal average weight for height as given in Bardeen's tables, plus or minus twelve per cent., is the optimum weight for a diabetic child. By following the height-weight-index-growth curves the practitioner may compare with the standard at any age and learn valuable facts as to the child's growth rate as indicated by the tendency of the patient's curve to parallel, to approach or to depart from the standard curves. The tables of Holt and Fales are probably the best for determining the caloric and protein requirements at the various ages. About two-thirds the amount shown in these tables should be adopted as the optimum ration for the diabetic child. (Bib. XLIII).

There must be a proper maintenance of the ketogenic ratio. Nixon says that diabetic children require a generous carbohydrate allowance inasmuch as an excess of fat over carbohydrate will induce, even in a normal child, cyclical vomiting, acidosis and acetonemia. (Bib. XXVII). A positive protein balance must be maintained in order to preserve the protein equilibrium. (Bib. XLIII). Geyelin and Mackie believe that the era of high fat, low carbohydrate diets has passed because of the untoward effects of such diets. Such diets have revealed that continuous elevations of the blood fats and blood cholesterol above normal limits induce a reduced sugar tolerance. Many authorities now believe that these high blood levels play a role in the development of vascular changes in later years. Joslin believes that a diet containing one hundred grams or more of carbohydrate, given soon af-
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ter diabetes develops, may prevent the appearance of premature arteriosclerosis. Also, animals fed on a high fat, low carbohydrate diet respond less to insulin therapy. Geyelin and Mackie write that a change in diet in which the fats were decreased and the carbohydrates considerably increased resulted in a very small increase in the insulin requirements immediately following the dietary change, and, later, there was frequently a lessened insulin requirement and an apparently permanent increase in carbohydrate tolerance.

Ladd has declared that a diet containing the requisite number of calories, sufficient proteins to maintain a positive nitrogen balance and a ratio of three to four grams of carbohydrate to each gram of fat had resulted in a more rapid improvement in diabetic children than any earlier dietary regime had ever secured. Ladd gave adequate insulin to maintain an absence of glycosuria and a blood-sugar concentration within normal limits.

In studying the results of treating ninety-five diabetic children in the Toronto Hospital for Sick Children, Boyd discovered that only fifteen per cent. could receive an adequate diet without insulin and that not one of these had an initial tolerance in excess of one hundred grams of carbohydrate. Furthermore, in the remaining eighty-five per cent., a basal diet without insulin did not maintain a sugar-free urine. Insulin administration yields more successful and quicker results in children than in adults. (Bib. XLIII).

In mild cases of diabetes in children, the carbohydrate may be pushed to the morning and evening meals, and two doses of insulin, administered thirty to forty-five minutes before the morning and evening meals, respectively, may provide for the excess burden on the pancreas. In the more severe cases, three injections daily may be required. In the most severe cases, an additional administration at midnight may be necessary to prevent the spilling of sugar into the urine during the latter hours of the night.
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The entire twenty-four hour urine output should be fractionated into that voided between evening and morning meals, that voided between morning and noon-day meals and that voided between noon-day and evening meals. The three separate analyses will give all information necessary for determining the size of the various doses which vary with the amount of sugar spilling into the urine, the time of its occurrence and the proportion of carbohydrates given at each meal.

The site of insulin injection should be constantly shifted to prevent tissue thickening and induration at a too narrowly restricted site of injection with consequent delayed, irregular and insufficient insulin absorption. The good practitioner must always pay attention to the smaller details (Bib. XLIII).

Priscilla White of Boston writes that there are twenty thousand children in the United States who are diabetic or potentially diabetic. (Bib. XLIV). This writer believes that ten years will be required to tell which combination of diet; that is, high carbohydrate, moderate carbohydrate or low carbohydrate diet will best fulfill all of the requirements during the developmental years of life. At the present time, according to White, it is probably safer not to resort to the dietary extremes. A low carbohydrate, high fat diet seems to lower the tolerance for carbohydrate whereas the reverse type of diet seems to strain the diseased pancreas. However, many modern investigators do not accept the latter view. The year, 1930, marks the seventh year of insulin therapy. Insulin does not seem to induce arteriosclerosis in diabetic children. During the pre-insulin days one of every three diabetic children began to show arteriosclerotic manifestations at seven years. Ten insulin children showed no evidence of arteriosclerosis when X-ray examinations of the legs were made. (Bib. XLIV).

The treatment of diabetes in children was almost hopeless prior to the
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discovery of insulin. The most capable clinicians coped somewhat with the situation and were able to prolong the lives of a few young diabetics. However, the necessary strict limitation of food intake produced a stunted development and increased susceptibility to disease. Under modern regimes diabetic children may undergo normal growth and development and live happy, comfortable lives.

**The Effect of Liver on the Blood-Sugar.** Blotner and Murphy declare that liver has a beneficial effect on the blood-sugar of diabetic individuals. This new teaching opposes the earlier view that liver is an unsuitable diet in diabetes due to its glycogen content. The liver fractions employed in the treatment of pernicious anemia have no effect on the blood-sugar whereas other liver fractions which are ineffective in treating pernicious anemia lower the blood-sugar level like whole liver. (Bib. XLV). These observations indicate that liver contains a blood-sugar reducing substance which is active when administered orally, non-toxic and similar in its effect to that of insulin. Blotner and Murphy believe that 180 grams of liver are equivalent to ten or fifteen units of insulin in reducing blood-sugar concentration. Liver must be fed daily for from three to five times a week. (Bib. XLV). Murlin, Pierce and Gregg have offered the explanation that the insulin content of fresh liver may produce the reduction in the blood-sugar level. Bowen reports that there is no evidence of a blood-sugar lowering effect of liver as determined in a case of combined diabetes and pernicious anemia.

**Diabetic Nostrums.** Large numbers of diabetic nostrums have been placed on the market in recent years by exploiting companies. Pancretone is one of the many fraudulent preparations dishonestly exploited by the Wabash Chemical Company of Chicago as a "non-specific" that will cure diabetes. These nostrums are menaces to those of the laity who choose the evil of self-treatment without the supervision of a physician. Chemical analysis of
Pancretone showed that it was essentially a "digestive tablet" containing an amyloolastic enzyme to which was added considerable calcium carbonate and corn starch. Any beneficial effects that may follow the use of Pancretone are necessarily due to the dietary restrictions which attend its use. (Bib. XLVII). All such nostrums are palpable frauds and constitute a real menace to unknowing diabetic individuals. Physicians should warn diabetic individuals of this fact. Bertram reports that Fornet's pills, which contain insulin and bile salts, are absolutely ineffective. (Bib. XLIX).

The Value and Action of Synthalin. Bertram states that synthalin, a derivative of guanidine, which was discovered by Frank, Nothman and Wagner, has proved to be the most effective substitute for insulin. (Bib. XLIX). Von Noorden has advised the use of glukhorment which contains insulin. Bertram believes that synthalin yields the best results in mild cases of diabetes, in which the pancreas may be functional, because synthalin stimulates insulin secretion by its action on the vagus. However, synthalin has slight or no effect in the severe cases. In large doses synthalin produces gastric symptoms and probably has a toxic action on the cell. Glukhorment has a weaker effect due to its small synthalin content. Galegin also has a weak effect; however, von Noorden believes that galegin by mouth yields some benefit and is safe. Bertram states that the guanidine bodies do not have the same primary action as insulin. (Bib. XLIX).

The original report on synthalin (diguanidine decamethylene) in 1926 by Frank, Nothmann and Wagner has been followed by a large volume of investigative work on its effects. (Bib. L). Attention has been given to its action on carbohydrate metabolism, on glycogen storage and on the respiratory quotient. When we compare the clinical with the experimental findings, we discover considerable diversity in the conclusions of the various workers.
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Its mode of action in lowering the blood-sugar concentration is not definitely known. Synthalin has a marked effect on hyperglycemia only in the partially diabetic dog. Synthalin has proven effective only in the less severe forms of diabetes. (Bib. L).

Zunz and Le Barre believe that synthalin acts on the nerve centers and causes, through the vagus, an increased insulin secretion. Section of the vagus resulted in failure of response to synthalin. This explanation may account for the action of synthalin on the partially diabetic dog and on the diabetic patient. In both of these instances there is some functioning pancreas that might be stimulated to secrete insulin. (Bib. L).

According to Bollman, Mann and Magath, the deaminization of amino-acids is a function of the liver. (Bib. LI). They asked the question if synthalin were not sufficiently injurious to the liver to interfere with this function. Blatherwick, Sehyun and Hill showed that deaminization ceases completely in the dog as soon as the liver is removed. (Bib. LII). They showed that rabbits were unable to deaminize glycine after the injection of synthalin, and they construed this as evidence of impaired liver function. They interpreted their results in that the rise in amino-acid nitrogen was probably not solely due to liver injury, although such may have been the case. They found that synthalin administered by mouth failed to produce hypoglycemia in rabbits. An acute nephritis was produced by parenteral administration. Subcutaneous and intravenous injections usually decreased the blood-sugar.

Balli and Tiber believe there are two possible explanations for the hyperamino-acidemia accompanying the hyperglycemia following synthalin administration. This increase may be due to an increased protein catabolism with which the deaminization process is unable to keep pace. This may be illustrated by a rise in the amino-acid and urea nitrogen in the blood of a nor-
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mal animal following a protein meal. The other explanation is a failure of the hepatic deaminizing function. The experimental findings do not point conclusively to either theory, but the evidence seems to favor a failure of deamination as the more plausible explanation. (Bib. LIII).

Ralli's and Tiber's experiments showed a definite rise in amino-acid nitrogen associated with an increase in blood-sugar when synthalin was given to a completely depancreatized dog. This result becomes most striking when we note the decreased amino-acid content of the blood and the hypoglycemia following insulin administration as shown in the experiments of Luck, Morrison and Wilbur. (Bib. LIV). Ralli and Guion showed that the amino-acid nitrogen of the blood was reduced concomitantly with the blood-sugar concentration following the administration of synthalin to a partially depancreatized dog. (Bib. L and LIII).

It is interesting that, in the experiments of Lewis and Izume, hydrazine produced a hypoglycemia and an attending increase in the amino-acid content of the blood. They construed this rise in amino-acid nitrogen as being referable to liver injury and the hypoglycemia as being due to a failure of the glycogenetic function of the liver. (Bib. LV and LVI).

Much investigative work is being carried on to-day, especially in Germany, in regard to the value and action of synthalin, and, at present, the outlook is not very promising that the guanidine bodies will ever prove to be an effective substitute for insulin.

Foreign Protein Therapy in Diabetes. Leyton believes that foreign proteins; such as, novoprotein, phytoprotein, aolan, protasin and others, yield a favorable influence as a supplement in the treatment of diabetes with or without the use of insulin. (Bib. LVII). However, other investigators report that there are no apparent benefits resulting from its use. Results are conflicting, at present, in regard to foreign protein therapy.
Infections, Surgery and Other Complications in Diabetes. Infections complicating diabetes are much more serious than under ordinary conditions. If possible, free drainage should be established at once. The diabetes should be treated vigorously. The patient's caloric intake should be increased above the ordinary requirements, and, usually, the bulk of the food should be decreased. Excellent results are obtained with milk, cream and egg mixtures with orange juice. For some unknown reason, the control of acidosis and glycosuria during infection requires much more insulin than in the absence of infection. (Bib XL). Hypoglycemia from insulin overdosage must be avoided during the recovery period. The acidosis should be cleared up by administering sufficient insulin. Orange juice or other carbohydrate should be given to prevent hypoglycemia, when necessary. More frequent and smaller doses of insulin usually give the best results. It is often extremely difficult to maintain the proper balance between the diet and insulin.

Campbell believes that the glycosuria or hyperglycemia per se do not prevent repair; however, the reparative process is aided materially by controlling normal cellular metabolism through the administration of insulin. (Bib. XL). There is no doubt that diabetic individuals are more susceptible to infection and are frequently the victims of furuncles, carbuncles, abscesses and other local infectious lesions. Cleanliness and constant control of the diabetic condition are necessary in the prophylaxis and cure of various infections.

Nixon states that a fat-poor or fat-free diet is a distinct advantage in preparation for a surgical operation or for anesthesia. A large store of glycogen in the body reduces operative danger. Funk writes: "Let us not forget that sugar (glycogen) is the food, and the only food, upon which muscle can live. Especially to be remembered as regards the heart." (Bib. XXVII).
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Chloroform, which causes liver damage, should never be given and ether seldom given as the anesthetic for an operation. Spinal anesthesia, paravertebral nerve block, or gas and oxygen should be given to induce anesthesia, if such is possible. Additional insulin is administered to safeguard against postoperative acidosis. No purgatives are given; however, an enema is permissible, when necessary. Morphine or morphine-scopolamine should be used as a preliminary to anesthesia, according to Campbell. (Bib. XL).

If the preparation is thorough and proper, the diabetic metabolism probably imposes no greater risk than that encountered by a similar operation on a non-diabetic patient.

In emergency surgical cases, a glass of orange may be given by mouth previous to the operation. If vomiting occurs, twenty-five grams of glucose in fifty per cent. solution may be given intravenously and twenty-five units of insulin subcutaneously. After operation, the case is treated as a potential case of acidosis. (Bib. XL).

In the average case, a glass of orange juice should be given three hours before operation and again one hour later. The patient should be instructed to lie on his right side. Fifteen units of insulin are injected each time the orange juice is given. A diabetic diet is given as early as possible after operation. If the patient is unable to take food for some time, the orange juice and insulin are repeated every three or four hours in order to prevent the appearance of acidosis. It is not necessary to give insulin preoperatively or postoperatively in the milder cases of diabetes. Both insulin and proper dietary measures may be necessary for some weeks in the severer forms of diabetes. (Bib. XL).

A decreased blood supply due to arteriosclerosis, which so commonly complicates diabetes, probably underlies the occurrence of gangrene in the feet. There is little therapy that is effective in preventing the development of
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Arteriosclerosis with the exception of early diagnosis and adequate treatment of the diabetes. (Bib. LX). Some authorities believe that hypercholesteremia is the dominant factor in the development of arteriosclerosis in diabetes. The early discovery of circulatory disturbances in the extremities may open the way to instituting measures to increase the local collateral circulation and prevent or postpone the occurrence of diabetic gangrene. The skin reaction to histamine depends upon adequate circulation. Starr has made use of this test in determining the condition of the circulation by observing, in cases of impoverished or lessened circulation, a delay in the appearance and imperfect development of the normal reaction (wheat formation and reddening) to the application of histamine on the foot, while the reaction to histamine above the knee remains normal. After the gangrene has developed, the reaction to histamine may aid in choosing the most effective mode of treatment and in determining the level at which amputation may be done successfully. (Bib. LX).

In Summary... In diabetes mellitus the cell has partially or completely lost its capacity for the utilization of sugar. The pancreatic hormone, insulin, which is essential for the oxidation of sugar in the body, is deficient or lacking. This metabolic derangement produces disturbances in fat metabolism which result in ketosis.

The real search for a curative pancreatic ferment received its impetus by the declarations of Opie in 1902 and Ssobolew in 1902 that the islands of Langerhans were the glandular tissues involved in diabetes mellitus. In 1916 Sir E. A. Schafer gave the name of "insulin" to the internal secretion of the pancreas. The presence of the proteolytic ferment, trypsinogen, caused the great difficulties which attended the attempts of many years to isolate a pure extract of the island tissue. F. G. Banting, assisted by C. H. Best, was the first investigator to isolate insulin in a purified...
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state, effective for the treatment of diabetes in human individuals without toxic reactions. A new era of investigation was opened by the discovery of Banting and Best that the fetal calf pancreas of under five months' development was lacking in digestive pancreatic juice but not in its internal secretion. Collip was instrumental in discovering the purification of insulin by means of fractional precipitation with alcohol. The advent of the discovery of insulin marked a new era in the therapy of diabetes which has supplanted the handicapped attempts of the past to control this deficiency disease by means of a purely dietetic and hygienic regime. As we trace the history underlying the ultimate isolation of insulin, we appreciate the value of a theory which finally found expression in practical terms.

The dietary carbohydrates do not serve as the only source of glucose, for glycerol and certain amino-acids yield glucose and glycogen during metabolism. Insulin controls the blood-sugar concentration and the oxidation of glucose.

The glucose tolerance test has proven to be very valuable as an aid in the diagnosis of diabetes and in determining the severity of the disease.

The pancreas of cattle serves as the main source of insulin. Active preparations of insulin are extracted from fetal pancreases which lack functional acinous tissue. When administered orally, insulin has no effect. Subcutaneous injection is very effective, and intravenous injection yields a maximum effect. The administration of insulin reduces the blood-sugar concentration and overcomes glycosuria with secondary clearing up of the acetone bodies in the urine. Injection of insulin in excess may produce hypoglycemic convulsions which are quickly relieved by the administration of glucose. Insulin improves markedly the utilization of carbohydrates and increases the glycogen content of the liver. Secondly, the fat metabolism is rendered more complete, and the tissue proteins are conserved
more fully. It has been commonly believed that one unit of insulin will metabolize 1.5 to 2 grams of glucose. However, Williams, who has co-operated for six years with the Eli Lilly Company in the clinical testing of insulin, recently made the report that one unit of insulin causes the utilization of approximately four grams of glucose. Other investigators have not accepted this value for insulin.

Diabetes can now be controlled under proper conditions and under well-directed management and intelligent co-operation on the part of the patient. Treatment resolves itself into the proper solution of a problem in metabolism in terms of diet and the adjunct of insulin administration when the latter is necessary.

The education of the patient is indispensable to the successful management and treatment of diabetes. A manual, such as has been prepared by Wilder and by Joslin and others, should be made available for every individual who suffers from diabetes.

Joslin advocates that the diabetic diet should yield, except for brief intervals, the minimum number of calories required by a normal individual under similar conditions. Most clinicians restrict the total carbohydrate in the diabetic diet to seldom more than 100 grams, which constitutes a reduction to approximately one-fourth of the standard carbohydrate allowance for a non-diabetic individual.

The amount of protein required by diabetic patients varies with the weight, age and occupation of the individual as well as with the renal function. Joslin believes it is a safe rule to increase the protein content gradually to that amount required by a normal individual.

Results with the earlier undernutrition methods of treating severe cases of diabetes have certainly not been ideal. The extreme emaciation which resulted seemed to be harmful in its effect. Glycosuria cannot be controlled
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on a high protein diet.

The "high fat diet" of Newburgh and Marsh has met with disfavor because such a diet causes incomplete catabolism of the fats with all of the complications that arise in conditions of acidosis.

Woodyatt's "balanced maintenance diet" allows one gram of protein for each kilogram of body weight. The ketogenic-antiketogenic ratio is expressed as follows: 

\[
\frac{G+0.58 P + 0.1 F}{0.46 P + 0.9 F} = 1.5, \text{ when the ratio of fatty acids to glucose is at its maximum without developing ketonuria.} 
\]

This diet has been one of the most popular of all, and the formulas as devised by Woodyatt have been very extensively used. A knowledge of the patient's glucose tolerance is necessary in following Woodyatt's formulas.

Falta disgraces any departure from a normal diet. He advises the use of adequate doses of insulin without periods of dietary restriction.

Jansen gradually builds up a permanent diet which gives 1.5 grams of protein and thirty-five calories per kilogram of body weight.

Petren's regime of a high fat diet is an abrupt departure from the general modern therapeutic trend of the high carbohydrate, low fat diet.

Forges adopts the unusual view that intense pancreatic activity stimulates increased secretion of insulin. This is quite a contrasting principle and radical departure when viewed in the light of our universally accepted principle of rest as a most valuable and restorative procedure. Forges believes that decreased insulin secretion results from rest of the pancreas.

K. von Noorden of Vienna believes that carbohydrate tolerance is increased from 80 to 200 per cent. when a low fat diet replaces a high fat diet. He believes that protein restriction is not advisable.

Mixon disgraces the starvation treatment and the high fat dietary of
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pre-insulin days as being unnecessarily and unwisely grafted upon the insulin method of treatment. He points out that glycogen storage is assured by a diet rich in carbohydrate and poor in fat. Nixon advises placing the patient on an adequate maintenance diet, replacing the fats so far as possible with their equivalent of carbohydrate; that is, 2.25 ounces of carbohydrate for every ounce of fat. He believes that starvation of the pancreas lessens the capacity of this organ to secrete insulin.

Hare points out that a higher blood-sugar level with intermittent glycosuria is compatible with a vigorous life and sense of well-being in the diabetic patient since an increased blood-sugar level results when the glycogen reserves accumulate. Hare believes that a "maintenance diet" or normal nutrition diet should be prescribed from the beginning since undernutrition induces a period of invalidity.

Foster and Lowrie state that placing the patient at once on a full maintenance diet with sufficient insulin to keep the urine sugar-free shortens the hospitalization period, prevents unnecessary incapacitation which might follow a period of severe under-nutrition and prevents the mental depression that accompanies starvation. They point out that diabetic symptoms become more severe in the malnourished state. They believe that, since insulin is now available, no diabetic should receive a diet containing less than fifty grams of carbohydrate, even though the diabetes be severe. The carbohydrate allowance is increased as the tolerance becomes greater.

Foster of Detroit states that the fatigability so characteristic of malnourished diabetic individuals is overcome only by raising the level of nutrition. Insulin has enabled modern practitioners to make a remarkable departure from the early pre-insulin arrangement of a diabetic diet on a "can take" and "cannot take" principle.

Foster of New York advises one gram of protein per kilogram of body
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weight and the adoption of a maintenance diet at once. Many have used the method of Foster in calculating diabetic diets. He states that obesity in diabetes indicates a mildness of the disease because weight loss would ensue if the condition were severe. A moderate carbohydrate content is urged in giving a reducing diet because acidosis would supervene due to the patient metabolizing his own excess body tissues. Foster points out that large amounts of fat in diabetic diets tend toward lipemia and ultimately to vascular hypertension and arteriosclerosis. Most of the modern investigation seems to point to this fact; namely, that arteriosclerosis results in earlier years from excess dietary fat or insufficient carbohydrate. Diets high in carbohydrate and low in both protein and fat yield better and prompter results in instances of arteriosclerotic combinations; such as, retinitis and circumscribed gangrene of the feet. Liberal doses of insulin should be given.

The high carbohydrate, low fat diets of Sansum, Blatherwick and Bowden, contain two or more grams of carbohydrate to each gram of fat. They state that acidosis can scarcely occur, even with co-existing sugar in the urine, because the high carbohydrate factor gives a large margin of safety. These investigators claim that later vascular involvement is not so liable to occur on account of overcoming the acid-ash type of acidosis by means of the milk, potato and fruits which they give. Sansum and his co-workers believe that the greatest contribution to the modern treatment of diabetes is the knowledge that reduction in fat increases the carbohydrate tolerance, especially in children. The cause for this, when well understood, may open up new avenues of approach for the control of diabetes.

Williams states that the "insulin coefficient", determined by subtracting the number of units administered from the total number of units required to metabolize the food, is not materially affected by occasional
dietary indiscretions, even with a high glycosuria and high blood-sugar levels. Williams states that satisfactory progress in a diabetic patient would be indicated by a rise in the insulin coefficient of five to ten units a year.

Nixon presents a summary of the advantages secured by a diet rich in carbohydrates and poor in fat; (1) It offers contentment and satisfaction; (2) The regimen is more easily observed; (3) The serious danger of ketosis is removed; (4) Arteriosclerosis is delayed; (5) The most important advantage is that a fat-poor diet increases carbohydrate tolerance and the prospects of pancreatic regeneration.

In the treatment of diabetic coma, insulin alone does not produce satisfactory response. Other measures are helpful and necessary. Fluids are forced to combat the dehydration. Caffeine sodium benzoate or digitalis preparations hypodermically often appear to be effective in combating the circulatory insufficiency, acro-cyanosis, hypotonia and tachycardia manifested in some degree by nearly every patient with diabetic coma. Bowen and Hekimian give carbohydrate with the unsulin when the initial blood-sugar is low. The use of sodium bicarbonate often seems to be helpful.

John of Cleveland orders a gastric lavage for vomiting in comatose cases, using warm and slightly alkalinized water. He stresses that there is very little danger of overinsulinization inducing insulin shock in diabetic coma. Coma is the most acute emergency that arises in diabetes and insulin should be given in large amounts immediately and persistently. We know that insulin administration is the best assurance against acidosis passing into coma. Campbell of Toronto advocates that glucose or other carbohydrate be given with the insulin in the proportion of one gram of carbohydrate to each unit of insulin in order not to give an excess of the
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hormone. This clinician believes that most comatose cases which terminate fatally could have been saved by giving an initial dose of sixty units of insulin at once. He combats ketone production by giving adequate caloric requirements in foods other than fats.

Foster of New York says that twenty to forty grams of dextrose given every two to three hours with adequate insulin will prevent clinical acidosis preoperatively and postoperatively. Acidosis is the surgeon's greatest hazard.

Before the advent of insulin, the mortality rate accompanying coma was 100 per cent. The average mortality rate of cases now reported in the literature is approximately 25 per cent. John's mortality rate in diabetic coma has been only 5.6 per cent. Although this marks a tremendous gain, the rate will undoubtedly be still further lowered.

Lawrence believes that he caused the recovery of two cases in desperate diabetic coma by giving extremely large quantities of intravenous fluid, hypertonic saline and gum acacia solution.

Dodds and Robertson urge the important procedure of instituting vigorous measures to support the circulation since they believe that the cause of death in uncomplicated cases of diabetic coma is circulatory failure rather than the condition of ketosis or nitrogen retention.

It appears therapeutically sound to give carbohydrates freely with the insulin because insulin may exhaust the blood-sugar and yet be quantitatively inadequate to burn up all of the ketones. Glucose administration is the only effective procedure in comatting ketosis.

Foster of New York believes that two grams of protein per kilogram should be allowed during the growth period of childhood and that the total food allowance should also be increased. Most modern therapists urge a similar principle. Nixon says that diabetic children require a generous
sufficient proteins to maintain a positive nitrogen balance and a ratio of
three to four grams of carbohydrate to each gram of fat had resulted in
a more rapid improvement in diabetic children than any earlier dietary re-
gime had ever secured. Ladd gives adequate insulin to prevent glycosuria
and to maintain a blood-sugar concentration within normal limits.

According to Priscilla White of Boston insulin does not seem to induce
arteriosclerosis in diabetic children but seems to prevent its development.
White believes that, at the present time, it is probably best not to re-
sort to the dietary extremes.

The treatment of diabetes in children was almost hopeless prior to the
discovery of insulin. The most capable clinicians were able to cope some-
what with the situation and to prolong the lives of a few diabetic children.
Under modern regimes diabetic children may undergo normal growth and de-vel-
opment and live comfortably.

Blotner and Murphy have shown us that liver is a suitable and valuable
food in diabetes despite its glycogen content. The liver fractions employed
in the treatment of pernicious anemia do not affect the blood-sugar whereas
other liver fractions which are ineffective in the treatment of pernicious anemia lower the blood-sugar level like whole liver. Blotner and Murphy showed that liver contains a blood-sugar reducing substance which is active when given orally, ton-toxic and similar in its effect to that of insulin. They believe that 180 grams of liver are equivalent to ten or fifteen units of insulin in lowering the blood-sugar level.

Large numbers of diabetic nostrums have been placed on the market in recent years. These nostrums are palpable frauds and constitute a real menace to unknowing diabetic individuals who attempt to control diabetes without the aid of a physician.

The original report on synthalin (diguanidine decamethylene) in 1926 by Frank, Nothmann and Wagner has been followed by a large volume of investigative work to discover its nature and action. A comparison of the clinical and experimental findings shows considerable diversity in the conclusions of the various workers. Its mode of action in lowering the blood-sugar percentage is not definitely known. Synthalin has proven effective only in the less severe forms of diabetes. Zunz and La Barre believe that synthalin acts on the nerve centers and causes, through the vagus, an increased insulin secretion. In mild cases of diabetes there is some functioning pancreas that might be stimulated to secrete insulin. The production of hyperamino-acidemia by synthalin administration is probably due to consequent impairment or failure of hepatic deaminizing function. In large doses synthalin produces gastric symptoms and probably has a toxic action on the cell. At present, the outlook is not very promising that the guanidine bodies will ever prove to be an effective substitute for insulin.

For some unknown reason, the control of acidosis and glycosuria during a period of infection requires much more insulin than in the absence of infection. Cleanliness and persistent control of the diabetic condition are
necessary for the prophylaxis and cure of various infections.

Nixon writes that a fat-poor or fat-free diet is a distinct advantage in preparation for a surgical operation or for anesthesia. Spinal anesthesia, paravertebral nerve block or gas and oxygen should be used to effect anesthesia in operating on diabetic individuals. If the preparation is thorough and proper, the diabetic metabolism probably imposes no greater risk than that encountered by a similar operation on a non-diabetic patient. Orange juice and insulin are very effective in overcoming vomiting and acidosis preoperatively and postoperatively.

A decreased blood supply due to arteriosclerosis, which so commonly complicates diabetes, probably underlies the occurrence of diabetic gangrene. There is little therapy that is effective in preventing the development of arteriosclerosis with the exception of early diagnosis and adequate treatment of the diabetic condition. Starr has made use of the histamine skin test to determine the condition of the circulation by observing, in cases of impaired circulation, a delay in the appearance and imperfect development of the normal skin reaction (wheal formation and reddening) to the application of histamine to the foot, while the reaction to histamine above the knee remains normal. The skin reaction to histamine depends upon adequate circulation.
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