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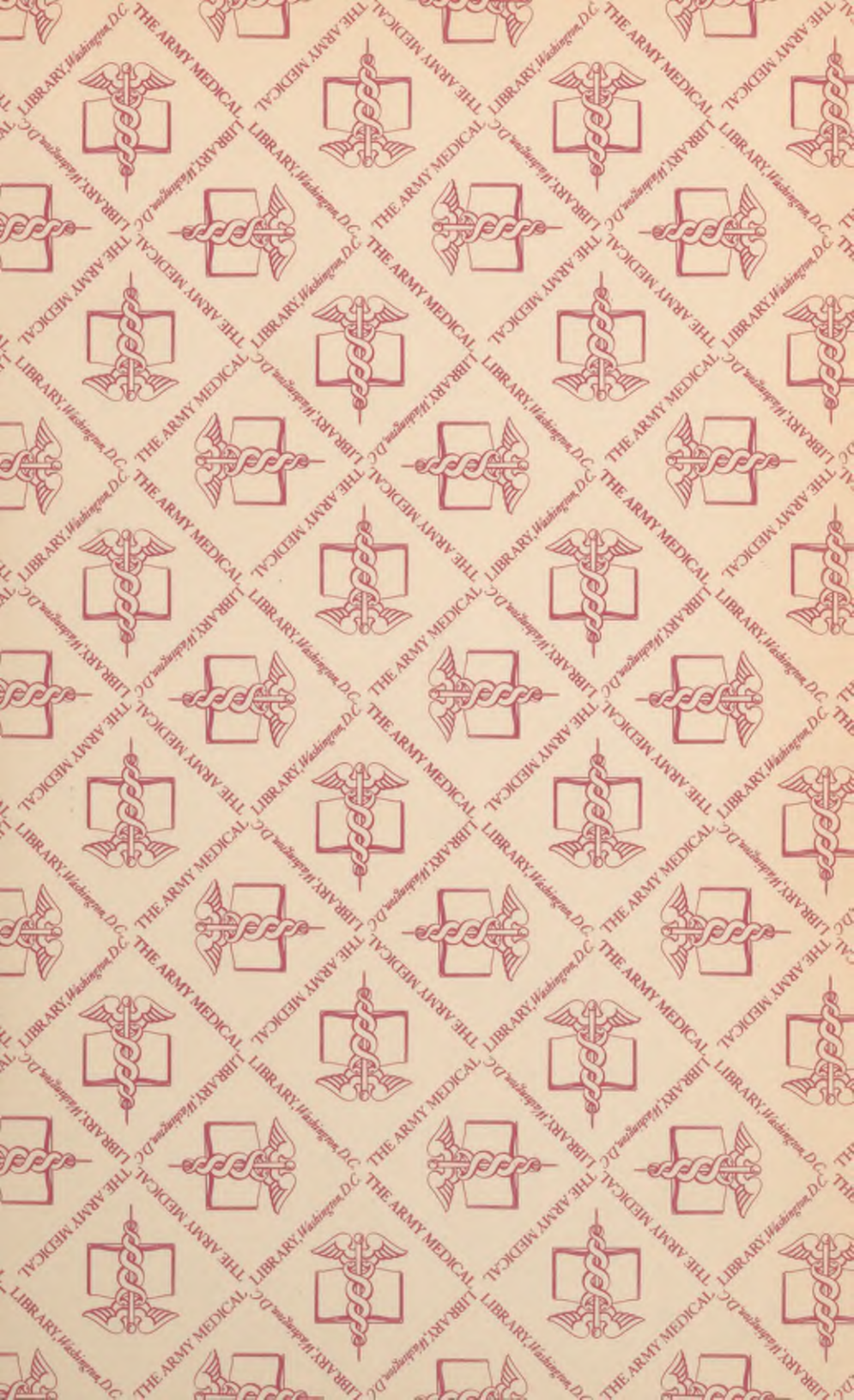
GARNRICK

ORGANOTHERAPY IN GENERAL PRACTICE NO. 2
DIABETES

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ORGANOTHERAPY *in* GENERAL PRACTICE

NO. 2

DIABETES



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DIABETES MELLITUS

Diabetes mellitus is a disease of metabolism sufficiently common and grave in prognosis to command the attention of and stimulate to elaborate research many of the ablest members of the medical profession. It has been estimated (Joslin) that in the United States there are at least half a million diabetics and an inspection of the statistics compiled for foreign countries and cities shows diabetes to be an important item in the mortality statistics all over the world.

For the United States Joslin gives the following figures¹: The deaths from diabetes in the registration area of the United States reached the maximum of $17\frac{1}{2}$ per 100,000 in 1915. For the next five years they decreased as follows: 1916, 17.1: 1917, 17: 1918, 15.9: 1919, 14.9: 1920, 16.1. The figures for Boston show a parallel course. The maximum figure is that for 1915, 26.1 per 100,000. For the years following, the figures are: 1916, 25.2: 1917, 19.1: 1918, 17: 1919, 22.9: 1920, 23.2. The figures for New York City for the five year period ending 1919 are 19.8 per 100,000.

Joslin's statistics offer much encouragement in view of often repeated statements that diabetes is rapidly increasing along with other "degenerative diseases"—cardiac disease, arteriosclerosis, etc. Joslin believes that the decrease in mortality cannot be accounted for by lessening frequency of diabetes and that the improvement in modern treatment must be credited with a share in the general result.

Not only has the death rate decreased but, in addition, a remarkable extension of the duration of life in the diabetic has taken place. The average duration of life in cases of fatal diabetes in the city of Boston between 1895 and 1913 was 3.3 years. During 1915 it was 4.3 years and in 1920 it was 5.3 years.² The prognosis in diabetes mellitus is, therefore, better today than ever before and the accidents of diabetes—acidosis, coma, gangrene, etc.—with careful attention to the details of treatment, are now very largely preventable.

Diabetes mellitus, as considered here and as encountered in everyday practice, is a disease of the pancreas (at least the pancreas is the central factor in the condition) resulting in deficient internal secretion and general inability to utilize glucose. The pancreatic disturbance may be either anatomic or functional, the exact pathology still remaining indefinite, but the fundamental characteristic of all true diabetes is definite lessening of the ability of the organism to metabolize sugar. The patient presents symptoms of progressive loss of weight, thirst, asthenia and hunger. Glycosuria, or the presence of sugar in the urine in abnormal amounts, is a constant finding and remains today a crucial point in diagnosis and in determining treatment. It may be mentioned that sugar is normally present in the urine in very small quantities. The quantity is not sufficient, however, to give a positive reaction to the ordinary clinical tests, but it has been shown by Prof. S. R. Benedict,

¹*Boston Medical and Surgical Journal*, June 8, 1922.

²*Boston Medical and Surgical Journal*, June 22, 1922.

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using a special technique for removing some substances which interfere with the reaction, that normal urine contains a small quantity of sugar, about one half of which is glucose.

ETIOLOGY

The Pancreas as the Central Factor in Diabetes

The nature of the factor giving rise to disease of the islands of Langerhans, or to functional disturbance of the production of the internal secretion from this tissue, is unknown. Many facts attendant upon the establishment of diabetes are known, however, and these, taken with a progressively enlarging knowledge of the mechanism of diabetes, have largely and favorably influenced the treatment and measures of prophylaxis. Early clinical observations and animal experiments had suggested a relation between the pancreas and diabetes, and an internal secretory function having some relationship to the carbohydrate metabolism was more or less clearly recognized by a number of observers before the researches of von Mering and Minkowski in 1889 established the relation between pancreatic function and experimental diabetes. These observers found that complete removal of the pancreas was invariably followed by diabetes and a glycosuria which remained constant. This glycosuria persisted irrespective of the food intake, and the other symptoms characteristic of diabetes were observed in the animals. They found, also, that the percentage of blood sugar increased, that acetone bodies were formed in the urine, that the liver lost its glycogen and became fatty, and that the condition was progressive and invariably fatal. If only a portion of the pancreas were removed, these changes did not take place. Subsequently, it was ascertained that an amount of pancreatic tissue as little as one-fifth to one-fourth of the organ was sufficient to protect the animal from diabetes. When these results were confirmed by other observers it was evident that a definite relationship had been described and the internal secretion of the pancreas, therefore, became an established fact based upon some of the most convincing experimental work in endocrinology. All opposition to the work of von Mering and Minkowski was successfully met, so that today the predominance of opinion remains that the pancreas is the central organ concerned in carbohydrate metabolism and that diabetes is a result of a break-down of its function in the utilization of sugar. Allen's statements as to this point are quite clear: "Clinical diabetes arises regularly on the basis of pancreatitis," and again, "It is now sufficiently established that the normal cause of diabetes is pancreatitis."

Disease of the pancreas may result from acute or chronic infection, or functional insufficiency may arise without known cause. Interference with the circulation or drainage from the ducts, obstruction due to gall stones, focal infection of the teeth or tonsils, syphilis or pus pockets in any site, may be found to be causative. The sexes seem to be about equally affected and diabetes occurs at every age of life. Heredity appears to be a factor and some races seem to be predisposed (Jews and Hindus).

**Obesity and
Overnutrition
Predisposing
Factors**

The relation of obesity and overnutrition to diabetes is one of the most important and practical from the standpoint of prophylaxis and treatment that has yet been observed. In 75% of a series of 1,000 of Joslin's cases, there was a definite history of preceding obesity. Between the ages of 31 and 40, only 12% of his cases who developed diabetes were under-weight, and after 40 years of age but 6% or less. In another series of cases he found a history of excessive indulgence in food in two-thirds of the number of cases. The observations of others fully confirm the remarkable association of diabetes with obesity and overfeeding, which justifies the statement of Joslin, "All other considerations in the etiology of diabetes drop out of account when the possibility is recognized of preventing the disease by simply maintaining a normal weight."²

Among theories of causation that of primary origin in the nervous system may be mentioned. Naunyn held that disturbances of the nervous system were equally important as disease of the pancreas in causing diabetes and the literature has always shown a percentage of authors who believed in a nervous origin. The "*sucre piqûre*" of Claude Bernard has seemed to those holding this view to offer some experimental confirmation (see page 8). Of recent years there has been a noticeable tendency to consider diabetes as a somewhat more complex condition than the advocates of the simple pancreatogenic theory admit. In most of these the important part of the pancreas in diabetes is recognized but the part of the other factors is emphasized. Cammidge, in *The Practitioner* for June, 1922, recognizes several types (pancreatic, hepatic, concurrent) of diabetes, some originating in organs other than the pancreas. These have been largely established upon the basis of the "difference-value" of the sugar and total carbohydrates in the blood.

"Having established by animal experiments and observations on cases of pancreatitis in the human subject that a relation of this description between the blood-sugar and difference-value curves is characteristic of disturbance of the functions of the pancreas, it seemed likely that by the same method it might be possible to ascertain whether diabetes was, or was not, invariably due to disease of the pancreas. As it happened, several of the earlier cases gave typical pancreatic, or opposed, curves, but as the investigation progressed it became evident that this type of curve was by no means constant and two others were subsequently differentiated. . . . Although the number of cases so far investigated is too small to allow of reliable conclusions being drawn as to the relative frequency of the various types, there is, I think, sufficient evidence to make it highly probable that clinical diabetes is not a single simple pathological entity, but a symptom complex, which may develop along at least three lines, of which disturbances in the functions of the pancreas is one."

Falta recognizes diabetes with gross lesions of the pancreas, par-

² *Boston Medical and Surgical Journal*, June 22, 1922.

ticularly the islet tissue, in which this defect is alone sufficient to explain the condition. This he calls "pancreatogenic" diabetes. There are, however, more frequently encountered types in which nervous manifestations are characteristic. He describes two such types, differing in the character of the nervous symptoms. In the first type, the psychic and nervous symptoms predominate and may characterize the condition for years. In this type, Falta suggests that it might be possible to demonstrate a constant hyperexcitability of a certain part of the sympathetic system, as a glycosuria of the adrenal type seems to always be present, attended by the other signs of adrenal action (vascular and cardiac signs.) The second nervous type is characterized by the predominance of the alimentary factor. The psychic factor is not in evidence and there are no manifestations of sympathetic hyperexcitability until late in the course of the disease. In the later stages of both types there is evident the psychic and nervous element.

Falta suggests that there may be a congenital weakness of the embryonic groundwork (*anlage*) of the islet tissue, which makes the adult islands more susceptible to injury — infection, intoxication, etc. — and this would explain the rapidly progressive grave diabetes in young children, but in the usual type of diabetes the pancreas is probably only relatively weak — as compared to the activity of the chromaffin tissue, due to a strong excitation of the nervous centers regulating this tissue. When the pancreas is entirely normal the balance between the pancreas and adrenal action is maintained. In the nervous types of diabetes, the hyperexcitability arises *primarily*, and in the pure pancreatogenic form it occurs *secondarily*. The causes of the abnormal excitation of the nervous system are unknown.

Falta does not regard experimental diabetes and clinical diabetes as identical and, therefore, looks further than the pancreas for an explanation of the cause. He says:

"In experimental pancreatic diabetes only the pancreas is absent, all the rest of the manifestations are secondary; in general human diabetes there exists, however, a disease of the whole apparatus regulating sugar metabolism (nervous centers in the medulla and brain stem, connecting paths, pancreas and chromaffin tissue), with insufficiency but not complete absence of one part and more or less independent hyperexcitability in the other parts."

Langdon Brown¹ regards diabetes as a clinical complex, the result of increased metabolism, a mechanism acting largely through the sympathetic and the endocrine glands. He stresses the importance of the sympathetic and the parasympathetic in the vegetative processes and in mobilization of blood sugar. Diabetes is a result of disturbance of this sympathetic-parasympathetic-endocrine system, in which the mobilization of carbohydrates is but one phase. The importance he assigns to these elements is expressed in the following:

"Diabetes is, then a sign of exaggerated metabolism, evoked through the sympathetic and the associated endocrine

¹ *British Medical Journal*, August 7, 1920.

glands, which first asserts itself in relation to the most abundant food material, but as it advances expresses itself in relation to all."

The question of the identity of experimental and clinical diabetes is important. If it can be shown that they are identical, many factors now regarded as causative by some authors will have to be related to diabetes in a less important role. By removal of only a part of the pancreas it has been possible, however, to produce experimental diabetes resembling in every essential respect the clinical variety, and the probability of their identity becomes greater.

Despite the fact that all opinions recognize the importance of the pancreas, it is remarkable that demonstrable histologic lesions of the pancreas have not been found in many cases of true diabetes and many cases in which well marked pathologic changes in the pancreas are found *post mortem* were not diabetic in life. However, it is probably true, as stated by Allen, that "the literature of diabetic pathology contains an overwhelming preponderance of cases of definite inflammatory changes in the pancreas." The site of the disturbance is generally held to be the islands of Langerhans and in many cases definite structural changes may be demonstrated, while the remaining pancreas tissue is unaffected (see page 11).

The nature of the internal secretion of the pancreas is unknown. It is, however, indispensable to the proper utilization of carbohydrates and is held by many to produce an inhibitory effect on the release of sugar into the blood. It appears to be opposed to the action of adrenalin and is related in action (although less definitely) to the thyroid and the pituitary. The action of these ductless glands—thyroid, pituitary, adrenals and islands of Langerhans—is undoubted in exercising an influence on carbohydrate metabolism in general, and various studies suggest their involvement in diabetes. Many authors, including Falta, have described an interrelationship between these endocrine organs and their involvement in the carbohydrate disturbance of diabetes and, although the pancreas is the central organ in the process, the other organs are important in regulating the metabolism, all acting in concert. Allen, however, does not hold such views and states that "No proof of direct participation of any other organ in the etiology has been determined."

Varying views as to the nature of the internal secretion of the pancreas are held, but most researches have ended with ascertaining certain effects resulting from its absence rather than determining the definite part taken by it in carbohydrate metabolism. Falta conceives it as follows:

"The pancreatic hormone is an exquisitely assimilatory hormone and governs glycogenesis in the liver and muscles. In the light grades of insufficiency the disturbance in carbohydrate metabolism occurs only when there are instituted great demands on glycogenesis in the liver (alimentary overloading of carbohydrates). In the severe disturbance, there occurs, in addition to the disturbance in anabolism, marked increase in the catabolic processes: therefore, a faulty decomposition of the higher and lower fatty acids (ketonuria)."

Schäfer holds a view similar to that stated above, which attributes an inhibitory function, and the result of many observations and researches up to the present time is to support the theory that the internal secretion of the islands of Langerhans exerts an inhibitory influence on carbohydrate metabolism, which in general is opposed to the secretion of the adrenal medulla. It may perhaps equally be held that it has a specific selective action on the glucose molecule in preparing it for combustion by the cells and in making its oxidation by the cells possible. That it has both functions is not improbable.

CARBOHYDRATE METABOLISM

As the outstanding characteristic of diabetes, irrespective of all theories of causation, is decreased capacity for the utilization of carbohydrates, some of the chief facts of carbohydrate metabolism may be briefly presented, preliminary to a discussion of diabetes pathology. The carbohydrates are the great energy producers of the animal organism and normally, by reason of their ease of combustion, meet the greater part of the energy requirements of the body. The carbohydrates of the food are absorbed into the blood as monosaccharids, principally as dextrose (glucose) and perhaps, also, in some small amount, as levulose and galactose. These sugars form one (and the most important) source of the glycogen which is stored in the liver and large muscles (about 50% in each) and liberated again as dextrose for physiological oxidation in amounts requisite for the changing needs of the organism. In addition to the carbohydrates, protein foods in the process of splitting into the simpler amino bodies also give rise to glycogen, and the glycerol resulting from the splitting of fats is converted into glucose. It is probable that all the carbohydrates, regardless of their source, endogenous or exogenous, and irrespective of their character, are first converted in the process of assimilation to dextrose and are then converted into glycogen for storage and reconverted into dextrose for the physiological oxidations. Even the closely related monosaccharids such as levulose are first transformed into glycogen and then to dextrose, for it is apparently only dextrose that is available in any appreciable extent for these oxidations in the tissue cells. It is well known that diabetics may continue to excrete glucose long after the withdrawal of carbohydrates and such amino acids (protein "building stones") as glycine, alanine, aspartic and glutaminic acids have definitely increased glucose excretion in the urine. In fasting diabetics, when all food is withdrawn, the tissues are drawn upon and by the resulting catabolistic process the body protein, glycogen and fat yield glucose which continues to be excreted in the urine, just as glucose from exogenous sources, and in amounts of from 50 to 100 grams per day in the case of an individual of ordinary body weight.

The liver is a temporary storehouse for the storage of sugar absorbed in quantities from the intestine and provides a means for the regulated release of dextrose and the maintenance of a balance for the organism's needs. Glycogen is transformed into dextrose through the agency of the powerful diastatic enzyme, glycogenase, which is found in the liver, blood and lymph. The mechanism of the action of glycogenase has

never been clear but it is very important, as an explanation of its action would explain, perhaps, hyperglycemia, glycosuria and in large measure the diabetic process. Most theories have largely assumed some inhibition of the action of glycogenase in the liver which as a balanced reaction may result in the release of sugar as this balance is disturbed. As sugar is consumed in the body, more glycogen is converted into sugar and normally the blood sugar content remains constant within narrow limits (between 0.1 to 0.2 per cent.). The regulation of this liver action may be through nervous pathways or, as is now the prevailing opinion, through hormone control. In either case, the effect probably is that of removing or lessening the inhibitory agent to glycogenase or a setting free of glycogen from some liver cell combination, so that the glycogenase is free to act upon it.

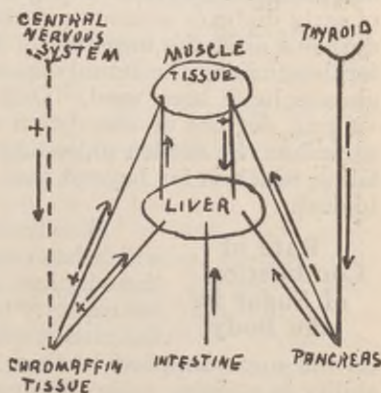
Endocrine Glands Associated with Pancreas in Sugar Metabolism

Since the experiments of von Mering and Minckowski, the pancreas is universally recognized as the central factor in carbohydrate metabolism. The explanation of the method by which this influence is exerted and the part of the other endocrine glands, principally the adrenals, thyroid and pituitary, remains to be explained. The influence of the thyroid is undoubted and in hyperfunction tends to lower carbohydrate tolerance and produce hyperglycemia and glycosuria after the ingestion of smaller amounts of sugar than usual — after 100 grams of glucose. Hypothyroidism, on the other hand, results in raising tolerance. The pituitary has an action resembling that of thyroid in lowering carbohydrate tolerance in states of excessive function. The adrenal glands also exert an important action in mobilizing sugar, and glycosuria may result through their stimulation or after injections of adrenalin. The action of all these appears to be of opposite kind to that of the pancreas and may be affected through their known action on the vegetative nervous system.

The following diagram, a modification by Falta of von Noorden's scheme, is helpful in understanding what is known of their relations (except the hypophysis).

The line from the intestine relates to the impetus received from the intestine to the liver for the storage of sugar (from absorbed food).

"The line of dashes represents nerve paths; the solid lines represent blood paths. The arrows show the direction of the excitation; the sign + or - behind them means whether the stimulus transmitted by the respective path increases or diminishes the specific activity of the organ in question, whether it acts assimilatorily or dissimilatorily."¹



¹"The Ductless Glandular Diseases," Falta.

Effects through Vegetative Nervous System and Adrenals

The sugar puncture (*piqûre*) of Claude Bernard, a puncture of the medulla between the 10th cranial and auditory nerves resulting in a glycosuria, was followed by much research, and the subsequent observation that stimulation of the great splanchnic nerve gave similar results led to the conclusion that there was a "sugar regulating center" in the medulla; the fibers of the splanchnic originating there and passing to the liver regulate the rate at which glycogen is transformed into dextrose in the liver. Another view, also assuming a nervous control in some part, involves the adrenals. This view holds that the adrenals are stimulated reflexly through the vegetative (great splanchnic nerve) nervous system and that epinephrin thus thrown into the circulation acts on the liver cells, causing a conversion of glycogen to sugar (overcoming a theoretical inhibitory action of the internal secretion of the pancreas). Support for this theory is found in the fact that after ablation of the adrenals neither *piqûre* nor splanchnic stimulation gives rise to glycosuria and that the action of epinephrin pharmacologically undoubtedly causes glycosuria. Moreover, such a mechanism would go far to explain the glycosuria arising during emotional states and nervous conditions. The facts in favor of a nervous or a nervous-endocrine mechanism in the regulation of sugar combustion are here presented, as it appears that in some degree they are constant factors in the process, but that they are minor and of less importance than the endocrine (pancreatic hormone) there seems no doubt. The pancreatic hormone, the thyroid, pituitary and adrenal hormones, and the vegetative nervous system appear to form a system for the control of carbohydrate metabolism that is as yet not well understood.

PATHOLOGY OF DIABETES

The normal individual has a high capacity for the metabolism of carbohydrates and excessive quantities are ordinarily oxidized without developing glycosuria. The amount which can be assimilated without leakage into the urine is the "assimilation limit" and ranges from 200 to 300 grams of glucose. The glucose tolerance test used in the diagnosis of early diabetes assumes a diabetes or a potential diabetes if glycosuria develops after the ingestion of 100 grams of glucose. Various methods for determining the actual capacity of the organism for the utilization of glucose have been used. Oral administration involves errors due to varying degrees of absorption and digestive disturbances themselves, as well as the sudden unloading of an amount of glucose into the circulation which is far beyond that with which the organism normally has to deal.

Rate of Combustion of Sugar in the Body

Woodyatt, Sansum and Wilder devised a method which has contributed more to our understanding of these limits than all others. These observers conceive the capacity for sugar utilization to be dependent upon the rate at which the cells are able to function in using up the sugar supplied to them. Therefore, to describe the functional ability in utilizing sugar, it is necessary to state both the total quantity of sugar and the weight per unit of time in which it is supplied. Their

procedure involved the use of a pump for the continuous control of the intravenous injection of sugar, by which means it was possible to determine the limits of the ability of the organism to burn sugar thus introduced. They found that if the sugar is supplied at the rate of .8 to .9 grams per kilogram of body weight per hour, it is burned by the organism and without any loss into the urine. When .9 to 2 grams per hour are supplied, glycosuria appears, and above 2 grams per hour a larger percentage of the glucose in excess of this amount is excreted in the urine.

It is characteristic of diabetes that the liver rapidly loses its glycogen store and carbohydrate feeding is useless in preventing this. The percentage of blood sugar rises and glycosuria develops (ordinarily, glycosuria develops when the blood sugar concentration reaches .17 gm. per cent.). The explanation of hyperglycemia and glycosuria will, therefore, largely extend our knowledge of diabetes, even though we agree with Abderhalden:

"Up to the present, the most pronounced symptom, that of glycosuria, has dominated the entire investigation of problems concerning diabetes, and it is very probable that this is the reason why the disease is, as a whole, so little understood."

A fuller understanding of the glycosuric process, however, would materially aid us, even if it did not inform us as to the ultimate (nervous?) causes. Theories as to the cause include defects in the storage mechanism, abnormal production of sugar and inability of the tissue cells to utilize sugar, thereby permitting its accumulation in the blood, and the theory of increased renal permeability. It is evident that in the diabetic process most of the phenomena of diabetes would be susceptible of more or less complete explanation by any of these defects. It has been shown that increased rate of supply of glucose in normal animals within certain limits increases the capacity for utilization and that only when these limits have been exceeded does sugar leak into the urine. Until these limits have been reached, the increased utilization prevents escape into the urine, even though the amounts are excessive, but when these limits have been exceeded the sugar rapidly escapes and is eliminated almost quantitatively. In normal healthy animals this power of increased utilization makes any excessive alimentary glycosuria almost impossible, for increased supply is met by increased utilization.

**Diabetes
a Condition
of Impaired
Sugar
Utilization**

It becomes evident, therefore, that the failure of the cells to utilize the sugar in which they are bathed and which eventually reaches a high concentration, is the fundamental reason for the hyperglycemia and the subsequent glycosuria. To account for a glycosuria from endogenous sources would be to assume that these increased utilization limits had been exceeded, with a consequent increased metabolic rate and a high respiratory quotient. It is well known that large numbers of cases of advanced diabetes, with heavy glycosuria, are characterized by normal or low respiratory quotient and no increase in the metabolic rate. That increased utilization does not take place is evidenced further by failure to obtain increased respiratory quotient by administration of glucose to diabetic animals. The diabetic process, therefore, is characterized fundamentally by an inability of the tissues to utilize glucose.

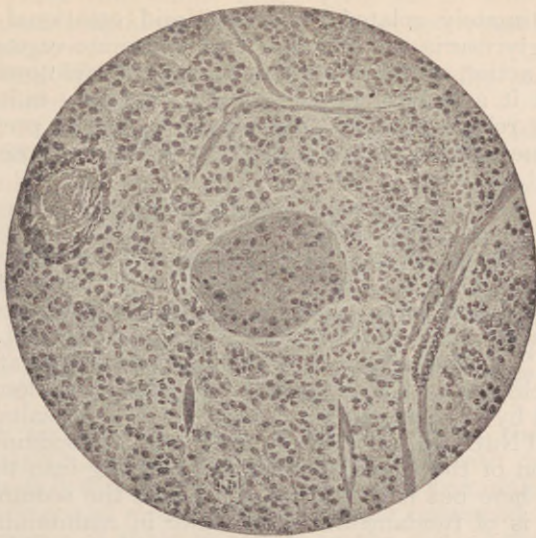
Starling and Knowlton endeavored to ascertain the rate of sugar combustion in the isolated heart of experimental animals and seemed to show that a normal heart, perfused with normal blood, consumes about 4 milligrams per hour for each gram of heart muscle, whereas the consumption of sugar in the heart of a diabetic dog was minimal or absent. Subsequent investigation of this data by Starling and Patterson revealed errors which make the conclusions unreliable, due to the fact that the heart preparations may either store away sugar as glycogen or may at the time of the experiment contain considerable glycogen, which may be burned without first using the sugar of the perfusion fluid.

Nature and Source of the Pancreatic Hormone

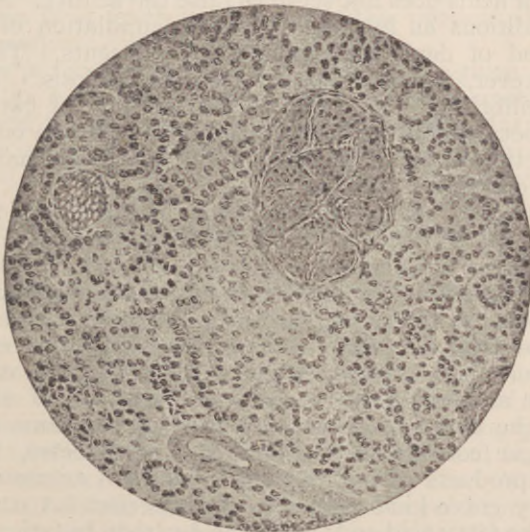
The immediate cause of the faulty utilization is the disease (functional or anatomic) of the islands of Langerhans of the pancreas. The islands were suggested as the seat of the internal secretion of the pancreas by Laguesse in 1893, and Opie has prominently sponsored the island origin of the antidiabetic internal secretion in this country. The precise part played by the pancreatic hormone is uncertain and may be either in regulating the conversion of glycogen to dextrose or in the catabolic processes whereby the sugar is consumed in the tissues. Some investigators hold the opinion that it has both these functions. While innumerable and conflicting hypotheses have appeared, our knowledge does not permit us to generalize further than the statement on page 6. Strong support for the theory of the islets as the seat of the internal secretion rather than the acinous tissue is given by the experiments of Banting and Best (see page 24). They seem to have proved quite conclusively that it is only from islet substance that extracts efficient in effecting modification of the carbohydrate metabolism can be obtained.

In diabetics there are found various pathologic states of the islands and in experimental animals the usual result following pancreatitis, artificially produced and accompanied by diabetes, is fibrosis and atrophy. Hydropic degeneration of the islands, also, is found in many cases of diabetes, although this is probably a result rather than a cause. There is no agreement among pathologists as to the significance or constancy of the several types of lesions described in the pancreas of diabetes. Diabetes has undoubtedly occurred in cases in which there was no demonstrable lesion in the pancreas. Whether these cases can be explained as functional deficiency without the development of structural defect and due to defects in the nervous control through the "sugar control center" or through defects of the associated glands cannot be answered positively.

Summary: Reviewing briefly some of the data discussed in relation to diabetes etiology and pathology we may summarize: Diabetes mellitus is a disease characterized fundamentally by decreased capacity of the organism for the utilization of glucose. The immediate cause of this defect is functional or anatomic disease of the islands of Langerhans of the pancreas, resulting in deficiency of its internal secretion. The more remote, or primary, causes may be in the associated endocrine glands — pituitary, thyroid apparatus or adrenals — and the vegetative nervous system with which the functional activity of these



Section from normal human pancreas, showing normal island of Langerhans.



Section from pancreas of diabetic subject. Island of Langerhans surrounded by sclerotic capsule and showing sclerotic and degenerative changes.

Specimens prepared especially for this work.

glands is intimately related. Nervous and emotional disturbances resulting in glycosuria act through this endocrine-vegetative system. The mode of action of the pancreatic hormone is unknown but there is evidence that it acts both in exerting an inhibitory influence on glycogenolysis or release of sugar from the liver, and in preparing for, or in some manner aiding in, the utilization of the dextrose molecule by the tissues.

ACIDOSIS OR KETOSIS

One of the danger points in the treatment of diabetes is the development of acidosis, always a grave complication and one which all treatment attempts to prevent. Acidosis is a general term descriptive of a disturbed relation between the acid and basic elements of the blood, in which the H^+ ion concentration is increased relatively at the expense of the basic elements. The remarkably constant reaction of the blood is maintained by the peculiar reaction of the "buffer salts", principally NaH_2PO_4 and $NaHCO_3$, acid sodium phosphate and sodium bicarbonate. No description of the chemical equilibria entering into these reactions can be given here but it should be noted that the sodium bicarbonate in the blood is of fundamental importance in maintaining the H^+ ion concentration requisite for health through the equilibrium $H_2CO_3 : NaHCO_3$, in which the H^+ ion concentration is constant. So long as the $NaHCO_3$, the "alkaline reserve," is present in sufficient concentration, the addition of acids does not serve to raise the acidity. Acidosis occurs in many conditions as a result of the accumulation of various acid substances and of depletion of the basic elements. The acidosis of diabetes, however, is but a special form of acidosis. The disturbed acid-base equilibrium is here due to the addition of two acids to the body fluids, beta-oxybutyric and aceto-acetic (acetone bodies), acetone and aceto-acetic having a ketone group, hence the name sometimes given to the condition — ketosis.

The presence of these acids, therefore, is the condition with which the physician has to deal in the acidosis developing during the course of diabetes. These acids are formed as a result of imperfect combustion of fat, for the complete combustion of which an adequate quantity of carbohydrates must be burned at the same time. The proteins also give rise to substances, which it has been shown are converted into substantial quantities of these acids. Apparently the easily oxidized carbohydrates are necessary to complete oxidation of the fats — the oxidation of the two substances proceeding at the same time. In the failure of sugar combustion characteristic of diabetes, therefore, the intermediate products of imperfect fat oxidation accumulate and acidosis of a very grave kind develops. In imperfect fat combustion, the oxidation of the fatty acid ends when the 4-carbon butyric acid is formed — $CH_3CH_2CH_2COOH$, no further oxidizing off of carbon atoms taking place. Further oxidation results in beta-oxybutyric acid, $CH_3CHOHCH_2COOH$, and aceto-acetic acid, CH_3COCH_2COOH , and acetone, CH_3COCH_3 (the latter probably unimportant).

Not only are the carbohydrates themselves effective in preventing the formation of these substances but protein as well, though in much

less degree. Those compounds which give rise to aceto-acetic acid are called ketogenic substances. Those which are converted into dextrose are antiketogenic.

Hubbard and Wright, as a result of their studies on acetonuria, reached the following conclusions¹:

"(1) That the mechanism which controls the formation of increased amounts of the acetone bodies can be regarded as a molecular reaction or balance between ketogenic substances such as the fatty acids and antiketogenic substances such as glucose; (2) that protein figures as an antiketogenic compound only to the extent of the glucose which it can yield in the organism; (3) that glycerol, when fed as a part of the fat molecule, figures as an antiketogenic compound only to the extent to which it forms glucose in the organism; and (4) probably that glycerol so fed does figure as an antiketogenic compound to the extent to which glycerol itself can yield glucose."

Their work and that of Shaffer is based upon the thesis that the intermediary product, aceto-acetic acid, is burned with difficulty but that on combination with dextrose, or one of the degradation products of dextrose, a compound results which is readily consumed.

The importance of these principles to the diet of the diabetic is at once apparent, as it becomes imperative to allow sufficient carbohydrates (antiketogenic substances) in the food to carry on the combustion of fats beyond the acid-forming stages. It is to be remembered also, that protein is of much less value for this purpose than the carbohydrates themselves. Woodyatt says:²

"There is for any given individual at any given time, a definite ratio between the quantity of glucose oxidizing in the body and the maximum quantity of ketogenic fatty acids that can be oxidized in the same time without the appearance of abnormal amounts of the acetone bodies. In other words, the quantity of oxidizing glucose fixes an upper limit to the quantity of ketogenic fatty acid that can be completely oxidized at the same time."

Carbohydrates should be given in the full amounts permitted by the degree of tolerance in the individual case, so that the urine shows no leakage. Acidosis under such treatment is not likely to result.

"It follows from the foregoing that the rationale of dietetic management in diabetes is to bring the quantity of glucose entering the metabolism from all sources below the quantity that can be utilized without abnormal waste; and to adjust the supply of fatty acids in relationship to the quantity of glucose so that in the mixture of food stuffs oxidizing in the body, the ratio of the ketogenic fatty acids to glucose shall not exceed limits compatible with freedom from ketonuria. When, as, and if, under these conditions of relative rest for

¹R. S. Hubbard and F. R. Wright, *The Journal of Biological Chemistry*, February, 1922.

²R. T. Woodyatt, *Archives of Internal Medicine*, August, 1921.

the pancreas, the glucose using function improves, then the food supply may be increased gradually in so far as this can be done without disturbing the above relations."¹

The regulation and maintenance of the proper ratio between these two classes of substance has been called the "ketogenic-antiketogenic balance." Various calculations have been made to determine the numerical value of this ratio, which range from 4 gm. fat to 1 gm. carbohydrate, to 1 to 1½ gm. fat to 1 of carbohydrate. These refer to the amounts of each which insure complete oxidation of the fat. Woodyatt says: "It would seem that for clinical purposes one will make no gross error if it is assumed that the ratio of higher fatty acids to glucose, which if exceeded will lead to acidosis, is likely to be close to 1.5 to 1 (in grams). This refers to the materials actually catabolized and to the diet only under stated conditions."

TREATMENT

As diabetes is a condition in which the fundamental defect lies in failure to utilize one of the principal foodstuffs—glucose—an intermediary product not only of carbohydrate but of protein and fat as well, it becomes evident why the diet has always demanded so much attention in treatment. The diabetic organism is apparently able to use a certain quantity of glucose as well as the non-diabetic, but when the lowered limits of utilization have been exceeded the percentage of blood sugar rises and, having exceeded a certain value, is excreted in the urine. The diabetic diet, then, must be so adjusted that the quantity of glucose is brought within the limits of utilization, sufficient energy is produced, acidosis avoided, and the nitrogen equilibrium maintained. The ratio of foodstuffs in the diabetic diet varies greatly from the diet of healthy individuals. In health, more than half the calories are derived from the easily burned carbohydrates, whereas, with the lowered capacity for glucose in the diabetic, the caloric loss from this source must be made up from the other classes of foods, principally the fats (with their nine calories per gram as against four calories of protein).

The education of the patient is important and should include as much information on the practical subject of diet and cookery as is possible, as well as instructions in the methods of making a simple test for glucose in the urine. The patient must also realize that, with the reduction of his energy-producing powers, a readjustment in his habits of life is necessary and that a less vigorous, less active life is of the utmost importance.

Untreated diabetes becomes progressively worse, whereas with proper treatment, even in high grade diabetes, it is usually possible to prolong life and permit of a fairly normal existence with comparative freedom from the disturbing subjective symptoms. In milder diabetes, the results are vastly better and not only is the diabetes not progressive but definite improvement in the direction of a return to normal may be accomplished. Exercise within the limits of the patient's capacity is desirable. A systematic and limited use of the muscles of the body

¹R. T. Woodyatt, *Archives of Internal Medicine*, August, 1921.

apparently aids metabolism and contributes to the general well-being. The large muscles, storehouses of glycogen, are given work which uses up glycogen, reduces blood sugar, and may increase in some degree the sugar tolerance. This is particularly important for the obese diabetic. Advanced diabetes is not so well treated by exercise, but for the maintenance of general health some regulated exercise is necessary in all but the most urgent cases. Exercise, however, should always be regulated so that the strength of the patient is not overtaxed and should be increased gradually, the guide being the subjective and objective symptoms in the patient. The cultivation of a tranquil, placid state of mind and mental repose is important and the relation of the psychic condition and the nervous system to diabetes has been described (see page 4).

INDIRECT THERAPY

Dietetic Treatment

Despite the extensive research which has been carried on all over the world, there is no accepted and generally used system of dietetic treatment. Numerous empirical systems have appeared and have proved of value in many cases in which they have been used (milk, potato, oatmeal, rice cures), but a rational system, applicable to all classes of diabetes and subject to calculated control to meet various conditions and with the various foodstuffs, has yet to become universally accepted and adopted. The regulation of the diet by the system and with the formulæ devised by Woodyatt appears to meet such requirements and will be described. Before this, however, the older and more conventional, yet very efficient, methods for diet control will be discussed.

The basic, underlying principle of dietetic diabetic treatment is that of undernutrition, which requires that in addition to restriction of certain kinds of food (carbohydrate) the total quantity shall be reduced. This principle will remain an enduring tribute to the American investigator, Frederick M. Allen, and stands as the most substantial contribution to the modern dietetic treatment of diabetes. It seems probable that the success of the various empirical systems of treatment which have been found of value may have been largely due to their conformity to this principle.

Modern research on diabetes diets takes into account the endogenous sources of food and the character of the metabolism and nutrition of the body during fasting. The dangers of the old high protein diet are generally recognized. Protein yields not only a large percentage of glucose (58%) but it also yields a high percentage of acids capable of causing acidosis. The increased metabolism and heat production of diabetes are also due to the stimulation of the protein — the "specific dynamic action" of Rubner. The increased nitrogen content of the urine observed under the older methods of treatment was due "to the large nitrogen content of the diabetic's diet, either because of his own tendency to replace with protein the carbohydrate calories lost in the urine or because of the very high protein content of the contemporary diabetic diet."¹

¹Marsh, Newburgh and Holly, *Archives of Internal Medicine*, January 16, 1922, p. 115.

It has been observed that the urine of some diabetics cannot be made sugar-free by fasting and this appears to be the case in lean diabetics or in those in which for some reason body fat is not burned, who metabolize their body protein with the consequent production of more glucose than can be burned and with leakage into the urine. It is evident, therefore, that it is the protein which must be limited — to quantities sufficient to maintain nitrogen equilibrium — and the carbohydrates given in quantities up to the limits of tolerance.

The diabetic diet is a restricted diet and should meet the caloric requirement of the patient but not greatly exceed it. From 25 to 35 calories for each kilogram (2 1/5 lbs.) of body weight is perhaps sufficient for the majority of cases of diabetes. The undernutrition principle is devised to give rest to an active secreting tissue (islands of Langerhans), the progressive deterioration of which is conceived by Allen to be due to diets which make too great demands on its functional capacity, so that restriction of the carbohydrates (within the capacity for utilization) is of the first importance. The diet is first adjusted so as to make the urine sugar free. Various test diets have been arranged and may be used for the purpose. A diet composed of one gram of carbohydrate and one gram of protein for each kilogram (2 1/5 lbs.) of body weight will usually give a sugar-free urine and a normal blood sugar value within a few days. For the maintenance diet, the protein should amount to about one gram or a gram and a half for each kilo of weight. The carbohydrates should be in amounts less than the limits of tolerance (determined by the appearance of sugar in the urine) and the fats should be kept moderately low. The additional food should be added gradually to the diet in daily additions of about 5 grams until the maintenance diet is reached — carbohydrates under the quantity sufficient to give glycosuria, protein in amounts to establish a protein balance, and fats in moderate quantities to give increased calories.

Some of the measures included in the treatment usually referred to as the "Allen treatment" may be given as of proved practical value and forming good practice today. The patient is subjected to a preliminary fast (from one day to a week), during which the urine becomes sugar free. After an interval of 24 hours, during which no sugar has appeared in the urine, the first food is given. In some instances carbohydrates (as green vegetables), in increasing amounts of 10 grams daily up to the production of glycosuria, are given and if there is acidosis this is the best plan for relieving it. It may be preferable, however, to give a protein diet (meat, fish, white of eggs, etc.) with bran biscuit, vegetables (boiled in three waters to free from carbohydrates but leaving bulk), agar jelly, etc. The amount of protein varies with the severity of the case — in mild cases 60 grams and in very severe cases 10. In severe cases the protein may be low at first and then worked up to as much as 60 grams. This protein diet is usually given until the blood sugar decreases and there is some loss in body weight, although the patient loses less strength than on any other diet. Carbohydrate is given as the next article of food and may be given before the protein has been added in full quantity. During this time the nitrogen balance of the body is maintained during

the period that is required to reduce the percentage of blood sugar to normal (from a number of days to months).

Maintenance Diet Carbohydrate is now added in as large quantities as possible, yet within the limits of utilization, so as to avoid a return of hyperglycemia. Fat may then be added and may require a reduction of the quantity of carbohydrates. The total protein of the maintenance diet is usually from 60 to 80 grams, or, in the case of children, as much as 2 grams per each kilogram of body weight. The requirements of calories is variable (depending on activity, weight of the patient, etc.) but in general from 25 to 35 calories per kilogram of body weight. Excess of calories is to be avoided, for hyperglycemia may result and compel reduction of the quantity or increased exercise.

Fasting Fasting undoubtedly affords rest to the pancreas with a lowered functional activity and a day's fast at regular intervals may be used as routine treatment. If not complete fasting, greatly reduced diet may be taken at intervals as part of the routine treatment. Food values may be calculated from tables and all foods should be carefully weighed. Calories are computed on the basis of 4 calories for each gram of carbohydrate and 4 for each gram of protein and 9 for each gram of fat. If at any time sugar appears in the urine, fasting may be resorted to until the urine is sugar-free.

The immunity of the diabetic to infection (pyogenic and many others) is markedly lessened and every patient should be instructed as to the danger of injuries and infections of the feet, fingers, etc. The dangers from this source are greatly lessened by maintaining a normal percentage of blood sugar.

TREATMENT OF ACIDOSIS

Immediate changes in the diet, withdrawal of fats, plenty of fluids, enemas and maintenance of the strength of the patient are demanded. Joslin describes his treatment as follows:

"If, despite our efforts, acidosis threatens, the following routine treatment is recommended: (1) Reduce the total metabolism by placing the patient in bed and providing a nurse, to save all needless exertion; (2) Administer abundant liquids — 240 c.c. — each hour in order to promote the excretion of acid bodies; (3) Promote evacuation of the bowels not only to favor digestion but in order to enable, if desired, enemata of salt solution or water to be given in case water is not retained by the mouth; (4) Wash out the stomach in the first stages of treatment, because, frequently, coarse food is retained, which leads to vomiting, and loss of valuable hours; and (5) Administer moderate quantities of carbohydrate — either levulose, which is readily obtained in the form of orange juice, or if this is disliked or for any reason contraindicated, oatmeal gruels and skimmed milk. I have avoided fat largely because it is more apt to upset the digestion of a patient upon the verge of coma, and second because from fat the acid bodies which lead to coma are formed. Recently, evidence has been

submitted that body fat will be consumed if extraneous fat is not given, but at present it appears safe in the presence of threatening acidosis to cling to the above-mentioned plan of treatment, and if the body is to burn fat to let it select its own dose."

Alkalies may be used, although every effort should be made to clear up an acidosis by dietary means before resorting to this therapy, but its administration should not be delayed too long if it is evident that the condition is not under control. Sodium bicarbonate may be given and Allen states that when given by mouth has never seemed dangerous and in some cases has appeared actually life-saving, in doses of from 40 to 100 grains daily. Bicarbonate may also be given by rectum (1 or 2 per cent. in physiological salt solution). Alkaline tablets (see page 30) may be administered in a dosage of 2 tablets every hour during the day until an approximate degree of alkalization has been accomplished. For prevention of acidosis or administration at intervals in routine treatment this dosage may be greatly lowered. This tablet has a distinct advantage over sodium bicarbonate in that the quantity necessary for alkalization is distinctly less. Alkalies, however, need not be administered as a matter of routine treatment, but occasionally, if indications of acidosis appear, several days' treatment may prevent its development.

Diet Computation of Woodyatt

Woodyatt¹ has undertaken the problem of diet in diabetes from a different standpoint. He takes into account that the endogenous supply of glucose must be considered as well as the exogenous; that glucose is formed from fats and proteins as well as from carbohydrates; that the total quantity of glucose must be adjusted to the quantity of ketogenic acids formed. The endogenous sources of food are usually ignored in computing diets. The results of the experiments of numerous observers show that a normal man, weighing 50 kilograms, may produce 1,500 calories a day during a fast. He, therefore, catabolizes 75 grams of protein, 125 grams of fat and some carbohydrate from the stored glucose. Now, since it has been shown that "when there was much fat present little protein was consumed; when there was little fat much protein burned; and when there was no fat, protein alone yielded the energy of life" (Lusk), it is evident that fat in the diet may avoid the consumption of the tissue fat and prevent too large catabolism of tissue protein. The experiment quoted from Lusk is given of a dog "which in starvation burned 96 grams of fat. Voit gave 100 grams of fat with the result that it burned 97 grams. The fat ingested simply burned instead of the body fat, but the total amount of protein and fat burned remained the same." From these observations Woodyatt concludes that if a diabetic produces from 1,250 to 1,500 calories by burning from 100 to 120 grams of his body fat during a fast this quantity of fat taken in the food should leave the metabolism in the same state as before. In one case the fat would come from the body tissue and in the other from the food, but the quantity requiring

¹Woodyatt, *Archives of Internal Medicine*, August, 1921.

internal secretions, enzymes and physiological work would be the same. "Fasting or placing on a fat-free, low carbohydrate diet to reduce glucose (in blood and urine) would not seem necessary or rational in the light of these facts." In fasting there is the danger that the body fat may be drawn upon to the extent that the subsequent body protein loss is so great as to weaken vital organs. Recognizing the difficulty of formulating diet instructions in terms of carbohydrate, protein and fat, and considering that these are not the substances which are finally used in the oxidations of the body but are reduced to simpler substances — protein to amino acids and glucose; carbohydrates to glucose; fats to fatty acids, glycerol and glucose — Woodyatt constructed formulæ expressing these ideas which make possible the calculation of a diet in which the glucose presented for oxidation from all sources, endogenous and exogenous, is taken into account and a proper balance of fatty acids to glucose is maintained. Upon the basis of the observations (page 14) that if a ratio of 1.5 to 1 of fats to carbohydrates is not exceeded, acidosis is unlikely to develop, the following formulæ have been constructed. The following tables give the percentage of intermediary products given by 100 grams each of fats, proteins and carbohydrates, and are used as a basis for these formulæ.

G = Glucose.

FA = Higher Fatty Acid

100 gm. carbohydrate during metabolism yields 100 gm. G and 0 gm. FA
 100 gm. protein during metabolism yields 58 gm. G and 46 gm. FA
 100 gm. fat during metabolism yields 10 gm. G and 90 gm. FA

"If C = carbohydrate, P = protein, F = fat, G = glucose and FA = higher fatty acids (plus ketogenic amino-acids expressed in terms of higher fatty acid), we may say — as shown above — that the quantity of glucose which any given combination of foods may introduce into the metabolism is expressed by the equation: (1) $G = C + 0.58P + 0.1F$ and that the quantity of higher fatty acid (and equivalents) may be expressed as (2) $FA = 0.46P + 0.9F$. When the ratio

$\frac{FA}{G}$ exceeds a certain value, ketonuria develops. Assuming that this ratio is 1.5, then $\frac{C + 0.58P + 0.1F}{0.46P + 0.9F} = 1.5$, when the

ratio of fatty acids to glucose is as high as it may be without ketonuria. Simplifying this we obtain $F = 2C + 0.54P$, or simply, (3) $F = 2C + \frac{P}{2}$. If it is agreed that the ratio FA:G

shall not exceed 1.5 and that the relationships expressed in equations 1 and 2 are given, then to estimate the optimal food combination or diet one may use equations 1 and 3. Given the quantity of glucose that the patient can utilize completely, assign this value to G in equation 1. Thus, if 100 gm. is the highest quantity of glucose derived from all sources that the patient can utilize, $100 \text{ gm.} = C + 0.58P + 0.1F$. In order to secure the maximal number of calories, the diet must clearly contain every possible gram of fat (at 9 calories per gram)

that the value of G and the relations expressed in 1 and 3 will permit, and consequently the lowest possible carbohydrate protein fraction (at 4 calories per gram). Also, as between carbohydrate and protein, the protein must be as low as possible and the carbohydrate as high as possible, for 1 gm. carbohydrate yielding 1 gm. glucose and 4 calories provides for the normal oxidation of 1.5 gm. of higher fatty acid. On the other hand, 1 gm. protein having the same caloric value as carbohydrate yields less glucose to support fat combustion and besides this yields acetone itself. If the body weight of the patient be 50 kg. and 1 gm. protein per kg. is selected as a conservative minimum; then P becomes 50 gm. and $F = 2C + \frac{P}{2}$ becomes $F = 2C + 25$. We have already made $G = 100$ gm. Now, the glucose yielded by the 50 gm. protein will be 0.58×50 , or 29 gm., leaving $100 - 29$, or 71 gm., to be distributed between carbohydrate and fat. In other words $C + 0.1 F = 71$. From this we obtain $F = 710 - 10C$. But we also have from the above, $F = 2C + 25$. So $2C + 25 = 710 - 10C$, solving which $C = 57$ gm. (57.08). Substituting this value for C in $F = 2C + 25$ we find $F = 139$ gm. (139.16). Then, the optimal food combination that will fulfill the conditions and relations specified is: carbohydrate, 57 gm.; protein, 50 gm.; fat, 139 gm. = calories, 1,680."

In like manner, the percentages of the foodstuffs may be calculated for any diabetic diet, in which either the protein requirement or the glucose tolerance varies.

Showing Optimal Food Combinations When $G = 100$ Gm.

(In the Equation $G = C + .58 + .1 F$); When FA: $G = 1.5$; and When the Protein is 0, 25, 50, 75 and 100 Gm. (i. e. 0; 1.0; 1.5; and 2.0 Gm. per Kg. for a Body Weight of 50 Kg.).¹

	P	C	F	Calories	Difference in Calories
(1)	*0.000	83.333	166.666	1833.327	76.25 (2) - (1)
(2)	25.000	70.208	152.916	1757.076	76.25 (3) - (2)
(3)	50.000	57.083	139.166	1680.826	76.25 (4) - (3)
(4)	75.000	43.958	125.416	1604.576	76.25 (5) - (4)
(5)	100.000	30.833	111.666	1528.331	

"*No. 1 is hypothetical and could only be considered as the nonprotein fraction of a larger combination."

"High-Fat" Diet of Newburgh and Marsh

In 1920 there appeared a report of a system of dieting which introduced a new principle and appeared to be in conflict with some of the principles which were regarded as axiomatic. This was the high-fat diet of Newburgh and Marsh.² In a report which dealt with a series of seventy-three cases and using what appeared to

¹Woodyatt, *Archives of Internal Medicine*, August, 1921.

²"The Use of a High Fat Diet in the Treatment of Diabetes Mellitus," *Archives of Internal Medicine*, December, 1920, Vol. 26, No. 6.

be an unusually high percentage of fat, they found that acidosis did not develop in any of the series, although the diabetes in most cases was of the severest type. All cases remained sugar free during treatment. In addition to the high percentage of fat in the diet, the protein content was small and so arranged as to contain .66 grams of protein per kilogram of body weight, a quantity which they demonstrated was sufficient to establish nitrogen equilibrium.

"The conditions necessary for the establishment of nitrogen balance at this low level are several. Chief among them is the presence of sufficient total calories in the ingested food; there must be enough fat or carbohydrate in the diet to supply all the body needs for heat and energy, so that the protein may be used only for restoring body tissue. The protein-sparing qualities of carbohydrate and fat were discovered by some of the earliest students of metabolism, and it is well known that carbohydrate is the more efficient of the two in sparing protein, though in a mixed diet fat may replace carbohydrate in isodynamic quantities. In spite of this difference in the effectiveness of the two foodstuffs, the ability of fat to spare protein cannot be doubted."¹

The high fat content of the diet gave a total number of calories which would have been difficult to obtain with carbohydrates in quantities not sufficient to cause glycosuria or with protein, and in the case of some of the younger patients the capacity for work was "astonishing."

Newburgh and Marsh also take into account those principles of metabolism which have been stated, with reference to the efficiency of fats in sparing protein and of their equality with carbohydrates for this purpose; that carbohydrates may not be entirely replaced by fat and that as long as a supply of fat remains in an animal the same quantity of fat will be burned, being drawn from its diet or the supply of body fat. They find from a study of their cases that as the caloric value of the diet is increased by the addition of fats, the protein catabolism is diminished and it is evident that fat is highly efficient as a "protein sparer." If the caloric value of the diet is too low for the energy requirements, the increased nitrogen metabolism may give not only increased nitrogen in the urine but also glycosuria (glucose from protein; in one of their cases the glucose from this source amounted to 20 grams), a condition to be avoided by the addition of more calories. Thus, by lowering the protein diet, the amount of carbohydrates may be increased and by limiting the endogenous protein metabolism further carbohydrate may be added. The addition of fat to the diet accomplishes these ends and maintains nitrogen equilibrium. Newburgh and Marsh, in view of the known facts of protein and carbohydrate metabolism, also suggest the fallacy of fasting:

"These facts show a fallacy of starvation in the treatment of diabetes. During the period of starvation, a subject well supplied with body fat burns this fat, and burns no less than he would if the fat were given him in the diet. This was demon-

¹Newburgh, Marsh and Holly, *Archives of Internal Medicine*, January 16, 1922.

strated by Voit's experiment on a dog, which has already been mentioned. In the case of the fasting lean diabetic, however, who cannot burn glucose, and whose supply of body fat is low, energy and heat are developed almost entirely by the combustion of protein. Destruction of body protein produces glucose exactly as much as does combustion of ingested protein. In the more severe grades of diabetes this is a factor of prime importance. Such patients become sugar free sooner if they are allowed a little carbohydrate and a relatively large amount of fat than they do if starved. . . . The same undesirable production of glucose from body protein occurs to a lesser degree when an under nutrition diet is used in the treatment of diabetes mellitus. If the total calories fed the patient are not sufficient to supply caloric requirement, body protein is broken down and glucose is produced. If an effort is made to supply enough protein in the diet to compensate for this excessive destruction of body protein, the ingested protein is a source of glucose. Just in so far as the carbohydrate burning function of the patient must be used for the combustion of glucose derived from protein, just so much more must his carbohydrate intake be limited. Fat offers the best agent in the diabetic for the sparing of protein, either endogenous or exogenous."¹ Their routine is as follows:

"When a patient enters the clinic, he is placed on a diet containing from 900 to 1,000 calories, of which about 90 gm. is fat, 10 gm. is protein and 14 gm. is carbohydrate. After the patient has been sugar free for one or two weeks, his diet is increased to about 1,400 calories, of which 140 gm. is fat, 28 gm. is protein and from 15 to 20 gm. is carbohydrate. In the cases of small individuals this diet is sufficient for prolonged use, and some of them are discharged with instructions to continue it. For larger persons, after another period of trial, a second increase is made, reaching 1,800 calories, containing 170 gm. of fat, from 30 to 40 gm. of protein, and from 25 to 30 gm. carbohydrate. Further additions up to 2,500 calories may be made to suit individual cases."²

Newburgh and Marsh as a result of their observations in the treatment of seventy-three cases reported in 1920 conclude:

"Patients with severe diabetes, as a class, do not remain sugar free on the usual high protein diet unless the total energy intake is kept so low that incapacity from starvation results. The only satisfactory diet is one which will keep the diabetic sugar free, which will prevent the occurrence of serious acidosis, which will maintain nitrogen balance and which will make it possible for him to resume the ordinary activities of life. With these four points in mind, we studied the effect of a high fat, low protein, low carbohydrate diet in the treatment of diabetes. Our experience with this type of diet in the management of

¹Marsh, Newburgh and Holly, *Archives of Internal Medicine*, January 16, 1922.

seventy-three diabetics has convinced us that it is capable of fulfilling these four specifications."¹

Maignon² in France has also used a "high fat" diet and observes that when fat is eaten by diabetics the effect is to decrease the amount of protein drawn from the tissues and to reduce the nitrogen content of the urine. He prescribes a diet rich in fat and oil, and to guard against acidosis gives sodium bicarbonate concurrently.

DIABETES IN CHILDREN

Diabetes in children has always been recognized as grave. The supposition of Falta (see page 4) relative to a congenital defect of the pancreas is borne out by many of the facts. Morse says:³

"It was formerly supposed that almost all of the cases in childhood were of the severe type, but more recent studies have shown that the two types are about equally common in the beginning, with a greater tendency for the mild to change to the severe than in later life. About two-thirds of my own cases were, however, of the severe type."

The duration of life is probably about three years. Von Noorden gives the average duration of his cases, developing before the seventh year and in which the disease was diagnosed after development into the severe type, as from one and a half to two years. The prognosis is usually grave. Allen states that "The ultimate outcome of youthful diabetes is still uncertain" and von Noorden "With few exceptions, diabetes in childhood knows no cure, no matter how mild it may appear in the beginning and how gradual its development in the first months or even years." Reports of recovery of diabetes in children are, however, not entirely rare. Riesman, at a meeting of the Association of American Physicians at Washington in 1915, described a mild type of diabetes in children, not progressive, which remains either stationary or ends in apparent recovery.

The treatment is the same as in adults but it should be borne in mind that acidosis develops much more readily in children and in view of their greater energy requirements and the importance of carbohydrates in preventing acidosis the rigid restriction of the diet, particularly of the carbohydrates, is dangerous. It would seem that in these cases more than the usual reliance should rest upon the direct substitutive and stimulative effects of pancreas therapy.

DIRECT THERAPY

Pancreas Therapy — A Direct Aid to Impaired Pancreatic Function It is evident from the conception of diabetic pathology that dietetic treatment, no matter how well selected and balanced, simply brings the work of the islands of Langerhans within the limits of their functional capacity and permits of a possible gradual, spontaneous upbuilding of this capacity, but it in no way exercises any specific therapeutic effect in restoring the injured islet tissue. The effective treatment of diabetes, therefore,

¹Newburgh and Marsh, *Archives of Internal Medicine*, December, 1920.

²*Comptes Rendus de la Société de Biologie*, January 21, 1922.

³*Boston Medical and Surgical Journal*, April 10, 1913.

will include measures for rebuilding the diseased insular apparatus and increasing its internal secretion. "Any positive means of augmenting the endocrine pancreatic function, even by a little, would give therapeutic results far surpassing those of the negative plan of sparing the function by diet."¹ Most of the recent research has been devoted to this phase of diabetic treatment. As a defect of an endocrine tissue, the treatment of diabetes follows the general principles of organotherapy in other endocrine diseases. The active principles found in the pancreas are the only known substances that act through the pancreas in substituting for its failing internal secretion and in rebuilding its active secreting tissue. In experimental diabetes it has been shown that if as little as 1/5 to 1/8 the entire gland is left in the animal a mild diabetes develops; if a lesser amount is left a rapidly fatal type ensues; and if a larger amount is left it is sufficient to prevent the appearance of diabetes. The small proportion of pancreas sufficient to carry on the normal carbohydrate metabolism suggests that a relatively small impetus from pancreas therapy in raising the functional capacity of the islet tissue would be sufficient to change a case from diabetic to non-diabetic, *i. e.*, to prevent glycosuria and enable the patient to metabolize a normal quantity of carbohydrate food. Actually this has been found to be the case.

The investigations of McLeod, Banting and Best,² using a specially prepared pancreas preparation, have brought the attention of the entire profession to the remarkable results of pancreas therapy. Their conclusions are that:

1. Blood sugar can be markedly reduced, even to the normal value;
2. Glycosuria can be abolished;
3. The acetone bodies can be made to disappear from the urine;
4. The respiratory quotient shows evidence of increased utilization of carbohydrates;
5. Definite improvement is observed in the general condition of these patients and in addition the patients themselves report a subjective sense of well-being and increased vigor for a period following the administration of these preparations.

Berkeley³ also, using a pancreas extract of his own preparation, found it of distinct value in diabetes. In a long series of blood tests on patients, the extract was found to cause pronounced blood sugar fall in 82 per cent. of the cases observed.

No pancreas preparation, however, has received as extensive clinical trial as Trypsogen. Its use has extended over a long period of years and the reports of its use show that it aids in the utilization of sugar by the body, depresses a relative adrenal hyperfunction, lessens polyuria, decreases glycosuria and often causes its entire disappearance, aids in reestablishing normal carbohydrate metabolism and exerts a remarkable

¹F. M. Allen, *American Journal of the Medical Sciences*, December, 1920.

²F. G. Banting and C. H. Best, *Journal of Laboratory and Clinical Medicine*, February, 1922, and May, 1922.

³F. G. Banting, C. H. Best, J. B. Collip, W. R. Campbell and A. A. Fletcher, *Canadian Medical Association Journal*, March, 1922.

⁴*American Medicine*, June, 1922.

action in improving the subjective symptoms of diabetes. As a consequence of the action of Trypsogen in augmenting the internal secretion of the pancreas and in improving sugar utilization, it has been found that the necessary dietary restrictions are less rigid in diabetes treated with Trypsogen and that the tolerance for carbohydrates is raised more rapidly. Trypsogen has been used for a period sufficiently long to warrant the conclusion that it is a dependable and necessary part of the routine treatment of diabetes mellitus.

SUMMARY OF FOREGOING PRINCIPLES OF DIABETIC TREATMENT

1. Determination of the quantity of glucose that can be utilized without waste and adjustment of the diet below this quantity, effecting a cessation of glycosuria and bringing the blood sugar to an approximately normal figure.

2. By means of weighed and calculated quantities of fat, carbohydrate and protein, adjust the diet to meet the caloric requirements and establish nitrogen equilibrium.

3. Adjust the ratio of fatty acids (from fats and proteins) to glucose to create a favorable ketogenic balance, in order to prevent acidosis.

4. Avoid a diet too high in either fats or proteins, for fat yields in metabolism 90% of fatty acids capable of causing acidosis, and protein yields 58% of glucose capable of causing a carbohydrate excess, with glycosuria and hyperglycemia, as well as 46% (calculated as ketogenic acids) of fatty acids capable of causing acidosis. Newburgh and Marsh, although using higher fat percentages than were formerly thought possible, recognize the necessity of adequate carbohydrate diets.

"While a partial replacement by fat of carbohydrate in a low protein diet will not affect the protein metabolism, complete withdrawal of carbohydrate and substitution of fat will not permit the establishment of nitrogen balance at low levels. Fat alone will not decrease the amount of nitrogen found in the urine of a fasting animal. It is generally believed that fat in a low protein diet loses part of its effectiveness when the carbohydrate calories fall below 10 per cent. of the total calories."¹

5. Instruct the patient in the principles of diet, methods of weighing food, making reports for the physician, conserving his energy and the technic of urinalysis, an explanation of the dangers of infections from small wounds, the necessity for regulated exercise and mental repose.

6. Any glycosuria, particularly if there is a tendency to persist, should be regarded as diabetes.

7. Meet any indications of impending acidosis promptly. The work of Newburgh and Marsh has demonstrated the value and safety of larger quantities of fat than has hitherto seemed wise, but it would appear good practice in all cases which show a tendency to acidosis to make the fat intake at least as low as those values calculated by Woodyatt.

¹Marsh, Newburgh and Holly, *Archives of Internal Medicine*, January 16, 1922.

8. Fasting may prove of value in rendering the urine sugar-free, preliminary to the determination of glucose tolerance or as a part of routine treatment. It is safer, however, in the practice of experts and with observance of the principles of diet described herein is probably necessary in general practice only rarely.

9. Routine treatment with Trypsogen. The desirability of direct treatment is now generally recognized and Trypsogen furnishes a means of directly affording aid to the impaired function of the pancreas, and aids in rebuilding and restoring to a normal condition.

DIABETES IN GENERAL PRACTICE

Many of the methods of the expert, in laboratory analyses and calculations of food values, are not possible for the general practitioner and the majority of diabetics are necessarily treated in accordance with general principles rather than by carefully calculated dietaries. In following out those general principles which are accepted as sound, the physician may bear in mind the following:

1. The urine should be made sugar-free and the diet adjusted so that it will remain so, but it should be remembered that it is not *sugar per se* that is harmful to diabetics but the inability to utilize it.

2. "The fasting procedure is applied with safety only in the hands of the expert." At a discussion of the Association of American Physicians, May 9-11, 1916, on the "Starvation Treatment of Diabetes," Dr. Abraham Jacobi, of New York, said:

"The starvation treatment of diabetes is very satisfactory to the experimental doctor, but what happens to the patient? I have seen patients with 5 or 6 per cent. of sugar go along in satisfactory health for five or ten or even twenty years. I have also seen starved patients, emaciated, suffering with cerebral anemia, complaining bitterly of other symptoms of nerve exhaustion, and now they are dead. They would not be dead if they had not been starved. Are not those living patients with glucose in the urine better off than those who died?"

The urine usually becomes sugar-free on a reduced diet. "Ordinarily, a diet consisting of one gram of carbohydrate and one gram of protein per kilogram of body weight, continued for a day or two, orients us definitely as regards the severity of the case in hand."²

3. The maintenance diet which the patient will regularly receive will be made up of as much carbohydrate (preferably as green vegetables) as can be given without the appearance of sugar in the urine (using Benedict's test. Joslin says:³

"I cannot escape from the impressions: (1) that in those countries where the diet consists largely of carbohydrate, the diabetes is mild; (2) that the diets of those diabetics who live longest, whether they show sugar or not, are those whose carbohydrate has never been long reduced to a very low quantity."

¹"Principles of Medical Treatment," Shattuck, 1921.

²"Principles of Medical Treatment," Shattuck, 1921.

³*Boston Medical and Surgical Journal*, June 22, 1922.

4. Protein will be given in quantities just sufficient to establish "nitrogen equilibrium." Clinically this is determined by observing when loss of weight ceases (usually 60 grams—about 2 oz.—per day is enough). Uncooked lean meat contains an average of 20% protein, so that 10 oz. of lean meat per day would furnish the ordinary requirement if protein in no other form was given. Fish contains slightly less protein than meat. It should be remembered that the more protein (meat, fish, etc.) given, the more the other classes of foods must be reduced, as protein itself gives rise to sugar.

5. Fats can be given in larger quantities than has hitherto been regarded as safe. If much fat is given, however, the protein should be low and the carbohydrates in large enough quantities to insure oxidation of the fatty acids (a ratio of 1.5 grams fatty acid to 1 gram glucose).

6. The total quantity of all food should be reduced to a level which will just supply the energy requirements.

7. The quantities of fat, carbohydrates and protein should be approximately the same for each meal.

8. The patient must be instructed to make his habits of life (muscular efforts) correspond to his reduced energy production, to avoid scratches and injuries to the extremities, with possible infection, and as to the necessity of adhering to the prescribed diet.

9. Trypsogen should be given in a dosage of 2 tablets after each meal, and the daily amount may be increased by 1 tablet a day until the patient is taking 6 or 7 tablets three times daily. In diabetes complicated with albuminuria, Trypsogen Without Gold and Arsenic should be used.

CLINICAL REPORTS

Indianapolis, Indiana
September 23rd, 1922

"As a late reply to yours in regard to my experience with Trypsogen in the case of my mother with protracted case of diabetes mellitus, it has been very satisfactory.

With slight attention to diet, I succeeded in bringing percentage of sugar from over 5% to less than $\frac{1}{2}$ of 1% in a few weeks, something I have been unable to do for several years."

—, Pennsylvania
September 11th, 1922

"You ask in letter if I ever used Trypsogen. Yes, one severe case diabetes, began several weeks ago. Patient used 600 tablets. Urinalysis September 10th, 1922, no sugar.

New York City
September 2nd, 1922

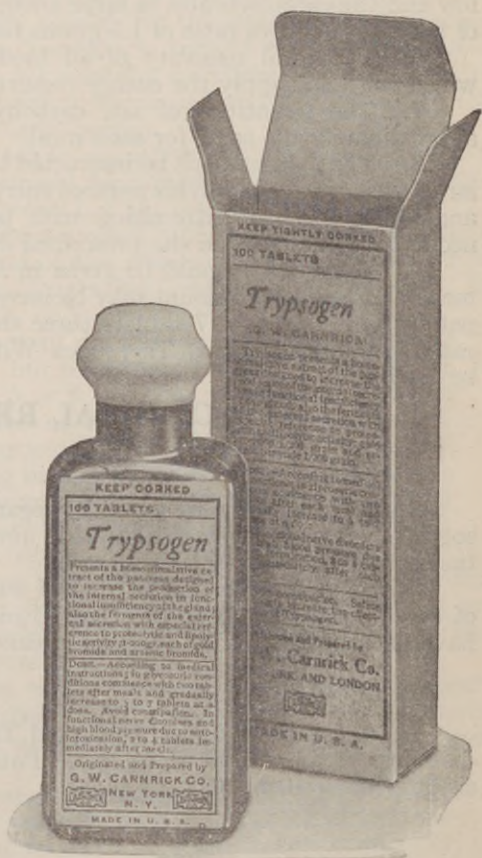
"Your Trypsogen is very good in diabetes. One of my patients, a bad case, urine loaded with sugar, thirst and urination terrible, has taken Trypsogen over a year now; urination is normal, no thirst, her weight has increased and she says she feels fine—never felt better. Sugar has not quite gone and she is still taking 4 tablets 3 times a day."

DIABETES MELLITUS

“Any positive means of augmenting the endocrine pancreatic function, even by a little, would give therapeutic results far surpassing those of the negative plan of sparing the function by diet.”—F. M. Allen, *American Journal of the Medical Sciences*, December, 1920.

Trypsogen augments the supply of the internal secretion of the pancreas, depresses the relative adrenal hyperfunction, lessens polyuria, decreases glycosuria and materially improves digestion and nutrition, as shown by a marked increase in weight and strength.

Dose: One or two tablets after meals. The dose should be gradually increased to at least five tablets after each meal.



G. W. CARRICK CO.

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New York, N. Y.

SPECIAL FORMULAE

Each formula is sold in bottles of 40 and 100 capsules or tablets.

No. 1 Pluriglandular Comp. Male

Hypoadrenia, Asthenia, Low Blood Pressure, Fatigue Syndrome

Thyroid	grs. 1/10	Dose: 1 or 2 capsules 3 times daily.
Pituitary	" 1/40	
Suprarenal	" 1/4	
Orchic	" 1/4	
Physiological Salts Comp.	" 1/4	

No. 2 Pluriglandular Comp. Female

Hypoadrenia, Asthenia, Low Blood Pressure, Fatigue Syndrome

Thyroid	grs. 1/10	Dose: 1 or 2 capsules 3 times daily.
Pituitary	" 1/40	
Suprarenal	" 1/4	
Ovarian	" 1/4	
Physiological Salts Comp.	" 1/4	

No. 3 Pineal Comp. Male

Backward Children, Mongolism, Retarded Mental or Physical Development

Anterior Pituitary	grs. 1/5	Dose: 1 or 2 capsules 3 times daily.
Thyroid	" 1/8	
Suprarenal	" 1	
Orchic	" 1 1/2	
Pineal	" 1/30	
Physiological Salts Comp.	" 1/4	

No. 4 Pineal Comp. Female

Backward Children, Mongolism, Retarded Mental or Physical Development

Anterior Pituitary	grs. 1/5	Dose: 1 or 2 capsules 3 times daily.
Thyroid	" 1/8	
Suprarenal	" 1	
Ovarian	" 1 1/2	
Pineal	" 1/30	
Physiological Salts Comp.	" 1/4	

No. 5 Orchic-Prostate Comp.

Enlarged Prostate, Sexual Neurasthenia, Vesical Irritation

Orchic	grs. 1	Dose: 2 or 3 capsules 3 times daily.
Prostate	" 2	
Calcium Glycerophosphate	" 2	

No. 6 Corpus Luteum Comp.

Vomiting of Pregnancy (Hyperemesis Gravidarum), Menstruation Psychosis, Mild Manic Depressive Insanity (Females)

Corpus Luteum	grs. 1	Dose: 1 to 3 tablets every 3 or 4 hours, which may be increased to 5 tablets in unusually severe cases.
Thyroid	" 1/10	
Physiological Salts Comp.	" 1/4	

No. 7 Parathyroid Comp.

Tetany, Uremia, Epilepsy, Paralysis Agitans, Nervous Tremor of Children

Parathyroid	grs. 1/20	Dose: 2 or 3 capsules 3 times daily.
Orchic	" 1	
Calcium Lactate	" 2	

No. 7 N. P. Parathyroid Comp.

Tetany, Uremia, Epilepsy, Paralysis Agitans, Nervous Tremor of Children

Parathyroid Nucleo Protein	grs. 1/20	Dose: 2 or 3 capsules 3 times daily.
Orchic	" 1	
Calcium Lactate	" 2	

No. 8 Thymus Comp.

Chronic Arthritis, Rheumatoid Arthritis, Arthritis Deformans

Thymus	grs. 3	Dose: 1 or 2 tablets 3 times daily.
Thyroid	" 1/10	
Pituitary	" 1/20	

No. 9 Mammary Comp.

Menorrhagia, Metrorrhagia, Subinvolution, Prolonged Menses, Uterine Oozing

Mammary	grs. 2	Dose: 1 tablet 3 times daily.
Posterior Pituitary	" 1/2	
Calcium Lactate	" 2	

No. 10 Suprarenal-Pituitary Comp.

Asthma, Bronchial Asthma

Suprarenal	grs. 2	Dose: 1 or 2 tablets 3 times daily, which may be increased when asthmatic aura appears.
Pituitary Entire	" 1	
Thyroid	" 1/10	
Anterior Pituitary	" 1 1/2	
Physiological Salts Comp.	" 1/4	

No. 11 Ovarian Comp.

Amenorrhea, Ovarian Hypofunction, Menopause.

Ovarian Substance	grs. 3	Dose: 1 or 2 tablets 3 times daily, which may be increased to 3 or 4 tablets from 5 to 10 days before the expected menstrual period.
Thyroid	" 1/10	
Physiological Salts Comp.	" 1/4	

No. 12 Renal-Pancreas Comp.

Nephritis, Prevention of Uremia.

Kidney Substance	grs. 2	Dose: 1 or 2 tablets 3 times daily.
Pancreas	" 2	
Physiological Salts Comp.	" 1/4	

TRYPSOGEN	Diabetes mellitus; glycosuria and defective carbohydrate metabolism. Also useful in certain pancreatic disorders, and as an adjunct in hypertension. <i>May be had without gold and arsenic at same prices.</i>	100 500 1000	SECRETOGEN	A physiological treatment of gastrointestinal insufficiencies and constipation, intestinal stasis, infantile diarrheas, marasmus and inanition.	100 500 1000
Tablets			Tablets		
Capsules		100	Elixir	Tablets. A homostimulative extract from the duodenum. Dose: 1 to 3 tablets before or after meals. Elixir. A homostimulative extract from the stomach and duodenum; contains 1/10 of 1% HCl. Dose: 1 to 3 teaspoonfuls before or after meals.	1/2 pt. 1 pt. 5 pts. 1 gal.
Caps. Dble. St'ngth	Presents the homostimulative principles that excite the production of the internal secretion of the pancreas when the gland is functionally deficient; contains proteolytic and lipolytic ferments; also 1/200 gr. each of gold bromide and arsenic bromide. Dose: 2 to 7 tablets or 1 to 3 capsules after meals.	100			
HORMOTONE	Neurasthenia; "run-down conditions"; sub-oxidation; neuroses; menstrual and climacteric disorders; cardiac asthenia; hypotension, etc. A combination of tonic hormones from thyroid, pituitary and gonads. Dose: 1 or 2 tablets 3 times daily before meals.	100 500 1000	KINAZYME	An aid to metabolism in tuberculosis and other wasting diseases; especially valuable in undernourished and backward children. Contains 1/45 gr. thyroid and 1/60 gr. whole pituitary in addition to pancreas, liver and spleen substance with calcium phosphate. Kinazyme (Old Formula) contains the same without the thyroid and pituitary. Same price as Kinazyme. Dose: 2 to 4 tablets or capsules after eating.	100 500 1000 100
Tablets only			Tablets		
			Capsules		
HORMOTONE w/o Post-Pituitary.	In neurasthenia associated with hypertension. Dose: 1 or 2 tablets 3 times daily before meals.	100 500 1000	FEROVARIN	To increase red corpuscles and hemoglobin content of blood in anemia and chlorosis. Contains 1/30 gr. of desiccated thyroid combined with desiccated entire ovary and the salts of the blood plasma in physiological proportions. Dose: 1 or 2 tablets or capsules 3 times daily after meals.	50 100 500 1000
VIRILIGEN	Indicated in lowered virility and sexual neurasthenia of functional origin. Presents desiccated extracts of anterior pituitary, suprarenal cortex, lymph, brain and spinal cord substance, testis and 1/10 gr. thyroid. Not sold in bulk nor sampled. Dose: 1 or 2 tablets or capsules 3 times daily before meals.	100 100	Tablets		
Tablets			Capsules		50
Capsules		100	Alkaline Tablet (G.W.C.Co.)	A coated tablet containing salts of sodium, potassium and calcium in physiological proportions. A valuable medication in hypo-alkalinity.	200 500 1000
Ampoules		1/2 doz.	PERISTALSIS COMP. (G.W.C.Co.)	A combination of the peristaltic principles of the duodenum, pylorus and spleen, together with 1/2 grain of purified ox gall and 1/4 grain pituitary. Dose: 1 tablet three times daily.	40 100
MAMMAGEN	To increase lactation in deficient milk supply in the nursing mother. Each tablet contains 1/2 grain desiccated entire pituitary substance with the hormones and vitamins of corpus luteum, placenta and mammary glands. Dose: 1 or 2 tablets or capsules 3 times daily after meals.	50 100 500 1000	Coated Tablets		
Tablets					
Capsules		50			

SINGLE GLAND PRODUCTS

Our organotherapeutic products are made from fresh glands of healthy food animals, in our own laboratory, under the supervision of competent chemists. All moisture has been removed from these gland products and they will keep indefinitely if contents are not exposed to moisture and bottle is kept tightly corked.

	In one bottle		In one bottle
Albuzyme	caps. 75	Ovary w/o	Powder oz.
Amylzyme	Powder oz. caps. 40 100	Corpus Lut.	5-gr. caps. 100
Brain	Powder oz.	Ox Gall	Powder oz.
Brain & Spinal Cord	2-gr. tabs. 100	Pancreas	Powder oz. 5-gr. caps. 100
Corpus Luteum	Powder 1/8 oz. oz. 2-gr. tabs. 50 100 5-gr. tabs. 50 100 5-gr. caps. 50 100	Pancreatin (U.S.P.)	Powder oz. 2-gr. tabs. 100 5-gr. caps. 100
	1 c. c. ampoules, 20% 1/2 doz.	Pancreatin & Soda	Tablets 100
Duodenal Sub.	Powder oz.	Parathyroid	Powder 1/8 oz. 1/20-gr. tabs. 100
Epinephrine	Powder 1 grain Chloride Sol., 1-1000 oz. 1 c. c. ampoules, 1:10,000 1/2 doz.	Parotid	Powder oz.
Glycogen	Powder 1 gram 1/4 oz. 1/2 oz. 1 oz. 2 c. c. ampoules (box of 6)	Pepsin (U.S.P.)	Powder oz.
Kidney	Powder oz. 2-gr. tabs. 100 5-gr. caps. 100	Pineal Gland	Powder 1/8 oz. 1/10-gr. tabs. 100
Lecithin	1/2 oz. jars 1 oz. jars	Pituitary	Powder 1/8 oz. 1 oz. 1/2-gr. tabs. 50 100 1-gr. tabs. 50 100 2-gr. tabs. 50 100
" Commercial		Pituitary, Ant.	Powder 1/8 oz. 1 oz. 1-gr. tabs. 50 100 2-gr. tabs. 50 100
Liver	Powder oz. 3-gr. tabs. 100 5-gr. caps. 100	Pituitary, Post.	Powder 1/8 oz. 1/10-gr. tabs. 100 1/2-gr. tabs. 100 (Liquor Hypophysis) 1/2 c. c. ampoules, Ob., 1/2 doz. 1 " " " " 1/2 doz. 1 c. c. ampoules, Surg., 1/2 doz.
Lymphatic Gl.	Powder oz. 3-gr. tabs. 100	Placenta	Powder oz. 3-gr. tabs. 100 5-gr. caps. 50 100
Mammary Sub.	Powder oz. 3-gr. tabs. 100 5-gr. caps. 100		
Marrow—Red Bone Glycerole	1/2 pt. 1 pt.		
Orchic Sub.	Powder oz. 2-gr. tabs. 100 5-gr. caps. 100		
Ovarian Sub.	Powder oz. 2-gr. tabs. 100 5-gr. tabs. 50 100 5-gr. caps. 50 100		



Prostate	In one bottle		Thyroid (U.S.P.) (cont.)	In one bottle	
	Powder	oz.		½-gr. tabs.	100
	2-gr. tabs.	100		1-gr. tabs.	100
Spleen	In one bottle		2-gr. tabs.	100	
	Powder	oz.	1-gr. caps.	100	
	3-gr. tabs.	100	2-gr. caps.	100	
Steapzyme	In one bottle		3-gr. caps.	100	
	caps.	75	5-gr. caps.	100	
			Tonsil	Powder	oz.
Suprarenal Gland (U.S.P.)	In one bottle		3-gr. caps.	100	
	Powder	oz.			
	1-gr. tabs.	100			
Suprarenal Cortex	In one bottle				
	Powder	½ oz.			
	1-gr. tabs.	50			
	2-gr. tabs.	100			
	3-gr. caps.	50			
Suprarenal Medulla	In one bottle				
	Powder	¼ oz.			
Thymus	In one bottle				
	Powder	oz.			
	3-gr. tabs.	100			
Thyroid (U.S.P.)	In one bottle				
	1/10-gr. tabs.	100.			
	¼-gr. tabs.	100.			

Nucleo-Protein Products

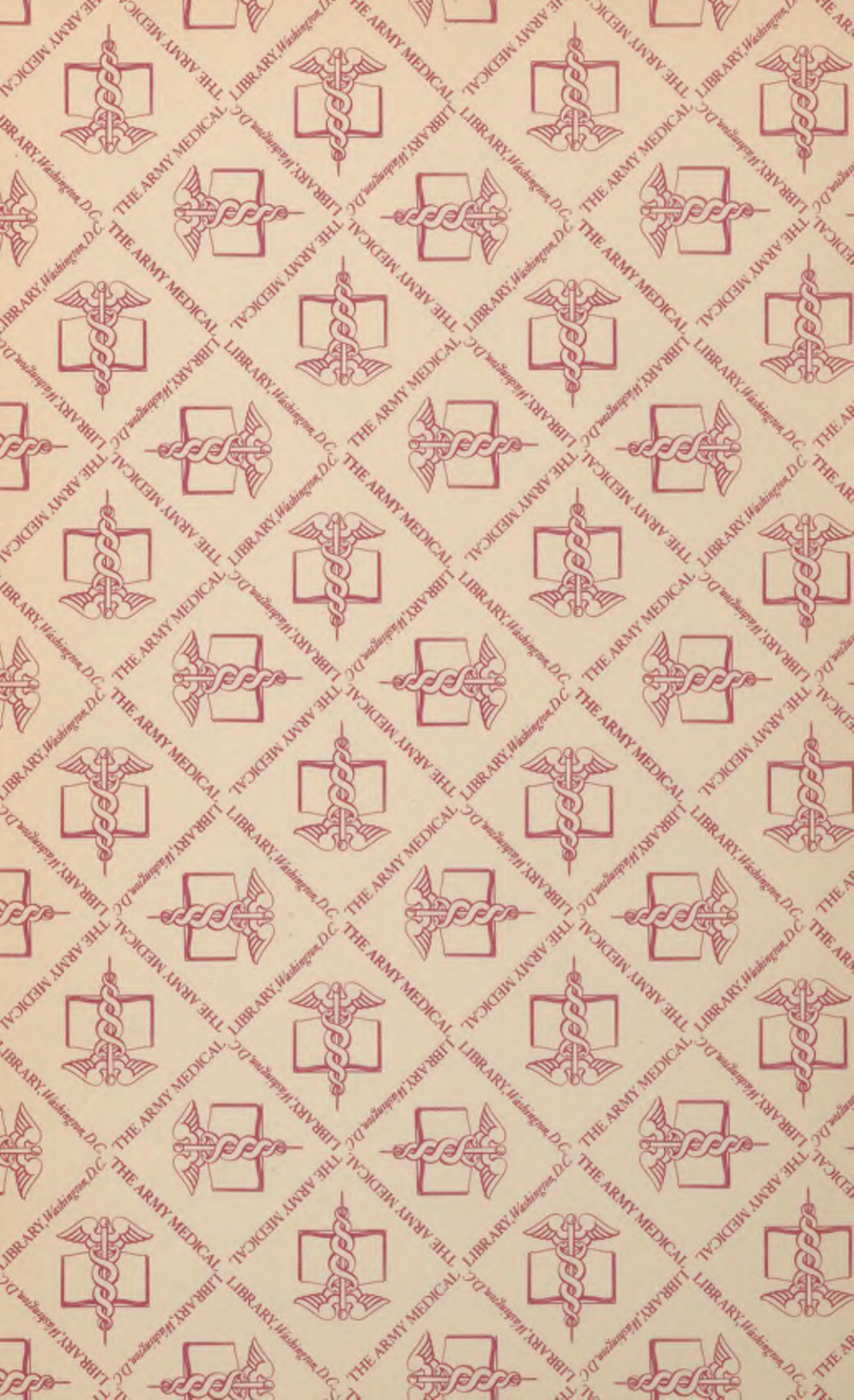
Ovarian	Nucleo-protein	10%
		100 Tablets
Parathyroid	Nucleo-protein	5%
		20 Tablets
Pituitary	Nucleo-protein	10%
		20 Tablets
Suprarenal	Nucleo-protein	10%
		100 Tablets
Thyroid	Nucleo-protein	1%
		100 Tablets
"	Nucleo-protein	5%
		100 Tablets
"	Nucleo-protein	10%
		100 Tablets
"	Residue	½ oz.

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