STARVATION DIABETES, THE REASON FOR THE USE OF GLUCOSE IN THE TREATMENT OF DIABETIC ACIDOSIS*

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In 1874 Lehmann[50] noticed that injection of sugar into the mesenteric veins produced greater glycosuria in fasted than in fed dogs. In 1890 Hofmeister[40] found that the administration of starch-gruel to previously fasted dogs often provoked glycosuria. Since then the phenomenon of starvation diabetes has been repeatedly reported in one connection or another; but its implications have not been fully recognized in the interpretation of physiological experiments and have received scant attention in the clinic. Its significance in connection with the treatment of diabetic acidosis has been especially neglected. The recent appearance, from one of the leading diabetic clinics, of a series of papers objecting to the use of glucose in the treatment of diabetic acidosis[42, 81, 82] has tempted the author to review the subject.†

Because Barrenscheen[4] and Nagasuye[72] found that a single feeding of glucose after a 3-day fast promoted no deposition of glycogen in the livers of dogs, starvation diabetes was first attributed to impairment of hepatic glycogenesis. Subsequent investigations have proved that this deduction was erroneous; the defect lies not in glycogenesis, but in the oxidation of glycogen by the tissues. Although this defect appears to be related to depletion of liver glycogen, this correlation is probably more or less fortuitous. Starvation diabetes seems to come on when an animal is subsisting upon a diet of fat and protein and is dependent upon the latter for the provision of carbohydrate. By such devious paths and profuse experimental data have these conclusions been reached, that compre-

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† The author must confess to another motive. A quotation in one of these papers[42] gives the false impression that his conviction of the beneficial effect of glucose in diabetic acidosis is faltering. Though the quotation is meticulously accurate, its context gives it a false significance. It is a description of the approximate amounts of glucose recommended for the initial treatment of diabetic acidosis on the author's service; not a statement of principle.

hensive chronological treatment of the literature must be abandoned for a more logical and selective method. The early history of the subject was summarized by Peters and Van Slyke.[77]

Johnston, Sheldon, and Newburgh[41] studied blood sugar and respiratory quotients of normal human subjects who received carbohydrate after various periods of carbohydrate depletion. They found that even on submaintenance diets carbohydrate was stored rather than burned under these conditions and that the proportion stored varied directly with the degree of antecedent carbohydrate depletion. du Vigneaud and Karr[94] found that the height and duration of the blood-sugar curves of rabbits after 3 gm. of glucose per kg. varied directly with the duration of a previous fast up to as much as 20 days. When Shope[83] gave a normal young woman who had fasted for 5 days a meal containing about 90 gm. of carbohydrate, she developed an excessive hyperglycemic reaction. Goldblatt and Ellis[27] found that after a fast of only 40 hours, glucose provoked more than the usual hyperglycemia, often accompanied by glycosuria.

Extreme reduction of carbohydrate in the diet, short of starvation, lowers the tolerance for glucose. Kageura[43] found that subsistence for two days on a diet containing only fat and protein raised the height of the peak of the alimentary blood-sugar curve 60 to 70 mg. per cent. Sweeney[92] investigated the effects of antecedent diets on the alimentary glycemic reactions of medical students. The blood sugar rose least after a high carbohydrate regime, most after starvation or a diet containing large amounts of fat with little carbohydrate. The sugar tolerance curves of 3 normal adults studied by McClellan and Wardlaw[64] rose far more after they had received diets containing only 25 gm. of carbohydrate than they did after diets containing 350 to 400 gm.

The excessive alimentary hyperglycemia of carbohydrate starvation is referable, not to impaired hepatic glycogenesis, but to defective combustion. After starvation, although a large proportion of administered glucose is retained, the respiratory quotient does not rise in the usual manner.[27, 64] Bergman and Drury[6] found that eviscerated rabbits utilized injected glucose more rapidly if they had been fed up to the time of evisceration than they did if they had been starved. The reaction to galactose, which must be converted to glycogen by the liver before it can be utilized, is not altered by starvation.[58]

Although starvation diabetes is usually associated with depletion

of liver glycogen, it is probably more closely related to the metabolic mixture, appearing when an animal is subsisting upon a diet of fat and protein, deriving its carbohydrate from the latter. For this reason it is harder to provoke starvation diabetes in the dog, which is inured to a diet of fat and protein, than it is in the rabbit or man, who normally consume large amounts of carbohydrate.[12] To demonstrate the phenomenon, Dann and Chambers[19] were forced to starve dogs for 17 days or more, during which the animals were exercised daily on a treadmill; while the alimentary glycemia of rabbits was altered strikingly by Himsworth[32] by only moderate reduction of dietary carbohydrate. If protein is the chief or only source of glycogen, carbohydrate seems to be used sparingly so long as fat is available. It appears to be the source rather than the quantity of glycogen that determines the rate of combustion of carbohydrate by the tissues. Although the liver of the rat after 24 hours of starvation contains only traces of glycogen, this is spent quite prodigally until it is almost completely exhausted. After 48 hours without food, however, when the glycogen has been partially restored from protein, it is used with great parsimony. Even when exogenous protein is the source of glycogen, the latter is used economically; the body is indifferent to the origin of the protein.[66] If starvation is prolonged until fat is exhausted the phenomena of starvation diabetes are modified. In advanced stages of starvation the nitrogen excretion of 7 of 11 dogs, studied by Chambers, Chandler, and Barker[13] increased greatly; simultaneously the R.Q. rose to slightly above 80 and ketonuria diminished. The metabolism of the remaining 4 dogs pursued an unchanged course. The members of the second group utilized fat for fuel throughout. Members of the first group, having exhausted their stores of fat were thereafter forced to subsist entirely upon protein. The combustion of carbohydrate was consequently accelerated, because a large proportion of the protein could only be burned after it had been converted to glycogen. At this stage, in contradistinction to the earlier stages of starvation, the R.Q. rose after the administration of glucose; the capacity to burn carbohydrate was partly restored when the continuing supply of carbohydrate was increased.

The phenomena of starvation diabetes have been attributed to variations in the secretion of insulin by those who hold that every fluctuation in the combustion of carbohydrate depends upon a change in the secretory activity of the islands of Langerhans. Such a theory

is not, however, compatible with the facts. It is even doubtful whether insulin should be regarded as the *primum mobile* of carbohydrate metabolism. The reactions by which carbohydrate is utilized appear to depend upon inherent properties of the enzyme systems of the cells. Insulin does not bring these into existence, but it controls their speed and direction. Even this control is conditioned by attendant physiological or pathological circumstances. Evidence for this view will be presented at greater length in subsequent sections of this discussion. Relevant to the immediate issue are the experiments of Bergman and Drury[6] cited above. Their eviscerated animals exhibited the phenomena of starvation in spite of the fact that they had no source from which insulin could be supplied.

In addition to starvation, exercise has a powerful influence on the oxidation of carbohydrate. Staub[90, 91] found that exhausting muscular work performed for one and one-half hours immediately after the ingestion of 20 gm. of glucose diminished the height and duration of the hyperglycemic reaction; if the work was done immediately before the glucose was taken the hyperglycemia was exaggerated. Bøje[8] studied the effect on 4 normal persons of exercise after ingestion of 1 gm. of glucose per kg. of weight. If the exercise was begun after the peak of the blood-sugar curve, 2 of the 4 frequently developed hypoglycemia severe enough to give them symptoms. Hypoglycemia was never provoked by exercise, however, unless glucose had been taken previously. Mills[65] found that, after a 10-mile walk taken before breakfast, glucose induced an excessively high and prolonged hyperglycemia, but the respiratory quotient rose less than usual. This abnormal reaction could be prevented by the ingestion of large amounts of carbohydrate on the preceding day. These responses illustrate the tendency of exercise to promote the combustion of carbohydrate preferentially. All the experiments are conditioned by the fact that they were conducted when the subjects were in the postabsorptive state when their hepatic glycogen had been somewhat depleted. Heavy or prolonged exercise rapidly exhausts the residue, after which they respond to exercise with excessive hyperglycemia. Glucose given before the exercise is preferentially consumed by the muscles, after which oxidation of sugar continues at an accelerated rate. Since glucose is not supplied rapidly enough by the depleted liver, hypoglycemia may ensue. Both the alimentary hyperglycemia that follows exercise in the postabsorptive

state and the hypoglycemia produced by exercise in the course of the alimentary hyperglycemic reaction may be prevented or mitigated by the provision on the preceding day of a large enough surplus of carbohydrate to insure a plentiful residuum of glycogen in the liver at the end of the night's fast.

Although the exact *locus operandi* of insulin upon the metabolism of carbohydrate is not known, it has been established that its preponderant action is to accelerate oxidation of muscle glycogen and that it has no direct effect upon the formation or breakdown of liver glycogen. It may, in addition, promote the hydrolysis of protein and the deamination of the resultant amino acids.[18, 52, 57] Formation of glycogen is not retarded by removal of the pancreas; if anything, it is accelerated. Every substance that is capable of forming carbohydrate is converted to glucose by the depancreatized animal. Since almost all compounds except glucose must be transformed to glycogen by the liver as a preliminary step in the conversion to glucose, this in itself constitutes proof that hepatic glycogenesis does not require insulin. In the normal animal insulin provokes hypoglycemia; in the liverless animal it hastens the appearance of hypoglycemia.[61] In fasting rats it tends to deplete the liver of glycogen, which is transferred to the muscles to meet the demands for accelerated oxidation, a reaction similar to that elicited by exercise. In muscular exercise, however, consumption of carbohydrate does not outstrip the supply because, as liver glycogen becomes depleted, the muscle substitutes other fuel. Insulin, on the other hand, promotes combustion of carbohydrate so exclusively that it exceeds the glycogenolytic powers of the liver and continues after the supply of hepatic glycogen is exhausted. The consequence is profound hypoglycemia.

Since insulin accelerates the expenditure of carbohydrate, it is not surprising that it can give rise to all the phenomena of carbohydrate starvation. After a period of prolonged over-insulinization the ketone bodies in the blood increase and gross ketonuria may appear.[85] Glucose at this time induces prolonged and excessive hyperglycemia.[9, 59, 74] These disorders occur not while insulin is still acting vigorously, but after its action is spent. At this time, if enough insulin has been given to exhaust liver glycogen, the animal is forced to subsist upon protein and fat, whereupon it behaves just as it does if it is reduced to the same state by any other means.

Conversely, starvation reduces the effect of insulin. In rabbits

that have subsisted on high fat diets the hypoglycemic reaction to insulin is unduly delayed and prolonged.[32] Normal men react less to a given dose of insulin after a high fat diet than after a high carbohydrate diet.[33] To a series of nondiabetic patients in the post-absorptive state, after diets containing various amounts of carbohydrate, Himsworth and Kerr[34] gave 30 gm. of glucose per sq. m. of surface area, with and without insulin. The hyperglycemic reaction, both with and without insulin, diminished steadily as the carbohydrate in the antecedent diet increased from 50 to 500 gm. Similar phenomena in rats have been described by Roberts and Samuels.[79]

So long as the ability to burn sugar is retained, the utilization of carbohydrate appears to be accelerated by hyperglycemia. This can be inferred from the course of the alimentary glycemia and the metabolic events that accompany it. It is to be expected, if the combustion of glycogen by the muscles and the formation of glycogen in the liver are conceived as chemical reactions, that increasing one of the reactive components should accelerate these reactions. More direct evidence that hyperglycemia has this effect is found in the demonstration by Soskin, Allweis, and Cohn[88] that when extra glucose was injected into depancreatized dogs receiving balanced injections of glucose and insulin, the blood sugar followed the course of a normal alimentary glycemia curve. The hyperglycemia induced by the extra glucose presumably accelerated deposition and combustion of glycogen. Wierzuchowski[95, 96] has shown that the rate of utilization of sugar by dogs increases steadily to a maximum with the rate of glucose injection, which is directly related to the concentration of sugar in the blood. The action of insulin is also influenced by the blood sugar. In the fasting depancreatized dog[21] and in diabetic patients[46] the reduction of blood sugar after a given dose of insulin varies directly with the degree of initial hyperglycemia.

Among the disorders encountered when the combustion of carbohydrate is impaired or retarded, the most prominent are increased protein catabolism and ketosis. If the defect in the combustion of carbohydrate arises from disability of the intermediary reactions by which glycogen is oxidized, hyperglycemia and glycosuria also occur. Of these disorders ketosis is generally considered most characteristic of carbohydrate starvation. The formation of ketone bodies by the liver was formerly believed to be the normal and obligatory pathway of fat metabolism; starvation ketosis was attributed to the inability of the tissues to oxidize these bodies without the simul-

taneous combustion of a certain amount of carbohydrate. It has now been established that fat can be burned and the overwhelming proportion is burned directly by the tissues without intermediary production of ketone bodies. Although minute amounts of these compounds may be produced at all times, their production assumes important proportions only when carbohydrate is not available or can not be burned. It has been suggested that these four-carbon acids are, under these conditions, substituted in the oxidative intermediary metabolic reactions of the tissues for compounds usually derived from carbohydrate.[15] The stimulus for their overproduction has, however, been a subject of controversy because of certain apparent anomalies connected with the conditions under which they appear.

Men develop ketosis of moderate severity when they are starved[20, 44] or when they are given diets consisting only of protein and fat.[63] The monkey (macacus) also develops starvation ketosis.[44, 70] The dog, on the other hand, tolerates starvation without appreciable increase in the production of ketone bodies.[16] Starvation in this carnivore involves no appreciable change in the metabolic mixture. Somogyi[86] would relate ketosis to the quantities of glycogen in the liver. Although there is a general correlation between these two functions, the evidence indicates that ketosis, like starvation diabetes, is more closely linked with the nature of the materials oxidized by the tissues. The apparent association with liver glycogen arises from the fact that the nature of the metabolic mixture is in turn correlated in a general way with the state of the hepatic glycogen stores. If an individual receives a diet containing adequate calories entirely or almost entirely provided by fat (derived either from his food or adipose tissue), with small or moderate amounts of protein, ketosis will ensue. This can be eliminated, however, by the administration of extremely small amounts of carbohydrate. The ketosis of starvation likewise can be abolished by carbohydrate alone in quantities quite insufficient to supply the caloric needs of the individual or even to reduce considerably the amounts of fat consumed. In both instances as ketosis diminishes the excretion of nitrogen also decreases.[5, 25] The nitrogen-sparing action of carbohydrate does not depend upon its value as fuel. For this purpose fat is equally effective; it depends on some more specific function for which protein alone can be substituted. The obvious inference is that a minimal quantity of products of carbohydrate is essential

for the operation of the metabolic machinery. If these are not provided by exogenous carbohydrate, they must be derived from protein and ketone bodies. The latter apparently can not be used alone or are less efficiently used. Protein is, therefore, broken down to provide carbohydrate when ketones are used. Conversely, ketones are produced to spare protein when protein is forced to assume the full burden of supplying intermediary products for oxidative metabolism.

This argument can be better pursued after the nature of diabetes has been considered, because metabolic processes are more completely dissociated in this disorder than in any other known condition. The happy chance that led Minkowski to select the dog for his experiments has been commented upon by Long.[51] In view of the differences in the reactions of species to removal of the pancreas, it is dangerous to draw close analogies between canine and human diabetes. Nevertheless, because the dog has been so long and intensively investigated, the details of the effect of pancreatectomy have been better defined in this animal than in any other.

Immediately after removal of the pancreas the respiratory quotient of the dog falls to approximately 0.71, denoting the combustion of fat without carbohydrate.[3, 14] When carbohydrate is given it is excreted almost quantitatively as glucose in the urine; when it is not given, sugar formed from protein is excreted.[3] If the dog is fasted or receives only protein, glucose and nitrogen appear in the urine in relatively constant proportions. Not only is no appreciable amount of preformed carbohydrate oxidized by these animals; but all other materials that can be converted to carbohydrate appear to be subjected to this transformation and excreted as glucose in the urine. This condition is generally termed complete or total diabetes. Obviously no diabetes can be complete in an absolute sense, since certain tissues, notably the testes and the brain, continue to derive their energy entirely from carbohydrate or its products, even when the source of insulin is gone.[26, 38, 39, 45] The respiratory quotients of skeletal[36, 78] and cardiac[17] muscles do appear to approximate that of fat. Even the qualified statement that carbohydrate is not oxidized by these tissues of the dog in the absence of the pancreas has been challenged by Soskin and associates.[87, 89] Although the validity of their experiments has been disputed on sound grounds,[3, 11] it would be rash to assert unequivocally that the combustion of carbohydrate

can not be initiated or accelerated without the pancreas, even in the dog, if the blood sugar is sufficiently elevated.

Although the utilization of carbohydrate in the depancreatized dog is reduced to a minimum, many of the reactions involved in the metabolism of carbohydrate remain intact or are even accelerated. Although hepatic glycogen is depleted, glycogenesis is not impaired; it may even be accelerated. This is evident from the speed with which sugars other than glucose, noncarbohydrate precursors of glucose and protein, are all converted to glucose; since none of these substances appears to form glucose until it has been converted to glycogen by the liver. Glycogenesis and glycogenolysis seem to be mendicant or ministrant processes, responsive to every demand of the tissues for combustion of carbohydrate. In no condition is the need for carbohydrate combustion more desperate and the hepatic response more generous than in the diabetic animal, although the response is almost a futile gesture. Glycogenesis is not retarded, but glycogenolysis is so enormously accelerated that the most vigorous synthetic activity can not maintain the glycogen reserves of the liver. By intravenous administration of glucose it is possible to surpass the speed of glycogenolysis and thereby to cause the deposition of some glycogen in the liver.[7] It is notable that when this is done, despite the fact that little or no sugar is burned, ketosis and protein destruction diminish.[69] Kosterlitz[47] also succeeded in building up liver glycogen by feeding diabetic animals fructose and sorbitol, although, like others, he was unsuccessful with glucose.

While both glycogenesis and glycogenolysis in the liver are accelerated, the formation of glycogen by the muscles seems to be retarded, but not abolished;[56, 60] muscles from depancreatized animals are never devoid of glycogen. When these animals perform severe muscular work, moreover, the lactic acid in their blood increases.[35] Lactic acid is also produced from glycogen in vitro by isolated muscles from depancreatized animals.[78] It follows that pyruvic acid and all the intermediary products between glycogen and these acids must also be formed. Nevertheless, the oxidative respiratory quotient of this muscle approximates that of fat. The lactic acid formed is reconverted to glycogen by the liver or utilized by organs that do not require insulin.[37]

The absence of insulin, therefore, retards or abolishes only those terminal steps in the train of oxidative reactions that lead to the formation from carbohydrate of CO_2 and H_2O and the provision of

energy. This is altogether in keeping with present concepts of the intermediary metabolism of muscle. It is recognized that a large proportion of the chemical reactions in which products of carbohydrate are involved are only conveyors or transmitters of energy which may have its ultimate source in either fat or carbohydrate. Regardless of the source of this energy, however, it can only be made to work by the continuation of these orderly processes which involve certain compounds of carbon, hydrogen, and oxygen which are ordinarily provided by carbohydrate. This the author[76] has termed the "operative metabolism," in contrast to the "energy producing metabolism," to which attention was earlier confined. If preformed carbohydrate does not supply these operative products, protein must take up the load except in so far as ketone bodies can serve as substitutes.

Although the processes of carbohydrate metabolism and the action of insulin upon them are qualitatively similar throughout the animal kingdom, species differ in their gross quantitative reactions to both starvation and removal of the pancreas. It has been already remarked that the dog is peculiarly refractory to starvation diabetes and develops no significant starvation ketosis. Even after pancreatectomy the ketosis does not become extremely severe. If, however, the depancreatized dog is given phlorizin, a procedure which drains it of all carbohydrate products, ketosis becomes maximal.[67, 69] Protein catabolism parallels ketosis. The cat follows a somewhat similar pattern in its reaction to pancreatectomy.[55] Lukens[54] has shown that the goat, which ordinarily has an extremely low blood sugar, develops only slight hyperglycemia and glycosuria and minimal ketonuria when its pancreas is removed. Urinary nitrogen increases moderately. The glucose: nitrogen ratio of the depancreatized goat is quite low and a portion of injected glucose is retained by the animal. The phlorizinized goat, however, has a G: N ratio similar to that of the depancreatized dog. The obvious difference between the phlorizinized and the depancreatized animal is the level of the blood sugar. Hyperglycemia enables the goat, then, to burn some sugar in the absence of the pancreas; it permits the dog to maintain enough of the processes for which carbohydrate is required to mitigate ketosis and destruction of protein. The pig reacts to pancreatectomy much as the goat does, except that it develops striking ketonuria.[53] The rabbit survives pancreatectomy for a long time without insulin, exhibiting profuse glycosuria without ketonuria.[29]

Greeley and Drury[31] have also adduced evidence that the utilization of carbohydrate by this animal can be increased by injections of glucose. In the duck, after removal of the pancreas it is hard to detect any disturbance of metabolism; its glucose tolerance test remains unchanged. Starvation, however, reduces the carbohydrate tolerance of both the normal and the depancreatized duck.[71] The depancreatized owl develops extreme hyperglycemia when given large amounts of food, but may even die in hypoglycemia if deprived of food.[73]

In view of these distinctions between species, deductions from animal experiments must be made with reservations, analogies between species must be drawn with caution. Only the greatest common divisor of the phenomena observed in all species can be accepted as universally applicable to human diabetes. What the effect of total removal of the pancreas in man might be has been long a matter of conjecture and inference. Some limited data on the effects of this operation have been obtained recently. The monkey, presumably, should offer the closest analogy to man. The *Macacus rhesus*, after pancreatectomy, according to Mirsky,[70] exhibits striking glycosuria with only mild ketosis; serious ketosis appears only if the animal is deprived of food. The intact animal is, however, like man, peculiarly susceptible to starvation ketosis.[44] There are now several reports of total pancreatectomy in man for the removal of pancreatic tumors. All agree that the resultant diabetes has been easily controlled by the injection of 30 to 50 units of insulin daily with generous amounts of carbohydrate.[10, 28] Brunschwig, Ricketts, and Bigelow,[10] indeed, assert that their patient was relatively sensitive to insulin, developing hypoglycemia on occasions. Unfortunately, survival in these cases was short and nutritive needs were met by slow parenteral injections of glucose or glucose + protein hydrolysates. It has been demonstrated by Ellis[22] and others[30] that great economy of insulin can be effected by such procedures. (This, by the way, is an argument for the use of such injections in the face of emergency.) The fact does remain that no condition approaching the gravity of the disturbances of metabolism seen in severe spontaneous diabetes has been produced in man by removal of the pancreas. The diabetes encountered in patients with carcinoma of the pancreas which has destroyed the gland is also relatively mild.[23, 93] In these cases, however, it is impossible to exclude the presence of some residual island tissue. Occasionally fulminat-

ing diabetes with severe ketosis occurs in acute hemorrhagic or interstitial pancreatitis.[24, 80] This condition is, however, accompanied by peritonitis, shock, or other features which greatly aggravate diabetes. Among these features it may not be amiss to mention starvation and vomiting.

In view of these facts, coupled with the consistent failure to demonstrate in the pancreas of patients with diabetes lesions of the islands of Langerhans that bear any quantitative relation to the metabolic disturbances, the assumption that clinical diabetes has its origin in diseases of the pancreas is hardly warranted. The disability that characterized the disease is, however, similar to the disorder produced in animals by removal of the pancreas. Furthermore, the reactions of the diabetic patient to insulin are qualitatively like those of the depancreatized animal. In the latter, one of the most consistent phenomena is the unfavorable reaction to carbohydrate deprivation which manifests itself particularly in an exaggeration of the inability to oxidize sugar, the appearance or aggravation of ketosis, and increased destruction of protein. It seems hardly reasonable to suppose that diabetes confers upon man a peculiar immunity to these evils, the ability to circumvent physiological reactions to starvation to which normal men and animals and diabetic animals are subject. It is established that the diabetic can not evade certain kindred responses. Acceleration of the combustion of carbohydrate and the action of insulin by hyperglycemia[46] and by exercise[62, 84] have been amply demonstrated. In a general discussion of the treatment of diabetes Lavietes and Peters[48, 49, 75] have presented some evidence that the diabetic is not protected from the deleterious effects of starvation.

In the history of the treatment of diabetes, starvation has occupied a peculiarly prominent position. To take full advantage of the fact that administration of carbohydrate and the maintenance of hyperglycemia increase the combustion of sugar is not practical, because the glycosuria and polyuria which these measures promote are distressing, to say the least. To minimize these ills it is necessary to restrict the use of carbohydrate. This, on the other hand, because it reduces the blood sugar and the utilization of sugar, tends to provoke ketosis. It was this dilemma that led Naunyn and others to alternate fasting (green days) with high carbohydrate (oatmeal or potato, etc.) days in their therapeutic regimes. For a time these practices were generally abandoned for the Allen[1] starvation treat-

ment. This, on the face of it, seems an altogether illogical therapeutic program in view of the effects of starvation that have been discussed. Nevertheless, it succeeded in maintaining for considerable periods the lives of severe diabetics who otherwise could not have survived. In theory the starvation treatment was intended to rest the pancreas in the hope that thereby it might be rehabilitated. In practice its beneficial effects probably arose chiefly from the general reduction of metabolism. It has been asserted that it overcame ketosis. If this could be substantiated it would constitute an extraordinary physiological paradox. There is, however, little evidence that it actually alleviated ketosis; in fact, as Allen remarked in the recent discussion of a paper by Root,[81] it not infrequently precipitated ketosis, compelling the administration of carbohydrate. Patients did survive ketosis under this regime and, thereafter, could be maintained free from ketonuria by diets containing small amounts of carbohydrate. If the diabetes was severe this success was attained only at the expense of nutrition. The metabolic state of these patients is reminiscent of the state of the malnourished dogs studied by Chambers, Chandler, and Barker.[13]

Proper treatment of diabetes requires a restriction of carbohydrate and a self-discipline on the part of patients to prevent glycosuria and its attendant evils. With the Allen starvation treatment these restrictions became so rigorous that adherence to the regime became almost a moral issue. The literature on diabetes in the era from 1915 until insulin was in general use abounds in papers in which acidosis is attributed to the failure of patients to adhere to dietetic regimes that could only have led to slow death from malnutrition or from tuberculosis and other diseases that prey on the malnourished. In all these publications it is implied that overindulgence, especially in carbohydrates, can diminish carbohydrate tolerance and provoke ketosis, a concept for which no physiologic basis has ever been established. The aim of treatment was to keep the urine free from sugar, regardless of the nutritive needs of a patient. Always there were some who protested against the austerity of this therapy. It was known that although loss of sugar in the urine increased progressively as the carbohydrate in the diet was raised above the amount required to induce glycosuria, there was a wide zone within which only a part of added increments of sugar were excreted, another example of the acceleration of carbohydrate utilization by hyperglycemia. This led some to advocate the pre-

scription of enough carbohydrate to insure the utilization of the largest quantity that could be accomplished without producing distressing polyuria. With the advent of insulin such expedients were no longer necessary; diabetic patients were at last able to live with, not for, their disease. Nevertheless, the moral attitude, including the doctrine that ketosis is the wages of dietary sin, has been slow in dying, although the prior assumption that dietary infractions are a sign of the ineptness of the physician would have a healthier effect on the quality of therapeutic practise.

Mirsky[68] has recently demonstrated that ketosis is eliminated or abated by administration of large amounts of carbohydrate in clinical diabetes, as it is in the experimental diabetes of depancreatized animals, although the quantities of carbohydrate required to abolish or minimize it may be so large that they produce an intolerable polyuria. At the same time he has again confirmed the observation that increments of carbohydrate above the amount that first induce glycosuria are not excreted quantitatively in the urine. In practice diabetic ketosis is usually precipitated by omission of insulin or by some condition that reduces the tolerance for carbohydrate. Among these conditions are usually recognized infections and injuries. To these we believe carbohydrate starvation precipitated by a number of causes must be added, and among the causes of carbohydrate starvation prolonged hypoglycemia must not be neglected. The fact that vomiting is such a consistent symptom of ketosis and that it so regularly marks the climax of the disorder may be more than a coincidence.

Diabetic acidosis and the coma in which it culminates mark the most extreme diabetic state. Carbohydrate combustion is reduced to a minimum; destruction of protein and production of ketone bodies are accelerated to an extreme degree; total energy expenditure is increased; dehydration and salt depletion, products of diuresis, vomiting and overventilation, attain such severity that they lead to circulatory collapse. The most urgent therapeutic indications are restoration of the fluid and salt supplies of the body and the integrity of the circulation, and elimination of the ketosis and glycosuria which are responsible for the salt and water depletion. In such a critical state these ends must be attained with the least possible delay. The fluid and salt deficits may be repaired at once by administration of saline, supplemented by transfusions, if circulatory collapse is extreme. Reversal of the metabolic disorder requires the use of

every measure that will accelerate the utilization of carbohydrate. Chief among these measures are the administration of insulin and the provision of sugar.

One reason that the use of glucose has been decried is the opinion that, since there is hyperglycemia, there is a large source of available glucose in the body. The actual quantity of glucose in the body seems large because it is expressed in mg. per cent, whereas in the diet it is expressed in grams. This glucose is probably the only reserve of carbohydrate that the patient possesses; there is every reason to believe that the liver in this condition contains minimal quantities of glycogen. The glucose in the body fluids, furthermore, must be derived in this state entirely from protein and the glycerol of fat. At the same time large proportions of the sugar are constantly being wasted in the urine. The chief immediate objective of therapy is to reduce the destruction of protein and the overproduction of ketones. It was under just such conditions that Mirsky, Heiman and Broh-Kahn[69] in their study, already cited, showed that this could be achieved by injection of glucose into depancreatized dogs even though such animals do not burn appreciable amounts of carbohydrate.

Presumably patients also must store a certain amount of glycogen in their livers before they will begin to oxidize carbohydrate. An attempt was made in a series of cases to evaluate the utilization of glucose by analyzing urine and both capillary and venous bloods at frequent intervals for sugar during recovery from diabetic acidosis. Despite the most vigorous treatment, no more glucose appeared to be used in the first 2 to 4 hours than could be accounted for by the amounts required to form liver glycogen. To accelerate this process we have given glucose regardless of the height of the initial blood sugar. After all, unless in his reactions man differs radically from the dog, there is little danger of exceeding the degree of hyperglycemia that facilitates the combustion of sugar. This limit Wierzuchowski[95, 96] set at about 2000 mg. per cent or higher.

After this initial lag in the oxidation of sugar, the blood sugar begins to fall and, when it does so, may decline with considerable speed. In fact the drop may be so precipitate that the patient rapidly develops hypoglycemia with its associated phenomena. To superimpose insulin shock upon the already existing circulatory collapse of diabetic acidosis is most unfortunate. It is highly probable that such accidents have been responsible for a certain number of

deaths during recovery from acidosis. The prevention of these catastrophes is another reason for giving glucose. As soon as the blood sugar begins to fall definitely the rate of administration of insulin should be retarded, while the administration of glucose is accelerated. If the patient is allowed to continue long enough in an unrecognized hypoglycemic state, the liver again becomes deglycogenated, and he may consequently revert to a state of acidosis from the subsequent starvation.

Although it has been our custom to give glucose at a comparatively slow rate in the initial stage of treatment and at a more rapid, but still moderate, rate during the recovery period, we are aware of no evidence that faster administration of larger amounts would necessarily have deleterious effects.

The average routine prescribed for the patient in diabetic acidosis, subject always to variation according to special indications, consists of the injection of 50 units of insulin as soon as blood has been taken for chemical analysis and for blood-grouping. An intravenous infusion of 500 cc. of 10 per cent glucose solution is then begun, together with subcutaneous injection of normal saline solution. The patient is prohibited from receiving anything by mouth. If this prohibition is regarded scrupulously there is no need to resort to lavage. There is no apparent logic in removing with the stomach tube salt solution that the patient so urgently needs. The glucose solution is given intravenously to avoid its local irritating effects and to assure its rapid distribution through the body. It is given in relatively concentrated form to avoid the introduction of large amounts of fluid into the blood stream during the state of circulatory collapse. The saline is injected subcutaneously for the same reason and because it serves as an index of the state of the circulation, which is also followed scrupulously by means of frequent observations of blood pressure. If the saline is not absorbed freely from the subcutaneous tissues it may be inferred that the circulation is not adequate and that transfusion is indicated. Enough saline is given to restore the body fluids.

After the first priming dose of 50 gm., glucose is given intravenously at the rate of about 10 gm. per hour with doses of 20 to 40 units of insulin at the same intervals until the blood sugar, which is determined frequently, begins to descend definitely. At this time glucose is given at a faster rate (about 20 gm. per hour), while the insulin is reduced to half or less of its earlier dosage, according to

the course of the blood sugar. Oral administration of fluids is not begun until the patient has been completely conscious and entirely free from all gastro-intestinal symptoms or signs for from 2 to 6 hours, depending on the severity of the original condition. Then it is instituted gradually, until the patient is able to take salty and carbohydrate fluids freely, when parenteral injections are discontinued.

The ultimate solution of this question must rest upon the sound assemblage of physiological evidence, supported by controlled clinical observations, not by *ad hoc* arguments from particular cases. An attempt has been made to array in some semblance of order the most significant items in the great mass of evidence that carbohydrate should be used in the treatment of diabetic acidosis because it promotes the oxidation of glycogen, supplements the action of insulin, reduces the destruction of protein, and diminishes the production of ketone bodies. It is hoped shortly to document this analysis by a parallel analysis of the large mass of clinical material that has been accumulated in this department.

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