METABOLIC ABNORMALITIES IN STARVATION DIABETES*

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Credit for having first described the phenomenon which was later to be termed "starvation diabetes" or "hunger diabetes" is properly ascribed to Claude Bernard. In his *Leçons sur les propriétés physiologiques et les altérations pathologiques des liquides de l'organisme,* published in 1859, he writes:[9] "It is possible to make an animal diabetic by making it absorb carbohydrate under certain circumstances: namely if sugar is given to it after 24 or 36 hours fast." His evidence for this statement is still older, since the report of one of his experiments showing glycosuria in a rabbit fed carrots after several days of fasting, is dated 1846. In 1873, and again in 1877, in his *Leçons sur le diabète* he stresses this observation:[12] "We can say that we are all potentially diabetic . . . If a man or an animal is fasted for some time, and then given a good meal with an abundance of carbohydrate, glucose will appear in the urine."

It had been known for a century or more that mild glycosuria of short duration is occasionally encountered in otherwise healthy persons. But Bernard was probably the first to recognize as a specific entity the glycosuria appearing when a period of starvation is broken by carbohydrate intake.

Lehmann,[44] as a preliminary to an investigation of the effect of arsenate on diabetes mellitus, performed some animal experiments on glycogen formation in the liver. Upon injecting glucose into a mesenteric vein of rabbits starved for 48 hours, he found to his surprise that no increase in liver glycogen occurred, and that glucose appeared in the urine. This result was contrary to the result of experiments by Claude Bernard[11] and by Schöpffer.[70] When the experiment was repeated on animals not starved, however, he found that in this condition no glycosuria appeared, while a slight increase in liver glycogen could be noted. Curiously enough, he did not relate his observation to Bernard's demonstration of starvation diabetes, although he seems to have been well acquainted with Bernard's work. Lehmann's result, published as

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a thesis in Dutch, might easily have escaped notice, had it not been reviewed* in detail by Hoffman[37] the following year in Naunyn's new "Archiv."

In 1890 Hofmeister,[38] in a more detailed study of the problem, demonstrated in dogs a diminished "assimilation" of carbohydrate after fasting, and showed that the glycosuria was not caused by an augmented intestinal absorption. He coined the term "Hungerdiabetes," and the phenomenon has since then often been referred to as the Hofmeister phenomenon.

Ten years later Hoppe-Seyler, Jr.[39] found that transient glycosuria could occasionally be observed in malnourished, half-starved persons during the first few days of hospitalization.

More recently the glycosuria of starvation diabetes has been studied by Winther.[82] He found that the glycosuria which appears when a high carbohydrate diet is forcibly fed to rats after they have been starved for some time is proportional to the length of the previous period of starvation.

Claude Bernard's discovery of starvation diabetes was one of the results of his ingenious application to many different phases of carbohydrate metabolism of a chemical method for the determination of glucose, namely, Trommer's copper sulfate method published a few years earlier.[77] By the same token, further developments in the investigation of starvation diabetes had to await the introduction and application of new methods for the study of carbohydrate metabolism.

The following review will discuss the metabolic abnormalities that have been shown to exist in starvation diabetes, dividing the topic according to the different methods of investigation that have been applied.

The blood-sugar curve after glucose administration

After the introduction of relatively easy and accurate methods[4, 45] for the determination of the glucose content of small quantities of blood, and the recognition of the normal postprandial blood-sugar curve, as well as the demonstration[40] of the renal threshold for glucose, it was found that the glycosuria of starvation diabetes was caused by an abnormal elevation of the blood sugar. Bang[4] was the first to publish the so-called pseudodiabetic glucose-tolerance curves from human sub-

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* This review contains an amusing misprint, which has been perpetuated ever since. The title of the thesis is given as Arsenate as *Genusmiddel* (a luxury) in Diabetes Mellitus, instead of *Geneesmiddel* (therapeutic agent).

jects given glucose after a period of inanition. This has since often been confirmed, and a period of fat feeding has been found to have the same effect as does starvation on the glucose-tolerance curve.[52, 73] du Vigneaud and Karr[81] showed that the height and the length of the glucose-tolerance curve are directly proportional to the duration of the previous period of starvation, while Adelsberger and Porges[2] demonstrated that a very short fast suffices to bring about these abnormal blood-sugar curves in man.

Himsworth later submitted the whole problem to a closer scrutiny.[31, 32, 33] He found that the elevation of the glucose-tolerance curve was inversely proportional to the amount of carbohydrate in the previous diet, and that only the carbohydrate content, rather than the fat, protein, or total calories of the diet, determined the curve. He also found in animal experiments that after hypophysectomy the difference of the glucose-tolerance curves on different diets was absent.[35] Later investigators, however, have not been able to confirm this finding.[25, 28]

The blood-sugar curve after injection of insulin, and the insulin content of the pancreas

The fall of the blood sugar after injection of insulin is dependent upon the previous diet, since a steeper fall occurs when the animals have been previously maintained on a carbohydrate-rich diet than when they have been fed on a fat diet.[1, 76] Himsworth[31] studied this relationship between the composition of the diet and "insulin sensitivity" in greater detail, and found also a relation between the blood-sugar curves after glucose and after insulin on different diets: the higher the glucose-tolerance curve, the flatter the insulin-test curve. His observations show that the cause, or at least the sole cause, of these abnormal glucose-tolerance curves can not be a lack of insulin in the body.

On the other hand, Best, Haist and Ridout[14] reported a low insulin content of the pancreas during carbohydrate deprivation. Even if it is true that in general no deduction can be made from hormone content regarding the rate of hormone liberation, it seems reasonable to assume that the low insulin content of the pancreas, when no carbohydrate is given, reflects a low insulin output.

The respiratory quotient after glucose administration and after injection of insulin

The problem of starvation diabetes was early attacked from another angle. In 1909 Johansson[41] showed that after glucose administration, the CO_2 output in the expired air was abnormally low following a fast of a day and a half combined with heavy muscular exercise. Since then several studies of the response of the respiratory quotient to glucose administration after fasting or fat feeding have been reported. After prolonged starvation the RQ rise after glucose was found to be very low or absent, [16, 19] while after 5 days on a practically carbohydrate-free diet the RQ response to glucose was abnormally low in human subjects.[55, 56] Johnston, Sheldon, and Newburg[42] showed, however, that a short period of starvation (1 day) or a low carbohydrate diet (2 days) did not alter the RQ rise of a 24-hour period when glucose was given, since only after more prolonged and severe restriction of the carbohydrate intake was the RQ response found to be abnormal. In contrast to these results are the observations showing that after a moderately low carbohydrate diet (20 to 25 per cent of the calories) the rise of the RQ curve in the first 4 hours after glucose is even higher than normal, in spite of the fact that the blood-sugar curves show the usual starvation diabetes pattern.[47] This same dissociation between the abnormalities of the blood sugar and the RQ can be seen in the paper by Dann and Chambers,[19] where the RQ and the blood-sugar response to glucose were determined daily during the period of re-feeding after starvation. The figures show that the RQ response became normal at a time when the blood-sugar curve was still abnormal.

No difference has been found in the RQ curves after injection of insulin in human subjects on a high or on a moderately low carbohydrate diet.[47]

Blood pyruvate, lactate, and phosphate after glucose administration

Wollenberger and Linton[83] have recently shown that the rise in blood pyruvic acid after administration of glucose is abnormal in starvation diabetes. When human subjects were given glucose after starvation for 6 days, the normal rapid rise and fall of blood pyruvic acid was replaced by a sluggish increase, starting later and lasting longer than is normal. The same was true of the blood lactic acid. Plasma inorganic phosphate fell slowly and the usual "retention" of urinary phosphate was either delayed or absent.

Studies of glycogen formation and peripheral glucose utilization

In 1914 Barrenscheen[5] reported that in perfusion experiments, the glycogen formation of the liver was very low in starved animals, but Dann and Chambers,[20] working with intact animals, were unable to confirm this result. The latter authors also found a small increase in muscle glycogen when glucose was administered after a period of starvation. No control experiments with fed animals were made.

Soskin and Mirsky[72] found that the blood-sugar fall which occurs following evisceration was of the same steepness in fed and in fasted animals. Drury[22] and Bergman and Drury,[8] using eviscerated rabbits, were able to demonstrate, however, a considerable difference in the amount of glucose necessary to prevent the blood sugar from falling in fed and in starved rabbits. After 2 days of fasting less glucose was needed, and after 3 days of fasting still smaller amounts were necessary. During fasting the glycogen stores of intact rats previously maintained on a high fat diet are more slowly depleted than are those of animals kept on a high carbohydrate diet.[69] Roberts, Samuels, and Reinecke recently published a series of papers on the metabolism of eviscerated rats on these same diets, in which they confirmed the finding of Bollman and Mann[15] that fat fed animals survive longer after evisceration than do those fed carbohydrate, and they showed that the fall in blood sugar in eviscerated, but not nephrectomized, animals is considerably slower in the animals previously maintained on the fat diet. This same difference in the fall of the blood sugar following evisceration was found when fasted animals were compared to animals fed a high carbohydrate diet. However, in eviscerated and nephrectomized animals no appreciable difference in the rate of blood-sugar fall was found.[59] By studying, in eviscerated animals, the glucose concentration of blood from the aorta and from the renal vein, they found a higher concentration in the blood leaving the kidneys in the fasted animals, while no difference of blood-sugar concentration was seen in animals fed up to the time of operation.[61]

This seemed to indicate that the apparent decrease in carbohydrate utilization in the starved eviscerated animals was caused—at any rate partially—by renal gluconeogenesis. Nevertheless, in later studies where fat feeding was used in the previous period in place of inanition, no such addition of glucose by the kidneys occurred.[62] The significance of these results is not clear, especially when it is remembered that renal gluconeogenesis has not been demonstrated in non-eviscerated animals.[61]

That carbohydrate starvation induces a real change in the ability of the peripheral tissues to utilize glucose has been found by Lundbaek and Stevenson[49] who studied the metabolism in vitro of the diaphragm from rats on different diets. The glucose utilization of the tissue from animals previously maintained on a high carbohydrate diet was about twice as great as that of animals fed a high fat, non-carbohydrate diet.

Absorption of glucose from the gastro-intestinal tract

The absorption of glucose is slower in rats fasted 48 hours than when the fasting period has been only 24 hours.[17, 23, 53] After a period of carbohydrate free diet the absorption of glucose from the small intestine has been found to be reduced by about 15 per cent in some experiments[50] and by about 40 per cent in others.[80] The results demonstrate, however, only that the absorption under these circumstances is slower, not that it is incomplete.

Reduced carbohydrate intake in starvation diabetes

Recent experiments indicate that when normal rats are maintained for a period of 1 to 2 weeks on a high fat, non-carbohydrate diet and are then shifted to a carbohydrate-rich diet, a considerable decrease in caloric intake occurs. No change of food intake was seen when the opposite change was made, i.e., if the rats were first fed a high carbohydrate diet and then shifted to a high fat diet. The same phenomenon, but more pronounced, was observed in rats with hypothalamic hyperphagia. When the latter animals had attained a high degree of obesity, their food intake upon change from a high fat to a high carbohydrate diet was reduced to very low levels or they stopped eating altogether.[48]

Glycogen formation in adipose tissue after starvation

In a series of papers Wertheimer,[79] Hoffmann,[36] Tuerkischer,[78] and Mirski[54] reported experiments which show that an accumulation of glycogen, and probably subsequent transformation of the glycogen into fat, occurs during re-feeding after a period of starvation. Normally only traces of glycogen are found in the body fat; but when young rats are starved for from 7 to 10 days and are then given a high carbohydrate diet, glycogen appears in their fatty tissues. After two days of re-alimentation the glycogen content is as high as 1 per cent, then it declines, reaching values below 0.03 per cent after about a week. During this fall an increase of fat is observed in the body of the animals.

As this glycogen formation has been found only during re-alimentation after starvation, and only if the food given is carbohydrate, it is presumably to be regarded as a phenomenon of starvation diabetes. It would seem of considerable interest to determine if the same glycogen formation would be found in experiments in which starvation was replaced by a period of fat feeding.

Blood lipids and ketones

As a result of the increased fat metabolism during starvation or fat feeding, the blood fatty acids, cholesterol, lipid phosphorus, and ketones are elevated.[43, 51] In man, where renal "thresholds" for acetoacetic acid and β-hydroxybutyric acid are relatively low, a short fast or a fat-feeding period induces ketonuria. This is especially the case in children.[74] In the rat, however, a considerable increase in blood ketones must occur before ketonuria sets in.[71]

When glucose is given following a period of starvation, the blood ketones decrease after a latent period of about one hour;[18] the ketonuria disappears entirely in the course of 1 or 2 days.[6]

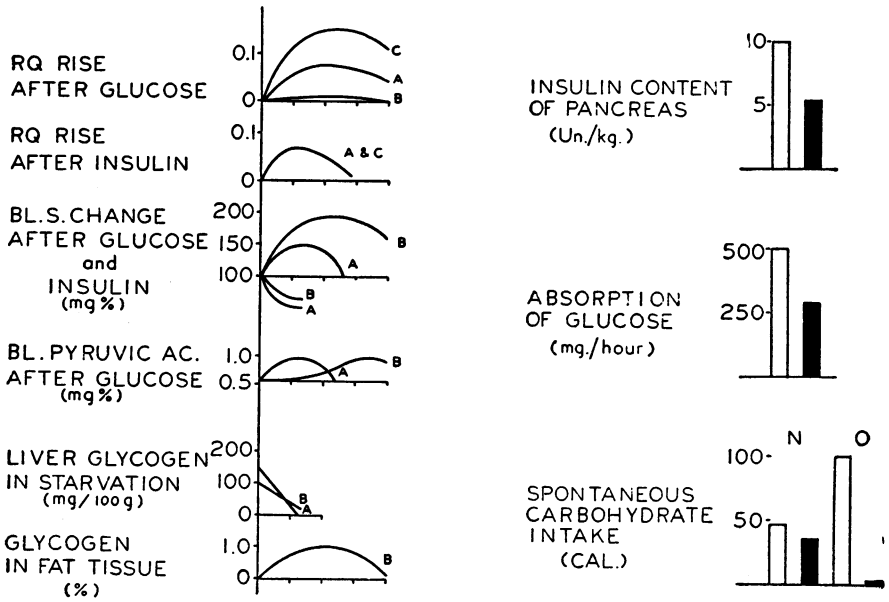
Discussion

During fasting or carbohydrate deprivation a profound change takes place in the intermediary metabolism of the body. The organism, which has hitherto relied upon the practically continuous influx of more or less carbohydrate-rich materials, is now forced to subsist on its own or exogenous fat and protein. But, as is well known, a certain amount of carbohydrate must be oxidized for the maintenance of life. That the central nervous system requires for its function a constant supply of carbohydrate is evidenced by the RQ of unity of the brain,[30] by the coma observed during profound hypoglycemia and by the very low arteriovenous oxygen difference in this same state,[29] and by the immediate relief of hypoglycemic symptoms by injection of glucose. Since the carbohydrate stores are never large, carbohydrate has to be formed in the body during fasting or fat feeding, and under these circumstances a decrease in the utilization of carbohydrate by tissues not having an obligatory carbohydrate metabolism would evidently be of advantage to the organism.

The period of carbohydrate starvation required to induce starvation diabetes must therefore be characterized by gluconeogenesis, and, presumably, by decreased peripheral glucose utilization. These two processes,

gluconeogenesis and glucose utilization, are under the influence of the total hormonal balance of the body. Is it possible to point to any specific endocrine function or functions which may be responsible for the change in carbohydrate metabolism occurring during carbohydrate starvation?

During fasting the liver and muscle glycogen of hypophysectomized rats is rapidly depleted,[68] and the RQ is high.[24] If crude anterior pituitary extract is given the loss of muscle glycogen is prevented and the RQ is lower.[24, 64, 67] That this "glycostatic effect" is related to a change in peripheral glucose utilization is seen from its occurrence also in eviscerated rats.[65]



Schematic representation of some metabolic abnormalities in starvation diabetes.

A (or white columns)—after normal or high carbohydrate diet;
B (or black columns)—after carbohydrate free diet;
C—after moderately low carbohydrate diet;
N—normal rats;
O—rats with hypothalamic obesity.
Abscissa—upper 4 curves in hours; lower 2 curves in days.

The pituitary influences gluconeogenesis as well, primarily by way of the adrenal cortex.[66] Injection of pituitary extracts rich in adrenocorticotropic factor,[7, 26] as well as injection of adrenocortical steroids[46] result in an increase in urinary nitrogen and a rise of liver glycogen. There is evidence of increased adrenocortical function during fasting.[75]

Finally, as mentioned above, the insulin content of the pancreas is decreased during carbohydrate starvation. This decrease, which is presumably associated with a decreased insulin secretion, might be thought to be secondary to an augmented pituitary function, especially since the injection (in dogs) of crude pituitary extracts has the same effect on the insulin content of the pancreas as does fat feeding.[13] Since it has been shown, however, that the effect of fat feeding persists after hypophysectomy,[27] the islet cells seem to be able to respond directly to changes in the demand of the tissues for insulin.

Beside the alteration of the hormonal pattern it is probable that during carbohydrate deprivation changes in the tissues occur, either autonomously or secondary to the changes in the production of various hormones. Both the fact that in the hypophysectomized animal the glucose-tolerance curve and the rate of depletion of carbohydrate stores are dependent upon the previous diet,[69] and the results of studies of glucose utilization by the rat diaphragm[49] point in this direction. It is conceivable that the decreased peripheral carbohydrate utilization, caused by a change of the hormonal status of the body, secondarily results in a partial "atrophy" of cellular enzyme systems responsible for the metabolism of glucose. However, the possibility of an autonomous cellular regulation, independent of the endocrine secretions, can not be denied.

Starvation diabetes is the abnormal state observed when an organism in which the above-mentioned changes have taken place is made to respond to exogenous carbohydrate. When glucose is given after a period of starvation or maintenance on a carbohydrate-free diet, the difficulties of the organism in handling this type of foodstuff are revealed by the manifold abnormalities described in this review.

It is not clear to what extent the observed phenomena are attributable to increased gluconeogenesis, or how much they are due to decreased ability to oxidize or store carbohydrate. The abnormal blood-pyruvate curve after glucose and the decreased glucose utilization of muscle tissue in vitro seem to demonstrate a decreased oxidation, and the same applies to the results of studies of the RQ (if this is taken to give a true picture of the oxidation of carbohydrate in the intact body).

The dissociation between the blood-sugar curve and the RQ curve after glucose administration, i.e., the finding that a moderate or short period of carbohydrate deprivation results in abnormal glucose-tolerance curves while the RQ response is still normal or even above normal, points to the possibility of different factors in the evolution of the

metabolism of carbohydrate starvation. It is possible that the aforementioned changes in cellular enzymes are developing more slowly during the period of deprivation, and that these are responsible for the extreme abnormalities seen, e.g., in the RQ response after prolonged starvation.

The carbohydrate which can not be metabolized after a period of carbohydrate lack is partially stored in the liver,[20] while part of it may be excreted in the urine. Moreover, the results of Tuerkischer and Wertheimer[78] show that during re-alimentation after a period of starvation, some of the carbohydrate is stored temporarily in the adipose tissues.

Finally, study of the eating habits of rats has shown a reduced carbohydrate intake in starvation diabetes. This reduction might be related to the slower rate of absorption of glucose from the gut, as well as to the reduced ability to handle carbohydrate after the absorption. In diabetic rats, which have also been shown to abstain from carbohydrate,[60] no reduction of the absorption capacity is found.[57]

The importance of starvation diabetes for the study of diabetes mellitus may be briefly mentioned.

First, studies of starvation diabetes are pertinent to the discussion of the dietary treatment of human diabetes mellitus, particularly to the question of the use of glucose in the treatment of diabetic acidosis. This side of the problem has been admirably dealt with recently by Peters[58] and needs no further comment.

Secondly, it is important for the problem of the etiology of this disease. The rôle of the previous diet in the development of diabetes mellitus has been discussed for centuries. Quite naturally, early clinicians believed that at least some cases of diabetes mellitus in rats were caused by overindulgence in sweet foodstuffs. This hypothesis seems to be supported in modern times by the results of Allen,[3] in which partially pancreatectomized, non-diabetic dogs were made diabetic by giving them a carbohydrate-rich diet, as well as by Dohan and Lukens' recent demonstration of islet-cell degeneration after prolonged glucose infusion in cats.[21] The opposite view is held, however, by Himsworth,[34] who has been particularly interested in the problem of starvation diabetes. By an analysis of eating habits in different localities, he came to the conclusion that diabetes mellitus was more frequent among people whose habitual diet is low in carbohydrate. Naturally, it is not so much the low carbohydrate content of the diet itself which is important, as the fact that periods of low carbohydrate intake are interpolated between single ingestions of carbohydrate, thereby causing repeated periods of starvation

diabetes. If this hypothesis is correct, it might be possible to induce diabetes mellitus in animals by alternating periods of low and high carbohydrate intake, or of starvation and high carbohydrate diet. In view of the reduced carbohydrate intake in starvation diabetes it would probably be necessary to use forced feeding in the high carbohydrate periods.

In any case, in human diabetes the heredity factor must be taken into account. As a conciliatory hypothesis it might be suggested that, given a pre-existing hereditary weakness of the insular apparatus (or of the hormonal balance which includes this), manifest diabetes mellitus might result from a very high carbohydrate intake, as well as from a changing diet with its periods of starvation diabetes.

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