BLOOD SUGAR REGULATION AND THE ORIGIN OF THE HYPERGLYCEMIAS.

I. GLYCOGEN FORMATION AND GLYCOGENOLYSIS.

By EINAR LANGFELDT.

(From the University Physiological Institute, Christiania, Norway.)

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The normal blood sugar concentration is from 0.09 to 0.10 per cent with a physiological latitude between 0.07 to 0.11 per cent. In a number of mammals the blood sugar concentration is also found to be 0.09 to 0.10 per cent (1).

This blood sugar concentration is constant in normal individuals, and the regulation is very finely adjusted. Normal feeding does not cause any change. By administering glucose the concentration is increased rapidly within a few minutes, whereafter it quickly decreases to the normal. Values more than 0.12 per cent are generally referred to as hyperglycemias.

The disclosure of the mechanism of this normal regulation and of the causes of its disorder is indispensable for the apprehension of the nature of diabetes.

The first workers on these problems considered the appearance of sugar in the circulating blood as a pathological phenomenon. The blood serum in diabetics was found to taste sweet (2). When it was proved that starch by digestion in the intestine forms sugar (3), and that sugar occurs in the blood of normal animals after feeding carbohydrates (4), the blood sugar was considered as physiological, but, however, as accidental and being closely connected with the digestion.

This was the opinion when Bernard (5) commenced the series of investigations which proved that sugar occurs normally in the blood and independently of the digestion. His statements that the vena hepatica in a meat-eating dog also contains sugar, that the isolated and washed liver produces sugar, that this
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sugar formation is of a fermentative nature, that the puncture of the medulla oblongata at the base of the fourth ventricle may produce hyperglycemia and glycosuria, and that the origin of this sugar is a polysaccharide (glycogen), which disappears after piqûre, are the epochal discoveries which form the starting point for modern research on diabetes.

Bernard supposed that blood sugar was secreted by the liver. This sugar secretion was, according to his opinion, regulated by the nervous system. He supposed that sugar combustion took place in the lungs. Between sugar combustion in the lungs and sugar secretion in the liver was a nervous connection by means of the vagus, via the medulla oblongata. The combustion in the lungs caused a reflex increase in secretion in the liver. Later, when sugar was proved to exist in all circulating blood, Bernard in his theory put the capillaries in place of the lungs, but did not, however, alter the theory as to blood sugar regulation by reflex. By a nerve path via the medulla oblongata, the liver received impulses to increase sugar secretion, and in this manner the blood was supplied with sugar in proportion to the requirement.

According to this theory Bernard considered diabetes as a nervous disease. And this view on diabetes as a disease of nervous origin, as well as his opinion of the blood sugar regulation as governed by the requirement of the organs for sugar, is still accepted by many clinicians. Von Noorden (6), however, introduced a change in this theory. He still assumed, as did Bernard, that the transformation of glycogen into glucose was governed by the requirement of the organs for sugar. But he supposed that this transformation took place on a chemical signal from the muscles to the liver, passing through the blood stream.

Many attempts have been made to examine the nature of the process that takes place by the transformation of glycogen in the liver. Bernard supposed that the diastase, found by him and later stated by many other investigators, might be an important factor in this process. The diastase occurs in vivo in the liver cells. This fact does not make these processes any easier to explain. The question is: How is it possible for the glycogen, which also occurs intracellularly, to exist in the same cell as the

diastase without at once being hydrolyzed to glucose. Bang (7) holds that the pure liver diastase is inactive and that an activator must be supplied. As far as another diastase, the ptyalin, is concerned, it has been proved that such activators exist. The dialyzed, inactive ptyalin is activated, as shown by Michaelis and Pechstein (8), by a number of neutral salts. Bang (1, 7) has, by experimenting on surviving frog liver, found that it is the same case with the liver diastase, as far as can be concluded from the increased sugar formation. Before the diastase can become active and before sugar really can be formed, the diastase must be in contact with sodium chloride. Normally, however, the resting normal cell is impermeable to sodium chloride. By the secretion of bile the liver cells absorb and excrete sodium chloride, and it is this process, which, according to Bang, maintains the normal blood sugar concentration. Bang has also found that adrenalin in the isolated frog liver surviving in Ringer solution, causes a heavy formation of sugar, and the mechanism of the adrenalin hyperglycemia is, therefore, according to Bang (1), established in that way; that is, the adrenalin makes the liver cells permeable to sodium chloride, which thereafter activates the diastase. The hypothesis is attractive, but the proofs are still missing that the adrenalin changes the permeability.

Another suggestion, made by Grode and Lesser (9) is that the glycogen and the diastase exist separately in the same cell, but under certain influences these two substances may come in contact.

Both of these hypotheses try to explain how it is possible for the glycogen to exist in liver cells together with the diastase. It can be explained according to both why sugar formation takes place in the surviving liver and especially quickly in the ground liver. But neither of them gives a satisfactory explanation of the mechanism of glycogen formation and of glycogenolysis. They do not explain how sugar is secreted apparently according to requirement. Neither do they explain how it happens that the blood sugar concentration is constant, even if the liver is free from glycogen, nor what causes the liver cells, apparently at the right moment, to transform the right quantity of glycogen into glucose and secrete it into the blood. A treatment of these questions and an investigation regarding the nature of these processes will always be incomplete, provided that they deal only with glycogenolysis.
The processes taking place are of two kinds, namely a glycogen formation and a glycogenolysis, and both participate in the blood sugar regulation. The conditions under which these processes normally take place and the influences, which under physiological and pathological circumstances may be prevailing, must be examined separately.

In this paper the conditions of glycogen formation and of glycogenolysis are dealt with. In Paper II the experimental data are given, and in Paper III an effort has been made to correlate the facts.

Glycogen Formation.

Bernard believed, as is well known, that glycogen is formed only from protein. The deposit of glycogen in the liver also, after feeding with carbohydrates, was, in his opinion, caused by the protein-sparing effect of carbohydrates. By the investigations of Pavy (10), E. Voit (11), and C. Voit (12) it was proved that animals fed carbohydrates form glycogen directly, even in a higher degree than proteins.

In 1903 Grube (13) commenced experiments to determine whether carbohydrates form glycogen in the artificially perfused liver. Grube experimented on turtles and is the first who has been able to prove a glycogen formation by the method of surviving organs, in which Martz (14) a few years earlier was not successful. Grube supposed that the reason why Martz was unable to observe any glycogen formation was that the latter used too strong concentrations of glucose in his transfusions, namely 2 and 2.6 per cent, and that these concentrations harmed the liver cells. However, it is difficult to agree with Grube in this objection, when the positive result which Doyon and Morel (15) obtained by injection of a 30 per cent solution of glucose into the vena mesenterica in a dog is taken into consideration. That the concentration is without importance was further clearly demonstrated by the formation of glycogen which Freund and Popper (16) observed by injection into the vena mesenterica in dogs of 1, 2, 5, 10, and 25 per cent solutions of glucose, and also by Parnas and Baer (17) by injections of 0.5 and 2.5 per cent solutions. Ishimori (18) also observed glycogen formation in a rabbit by injection of a 20 per cent solution of glucose into the
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vena mesenterica. In numerous experiments on rabbits Barrenscheen (19) obtained formation of glycogen in the isolated liver by 2 per cent solution of glucose. Barrenscheen also made the observation that 2 to 5 days after total pancreatectomy the dog liver cannot form glycogen in transfusion experiments; but after partial pancreatectomy the glycogen formation takes place normally.

It is therefore interesting to see what method is used by the different investigators. Grube in all his investigations used a liver-pancreas preparation and obtained positive results. Martz, however, who did not observe any glycogen formation in the liver perfused with solutions of glucose, experimented on isolated liver without pancreas. The other investigators quoted, all of whom obtained positive results, did not experiment on isolated livers, but only injected the sugar solution into the vena mesenterica, and the liver thus received the pancreas hormone in a normal manner.

By critical examination of the literature on this subject it is concluded that the pancreas is necessary for glycogen formation in the liver, an opinion already put forward by de Meyer (20) in 1909.

This opinion is further supported by other investigations made by Langfeldt (21). During examinations on alimentary hyperglycemia in normal dogs it was observed that blood sugar concentration increased rapidly; the maximum was reached after about 1 hour, whereafter the concentration again decreased quickly. The curve was pointed. The sugar concentration in the blood might increase to 0.17 per cent without sugar passing into the urine. As the sugar rapidly disappeared from the blood and was not excreted in the urine, we were forced to believe that it was either burned or deposited as glycogen. Combustion cannot explain the disappearance of such large quantities of glucose which have been used in these experiments, up to 30 gm. per kilo of body weight, in such a short time, and there is no other explanation possible than that it is deposited as glycogen. That a diffusion of glucose as such into the tissues should take place and that it should remain there in crystalloid state is impossible on account of the increase in the osmotic pressure which would occur. As long as the maximum glycogen formation in the body,
namely 37 gm. per kilo (Schöndorff (22)) is not reached, and since the presence of other carbohydrates is not proved, it is to be assumed that the glucose normally is rapidly converted into glycogen.

In partially depancreatized dogs we observed by similar alimentary tests that the rate at which the blood sugar concentration decreased lessened shortly before diabetes was manifest. A long time after the operation the animals were normal with regard to this point. The pancreas remnant secreted sufficiently to secure a quick glycogen formation. But gradually as the pancreas remnant sclerotized, this ability was reduced; that is, after the maximum was reached the blood sugar concentration did not decrease so rapidly by the tolerance tests as before. Otherwise the dogs were normal in this period, they did not have spontaneous glycosuria when fed normally, and the blood sugar concentration was normal at the beginning of the tolerance test. The only difference in the condition was that more time was required before the blood sugar concentration again became normal. Gradually, less and less glucose was required to produce a more lasting hyperglycemia. These alimentary hyperglycemias of long duration in fasting, partially depancreatized dogs cannot be caused by anything else but a reduced ability for glycogen formation—an ability which normally depends upon a sufficient pancreas.

On the basis of these experiments and of the experiments by other investigators it is therefore concluded that the formation of glycogen depends upon the presence of the pancreas hormone. There is probably also a formation of glycogen by means of the diastase as enzymatic glycogenolysis, like all enzymatic processes, is reversible. However, this process is, from a quantitative standpoint, subordinate compared with the specific glycogen formation by means of the pancreas hormone. But it explains why the liver never is entirely free from glycogen even after total pancreatectomy.

_Glycogenolysis._

That glycogen is transformed into glucose post mortem has been known since the days of Bernard; likewise that this post-mortem transformation is due to a diastatic enzyme, which can
be extracted with water and precipitated with alcohol. Bernard supposed that this enzyme also appears in vivo and that it acts in the sugar formation in vivo.

Not every one agreed with this. Thus Schiff (23) supposed that the liver normally was entirely sugar-free and that the diastase was formed post mortem in the blood. Tiegel (24) was of the same opinion and supposed that the diastase was formed by destruction of the erythrocytes. Pavy (25) at first was of the opinion that the sugar was formed post mortem and in such a way that the glycogen diffused into the blood, which had diastatic ability. The pathological sugar formation in vivo depended upon the contact of the glycogen with the blood. Seegen (26) did not acknowledge the existence of a diastatic liver enzyme, and Bial (27) denied that the liver itself produced a diastase, suggesting that it appeared to have immigrated from the blood.

Thus, while a number of investigators identified the liver diastase with the blood diastase, a number of other investigators, as Dastre (28), Paton (29), Cavazzani (30), and others, suggested that sugar formation was not of enzymatic nature, but was caused by a specific action of protoplasm.

There was no general agreement with Bernard’s theory of glycogenolysis. Nor was von Wittich’s statement (31) that glycerol extract from the washed, blood-free liver had diastatic effect, regarded as convincing. When Tebb (32) had shown that liver powder could be kept in alcohol for 6 months without losing its diastatic effect, and when Wohlgemuth (33), using the Buchner method, had produced a liquid with heavy diastatic effect, the enzymatic nature of sugar formation was considered as proved. Zegla (34), Macleod and Pearce (35), and others demonstrated the enzyme by the same method.

The existence of the diastase in the liver cells was now to be considered as a fact. For the further investigation of normal and pathological sugar formation it was necessary to know whether sugar formation in the liver really was a vital function of the liver cells, or whether it was independent of the nervous system and of the internal secretion.

The proof was given by Bang (7). In experiments on isolated frog livers surviving in Ringer solution, Bang proved that sugar formation in the liver is a vital and independent process.

A heavier sugar formation as a result of an increased glyco- genolysis may take place, however, under different influences. Glycosuria, after administration of inorganic acids per os or by intravenous injection, was recorded by Naunyn, von Frerichs, Pavy, and Külz (cf. Elias (36)). Ehrlich and von Frerichs (37) observed that the glycogen disappeared when frogs were put into water containing acetic acid.

The effect of acids on the metabolism of carbohydrates was examined by Elias (36), by Elias and Kolb (38), and by Elias and Schubert (39) in an extensive manner. They observed that small amounts of acids per os (rabbits and dogs) as well as by transfusion of the liver (turtles) caused glycogenolysis, which was followed by hyperglycemia and glycosuria.

One may conclude from observations made on partially depan- creatized dogs by Langfeldt (21) that an increase of the hydrogen ion concentration in the blood of the portal veins is able to produce a heavy glycogenolysis. On account of the absence of alkaline pancreatic juice in these dogs the acid gastric juice will not be neutralized in the intestine and consequently the hydrogen ion concentration in the blood of the portal veins is increased, when the gastric juice or the contents of the stomach are absorbed in the intestine.

In these dogs it was observed that the secretion of gastric juice itself, caused by giving water or bouillon, was able to produce a considerable hyperglycemia. In depancreatized, but yet not diabetic animals, a smaller, but distinct hyperglycemia likewise was produced in the same way, while a normal dog did not show any change in the blood sugar concentration.

Corresponding observations were made by Murlin and Sweet (40), who delayed the appearance of the glycosuria by ligation of the pylorus or by gastrectomy before pancreatectomy.

When all these facts are taken into consideration, the question arises: What is the nature of this acid action? Considering the known influence of hydrogen ion concentration on enzyme action in general, we are led to expect that the acid supply affects the diastase by altering the reaction of the mixture.
As far as all diastases hitherto examined are concerned, it has, as previously mentioned, been proved that pure diastase is inactive. Together with neutral salts, or rather, with the anions of these salts, the salivary diastase forms complex compounds, and these compounds have diastatic effect (Michaelis and Pechstein (8), Norris (41)). These different salt diastases have their optimum of action at different hydrogen ion concentrations; the nitrate diastase at pH 6.7, the chloride diastase at pH 6.9, the sulfate and phosphate diastases at pH 6.1.

If it should be proved that the liver diastase also forms such complex compounds with different hydrogen ion optima, it would remain to be determined whether the endocrinogenous hyperglycemias, the adrenalin, and the thyroiodine hyperglycemias—which are the only experimental hyperglycemias—are perhaps due to the formation of similar complex compounds with the liver diastase, resulting in a change in the conditions of reaction.

The present problem thus consists of an examination of the conditions of action of the liver diastase, acting on glycogen, the influence of the most important physiological anions, and of extracts from the endocrine organs.

The examination of these problems forms the experimental part of this work, and the results obtained form together with the reflections in this paper the basis for that theory on the blood sugar regulation and on the mechanism of the origin of the hyperglycemias, which will be presented in Paper III.

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