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THE ROLE OF THE LIVER IN DIABETES MELLITUS*

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LECTURE II

The liver and the muscles both contain glycogen, and the total amount in each is about the same, as the high percentage of glycogen in the liver makes up for the small bulk of that organ compared with the large bulk of the muscles, with their low percentage of glycogen.

Effect of Removal of the Liver

The action of the liver has been studied in various ways, one of which involved its removal. This study was made possible by the work of Mann and his co-workers (1922, 1923a, 1923b, 1927). They showed that when the liver was removed the animals developed hypoglycaemia, which could be relieved at once by giving glucose. The hypoglycaemia occurred even though the muscles still contained a good deal of glycogen which was clearly unavailable for transport elsewhere even though urgently needed. Mann suggests that the glycogen stores in the muscle are mainly reserved for muscular activity, and it would seem that the stores in the liver are used for the maintenance of the blood sugar. When a pancreatectomy is performed at the same time as the hepatectomy the conditions are identical with those produced by hepatectomy alone, but the animal does not live so long. The hypoglycaemia is relieved by sugar as usual. If the hepatectomy is performed twenty-four to forty-eight hours after the pancreatectomy, when the blood sugar is between 200 and 400 mg. per 100 c.cm., the blood sugar begins to decrease at once and the characteristic symptoms of hypoglycaemia appear; but these occur when the blood sugar is still fairly high, and sooner than usual. A similar result is obtained when the hepatectomy is not performed until forty-eight to ninety-six hours after the pancreatectomy, but the symptoms associated with hypoglycaemia occur at a still higher blood-sugar level. Glucose removes the symptoms, but the animals live only a short time.

The fact that insulin causes a decrease in the blood sugar in the absence of the liver proves that the liver is not necessary for the action of insulin. This is supported by the work of Best, Hoet, and Marks (1926), who showed that insulin caused sugar to be laid down in the muscles as glycogen when the hind legs of a dog were perfused with sugar and insulin. Himsworth (1933) has suggested that the liver secretes a substance that activates insulin, but it is difficult to see how this can be the case in view of these two series of experiments.

These experiments show that the liver plays a very important part, as it acts as a storehouse for glycogen, which is available for maintaining the level of the blood sugar and the needs of the body. It is interesting to note that Mann found that the animals kept well if only 15%

of the liver (i.e., between one-sixth and one-seventh) was left intact. This compares very closely with Allen's (1920) estimation of the amount of pancreas necessary to maintain life in a dog as one-eighth to one-ninth (12.5 to 11.1%).

The Phloridzin Experiments

The ability of the liver to maintain the level of the blood sugar is well shown by the phloridzin experiments (Nash, 1927). The latter drug lowers the renal threshold, so that glycosuria occurs although the blood sugar is not raised. If enough phloridzin is given there is much glycosuria, and the blood sugar eventually decreases and hypoglycaemia may occur; but before it does so the excretion of nitrogen in the urine increases and acetone bodies are excreted. The increased loss of nitrogen is an indication of the break-up of the body proteins that are being used to supply the sugar, while the formation of acetone bodies shows that either the fat or protein metabolism is upset. This can be prevented by giving sufficient sugar or protein, while the action of the phloridzin can be abolished by tying the ureters or removing the kidneys.

Effect of Starvation

The effect of starvation is in some ways similar to that of phloridzin, for if no food is supplied the body proteins are broken up, as shown by the daily excretion of 7 to 10 grammes of nitrogen, and the urine contains ketone bodies. The ketosis due to a fast disappears very soon after carbohydrate is given (Goldblatt, 1925). Himsworth (1939) pointed out that the severe ketosis of patients who are near diabetic coma can be abolished by giving large doses of carbohydrate either by mouth or intravenously. This was the real basis of von Noorden's oatmeal cure, although he also gave a diet containing only protein and fat before and after the oatmeal. Thus Hurlley (1915-16) found that the von Noorden egg-and-vegetable diet caused a decrease of the total sugar from 148 to 11.5 grammes and of the total acetone bodies from 39.8 to 5.2 grammes. The oatmeal diet with its 142 grammes of sugar raised the urine sugar to 93 grammes, but reduced the total acetone bodies to 1.2 grammes. Both the sugar and the acetone bodies increased rapidly when the original diet was given, and it was these observations which led me in 1915 to increase the diet much more slowly after starvation treatment.

Blood Changes following Ingestion of Sugar

The study of the changes in the blood which take place after sugar has been given by mouth or intravenously has added greatly to our knowledge. This work was made possible in 1913 by Ivor Bang's method of estimating the sugar in 0.1 c.cm. of blood or less. This enabled Jacobsen (1913) to discover that the blood sugar was not constant throughout the day, but increased for a time after a carbohydrate meal. One point of great importance is the

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effect of sugar on the capillary and venous blood. Before a dose of sugar these are usually identical, but after it the capillary blood contains more sugar than the venous blood for a time, and thus shows that the muscle takes up the sugar. In diabetes either the capillary and the venous blood are the same or the venous blood is a little higher than the capillary blood, and the giving of insulin restores the power of the muscles to take up sugar again. The part played by the liver is much more obscure. The percentage of sugar has been estimated in the portal and hepatic veins, and sometimes that of the portal vein is higher than in the hepatic vein, and vice versa. The actual amount of sugar laid down in the liver has been estimated by Soskin, Essex, Herrick, and Mann (1938) by an ingenious method. The inferior vena cava below the liver was ligatured, so that all the blood from the lower limbs returned to the heart by collateral vessels, and the blood in the inferior vena cava above the liver contained only blood coming from the liver. This operation enabled the amount of sugar entering and leaving the liver to be estimated before and after an intravenous dose of sugar. The experiments showed that as a rule the liver was giving out 20 to 50 mg. per minute more sugar than it took in. When it was given intravenously both the total intake and the output of sugar of the liver increased enormously, but the output was smaller than the intake for some forty-five to sixty minutes. In one experiment the gain of the liver was at the rate of 0.5 gramme per minute fifteen minutes after the injection. The liver therefore gained a good deal of sugar during this period, but then began to give out more than it took in. Soskin and Mann therefore concluded that these experiments were in favour of the homeostatic hypothesis put forward by McLeod. This postulates that whenever the blood sugar rises above the normal level the liver responds by diminishing its output of sugar into the blood. The figures do not show that the liver diminishes its output of sugar, for actually the output is much greater than before the sugar was given; but they show that the liver stores sugar so long as the blood sugar is raised, and begins to excrete it as soon as the blood sugar falls. The liver probably plays a very important part in determining the shape of the sugar-tolerance curve, and it may well be more important than the muscles.

Glycogen Storage

The mechanism by which sugar is laid down in the muscles seems a relatively simple one, as it is determined by the presence of insulin and is not dependent on the presence of the liver; but the way in which the glycogen is laid down in the liver is not so clear. In adult animals the giving of insulin does not seem to increase the liver glycogen even when the blood sugar is maintained at a high level. The only exception to this is the young rabbit, which lays down glycogen in the liver under the influence of insulin (Goldblatt, 1929). This is probably due to the action of adrenaline (Corkill, 1930), as it does not occur when the adrenals are removed (Cope and Corkill, 1934). The thyroid also exercises a control, for Burn and Marks (1925) found that feeding with thyroid, if long continued, rendered the liver free from glycogen. This reaction to insulin was, however, peculiar. At first the animals became very insensitive to insulin; but later on they became very sensitive when the liver contained very little glycogen, and might develop spontaneous hypoglycaemia. The action of adrenaline in producing hyperglycaemia was similarly at first much increased, but later it decreased. Thyroidectomy makes the animals more sensitive to the action of insulin, while adrenaline has less effect. The problem is a difficult one, however, and seems to depend on the amount of glycogen in the liver.

The hypophysis is very important, for when it is removed the animal is apt to develop hypoglycaemia (see Lecture I). This is brought on very easily when the animal is fasted, and also occurs when the pancreas is removed as well as the hypophysis. It is prevented by giving carbohydrate and also by protein, but not by fat (Houssay and Biasotti, 1930; Houssay, 1936). Soskin and Mirsky (1935) tried the same experiments with dogs which had been depancreatized as well as hypophysectomized. This causes a very mild diabetic condition, but excess of carbohydrate or of protein in the diet always produces hyperglycaemia, showing that the diabetic condition is still present. Feeding with fat, however, does not cause hyperglycaemia, and hypoglycaemia develops easily after a fast. Soskin (1930) suggests that the real reason why the diabetic condition is so mild is the failure of the liver to make glycogen from fat. He also found that a depancreatized dog with its hypophysis intact which is fed on a low-calorie diet of protein without fat has a milder diabetes and gradually develops a greater power of using sugar, whereas this does not occur when fat is present in the diet. This is at variance with the work of Petren (1924) and Newburgh and Marsh (1923) on man, to which I shall refer later.

Sugar Tolerance

One of the diagnostic signs of diabetes mellitus is the increase of the sugar in the blood. The reason for this has been much discussed, and Himsworth (1939) has brought forward evidence suggesting that the tissues of the diabetic were better able to use sugar when the blood sugar was high. This hypothesis is supported by the work of Soskin and Levine (1937) on eviscerated dogs. They found that the depancreatized dog uses less sugar than the dog with its pancreas intact, but that when the blood sugar increases the depancreatized dog uses more sugar, and at a blood-sugar level of 700 mg. it utilizes the same amount of sugar as a normal dog does at a level of 500 mg.

Since the diabetic animal can use sugar as well as the normal one when the blood sugar is proportionately raised, the old view of non-utilization must be abandoned. But the diabetic in attempting to use the sugar in this way wastes much of it; ketones are formed, and the protein and fat are broken up to supply these.

It has already been pointed out that starvation causes the appearance of acetone bodies in the urine, and it is at first sight difficult to understand why starvation was ever considered of value in the treatment of diabetes. Claude Bernard first observed that a dog which had been starved often passed sugar when it was given a high-carbohydrate meal. Himsworth (1935) has made observations on the sugar-tolerance and insulin-depression curves of healthy adults who took a series of seven diets in which the caloric value was the same but the proportion of carbohydrate and fat varied, the protein being kept within the limits of 80 to 90 grammes. The sugar-tolerance curves showed that when the carbohydrate of the diet was low and the fat high the sugar tolerance was poor; it improved with the increase of carbohydrate, and a sugar-tolerance curve suggesting a very mild diabetes was converted into one in which the blood sugar only rose about 20 mg. When a patient who has not got diabetes is kept on a very low carbohydrate diet for a long time he feels unwell and gradually loses strength and energy. This happened to one of my patients who had renal glycosuria but was supposed to have diabetes, and he finally became so weak that he could only play a few holes of golf instead of a full round. Himsworth (1936) reported the case of a doctor who had been treated for diabetes. Glycosuria had been found, but after a period of strict dieting the diagnosis had been questioned, and a sugar-tolerance test had been carried

out. This showed a decreased sugar tolerance, and the strict dieting had been persevered with. Himsworth showed that the sugar-tolerance curve was normal after a high-carbohydrate diet had been taken. The original error in diagnosis, which was due to the discovery of an abnormal blood-sugar curve, could have been avoided if the total amount of sugar excreted in the urine had been estimated after small and large amounts of carbohydrate had been eaten. If the patient has a true diabetes the amount of sugar excreted on a high-carbohydrate diet is much greater than on a low-carbohydrate diet; while in renal glycosuria there is very little difference whether the diet contains 50 or 250 grammes (Graham, 1916-17; 1923).

The changes in the sugar-tolerance curve on different diets raise the question of what determines the shape of the curve. When the action of insulin was first known it was generally assumed that it was responsible and that the abnormal curve was due either to the lack of insulin or a failure to secrete it, or to a lack of something to sensitize it. Soskin, Allweiss, and Cohn (1934) have questioned this view, and believe that the liver as well as the muscles plays an important part in taking up the sugar and so causing a fall in the blood-sugar curve.

Under-nutrition Treatment

Some of the recent work I have described makes the rationale of the old under-nutrition treatment for diabetes very difficult to understand. Although fasting had been used in the past it was placed on a sound basis by Allen's experiments on partially depancreatized dogs, as mentioned in Lecture I. This work was responsible for the under-nutrition treatment, which did so much to prolong the life of patients before the insulin era. The long period of fasting was very trying for some patients, and sometimes made them ill, and I have seen severe vomiting occur. Even in 1914-15 and in 1919-22 I never advocated more than a two-day fast, and I gradually increased the diet. As Joslin's (1937b) review of his average diet shows, the total caloric value was very low.

	Carbo- hydrate	Protein	Fat	Calories	C. : F. Ratio
	gm.	gm.	gm.		
Joslin, 1915-16 ..	26	54	76	1,035	1.19 : 1
1916 ..	43	60	82	1,185	0.90 : 1
1916-17 ..	43	60	90	1,259	1.06 : 1
1938	147	69	87	1,695	0.44 : 1
Graham (1938) 1919-22	30-40	60-70	120	1,485-1,567	1.43 : 1
1937 (average of 100 cases)	150	70	100	1,832	0.50 : 1

The diet I used in 1915 and from 1919 to 1922 was very similar to that used by Joslin, though the caloric value was higher, as I gave more fat. The C.:F. ratio in my diet was 1.43, in contrast with Joslin's 1.19 to 0.9—and my patients usually passed about 1 gramme of aceto-acetic acid in the day. Those with a mild form of the disease ceased to pass sugar, and the symptoms of thirst and polyuria disappeared. The patients improved greatly in health and were able to continue their work, but later on they nearly always relapsed and, although they benefited after one or more fasts, eventually died of coma or some intercurrent disease. The disappearance of the glycosuria and the betterment of the clinical condition suggested that the β cells had begun to improve and were regaining their granules; it was believed by many that it was essential to prevent any glycosuria, and the diets were very strict in consequence.

Although the fasting and under-nutrition diets were undoubtedly of great value, three questions are difficult to answer:

1. *Why were the patients better when the blood sugar decreased to within normal limits?*—According to Himsworth's (1939) and Soskin's (Soskin and Levine, 1937) views on the utilization of sugar, patients should use less sugar when the blood sugar is low and should presumably feel worse. I cannot find any answer to this question.

2. *Why do patients improve and maintain their weight on diets which are so low in caloric value—1,485-1,567?*—The total caloric value of Joslin's cases treated with insulin was 1,695, and that of my (Graham, 1938) series was 1,832. The patients maintain their weight very well, and sometimes gain so much that the caloric value of the diet must be still further reduced. The average figure for the caloric value of the diet of 63 healthy adults who took what they chose was 3,067 (Widdowson, 1936). This average figure is very misleading, for a man aged 29 took 4,955 calories a day and maintained a normal weight for his height and age, while a woman aged 28 took 1,772 calories a day and was slightly over weight. This work effectually disposes of the belief that all patients need 3,000 calories, and shows that some other factor must be present. In diabetes it seems probable (Lecture I) that some part of the hypophysis is overactive, and this may explain why patients require less food than in health.

3. *Why does the ketosis decrease when no food is given, since this always causes the appearance of a ketosis in a healthy person?*—The figures for the decrease are very striking. Thus in one of my cases when 212 grammes of fat was eaten the aceto-acetic acid dropped from 2.9 to 0.84 gramme on the hunger day and on another day from 3.7 to 1 gramme. In another case it dropped from 4.8 to 2 grammes, and after another seven weeks' treatment on the ladder diet the glycosuria disappeared and the aceto-acetic acid excretion was less than 0.2 gramme a day, on a diet which contained only 16 grammes of carbohydrate. The diets which Petren (1924) and Newburgh and Marsh (1923) used are still more difficult to understand, since these contain little carbohydrate and protein but a good deal of fat. Newburgh and Marsh were not satisfied with the results of the under-nutrition diets, as the end-stages of the patients with a severe form of the disease were pitiable, especially if the fasts were repeated at frequent intervals. They gave an initial diet of C. 10-12 grammes, P. 12-20 grammes, F. 85-95 grammes—calories 960—and found that patients who continued to pass sugar and acetone bodies on the severe under-nutrition diet would often cease to do so. The diet was gradually increased to C. 35 grammes, P. 50 grammes, F. 150-200 grammes—1,876 to 2,340 calories—and they thought that the general condition of the patients was immensely better than that of those on extreme under-nutrition diets. Diets of this kind have been used of recent years for the treatment of epilepsy and of *B. coli* infections of the urinary tract, and in the latter condition the method is of value because of the amount of β -oxybutyric acid which is excreted in the urine. A fairly severe ketosis can be produced in the great majority of cases, but it is not possible to do so in every one. It is clear that there must be some essential difference between the healthy person who develops a ketosis and the diabetic patient who loses a ketosis after a fast or after eating a low-carbohydrate-and-protein-high-fat diet. It is possible that the work on the hypophysectomized dog may offer an explanation. The spontaneous hypoglycaemia which occurs when the hypophysectomized dog is starved can be prevented by feeding with carbohydrate and protein, and not with fat, and the evidence is in favour of the view that the normal dog can make carbohydrate from fat. It can be argued that if the hypophysis is overactive in diabetes the liver will be more capable of making carbohydrate from fat, and this will explain why the diabetic loses a ketosis on a diet which causes ketosis in healthy people.

When to try the Dietetic Treatment

This discussion of the way in which the old under-nutrition treatment—high fat and low protein and carbohydrate—produced its effects raises the question of when dietetic treatment should be employed. I believe that it should never be tried in the following cases. (1) In young diabetics. It is impossible to give an adequate diet which will allow for growth and sexual development and provide

enough energy for the daily needs. When an adequate diet is given at once with a sufficiency of insulin most patients are able to reduce the dose and a few give it up altogether for a time. The patient must be prepared to start insulin again as soon as sugar reappears, whether it is due to an illness or to some unknown cause, and if this is done promptly he may be able to give it up again. (2) In all patients under the age of 60, unless they are grossly over weight. (3) If the patient is over 60 and is thin. This is especially the case if the patient has had an acute onset with thirst and polyuria, no matter how old he is.

Dietetic treatment may be tried in all people who are grossly over weight. The disease in these cases has often started insidiously and been discovered in the course of a routine examination of the urine. If I decide to try the effect of diet alone I give a fast of one day's duration, and then increase the diet each day in the following way:

- Diet I.*—C. 30 gm., P. 61.6 gm., F. 74.2 gm.; 1,060 calories.
Diet II.—C. 45 gm., P. 64 gm., F. 74.5 gm.; 1,130 calories.
Diet III.—C. 60 gm., P. 66.4 gm., F. 74.8 gm.; 1,200 calories.
Diet IV.—C. 75 gm., P. 68.8 gm., F. 75.1 gm.; 1,270 calories.
Diet V.—C. 95 gm., P. 68.8 gm., F. 75.1 gm.; 1,322 calories.
Diet VI.—C. 110 gm., P. 72.3 gm., F. 85.7 gm.; 1,528 calories.

If a patient can take this amount of carbohydrate and maintain a normal blood sugar he does not need insulin, and may keep well for many years. I believe it is unwise to reduce the carbohydrate below 100 grammes. If the glycosuria returns when 100 grammes of carbohydrate is taken insulin should be started without delay and the carbohydrate of the diet increased to 130 grammes or more. If the patient is over weight he should lose weight, and if he does not the protein and fat of the diet should be reduced until the weight does decrease.

The amount of food in Diet VI is about the same as that of the maintenance diet, which can be calculated from a knowledge of the weight and height. Many workers think that this diet is less trying than the short fast, and believe that the glycosuria and hyperglycaemia disappear equally well.

Another variety of diet is that used by Newburgh and Marsh (1923), which differs from the other diets in that both the protein and the carbohydrate are kept very low, while the fat is high. This diet certainly worked very well before the introduction of insulin, but, with its low carbohydrate and protein, it is a trying one.

Embleton (1938) has had very good results with another kind of diet, containing about 140 grammes of carbohydrate, and he lays stress on the kinds of carbohydrate which should be used: he limits the amount in the form of starch to 60 grammes, with another 40 grammes of lactose in milk and 40 grammes in the form of fruit. The total protein is high, since 77 to 98 grammes is given as meat, eggs, and fish, together with another 36 grammes in the milk. He does not limit the amount of fat, and the caloric value is probably over 2,200. Embleton gives this type of diet to the patients with mild glycosuria, obesity, and high blood pressure, and has found that the glycosuria disappears, the blood pressure falls, and there is a reduction in weight. He has also found that the sugar-tolerance curve in this type of case will often return to normal. It will be observed that the diets which are used with success in this kind of diabetes vary considerably.

The type of diet, however, which should not be used is that in which the so-called diabetic foods are added. These increase the protein and fat intake very considerably, and are responsible for a great deal of ill-health in the elderly diabetic who is afraid to start insulin.

Treatment by diet alone should only be continued if it is meeting with success, as shown by the absence of glyco-

suria and ketones. If either or both of these are present persistently the general health will begin to suffer. Insulin should be started as soon as the glycosuria has reappeared, and the diet improved by the addition of extra carbohydrate. If this is done early the general condition in some patients may improve so much that insulin may only be needed for a short while.

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SULPHYDRYL COMPOUNDS AND WOUND REPAIR

BY

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Wounds, their causation, pathology, and management, are at the present time subjects of more than usual importance. Even in peacetime almost every hospital shelters patients—victims of trauma, burning, sepsis, or venous stasis—in whom epithelization is virtually at a standstill and in whom only the end-results of scarring and deformity can be anticipated. The economic importance of hastening healing, both to patient and to hospital, need hardly be emphasized.

In this paper an attempt is made to summarize our knowledge of the broad principles underlying wound healing (and especially of epithelization), with particular attention to the part played in this process by the sulphhydryl (—SH) radicle. Some of my preliminary work will be mentioned in the hope that it may form a basis for further experiment and research.

Broad Principles of Wound Repair

Of the four main types of tissue of which the animal organism is composed—nerve, muscle, connective tissue, and epithelium—only two, connective tissue and epithelium, show, in the mammalia at least, any marked powers of regeneration or repair. This they do by virtue of the fact that, given conditions where proliferation is required, such a cell can change from its normally fixed and differentiated form into one at the same time more simple and more mobile. Thus the elongated fibroblast can become similar to and perhaps identical with the macrophage; the surface epithelial cell ceases to form keratin and becomes amoeboid. "The epithelia of the mucous membranes in