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Etiology of diabetes mellitus

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THE ETIOLOGY OF DIABETES MELLITUS

by

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INTRODUCTION

Today, due to the more accurate diagnoses by the physician; the longer span of life of the patients; and the more medically minded public, the problem of diabetes assumes increasing importance in both morbidity and mortality. According to Joslin (68), diabetes has advanced in importance as a cause of death in the United States from twenty-seventh place in 1900 to ninth place in 1938. There are over 660,000 diabetics in the United States, and this is still on the increase.

The purpose of this paper is to discuss the factors significant to the etiology of diabetes mellitus. It is interesting that despite the vast amount of research and experimentation on this subject no one is able to yet describe to you the actual cause of diabetes. Thus I shall discuss the multiple factors associated with the possible cause of diabetes, the discussion being based on past and current literature. Then I shall attempt to draw my own conclusions, generalized as they may be, as to the etiology of diabetes.

The name "diabetes", taken from the Greek and signifying, 'siphon', was first used by the Greek physician Aretaeus in 150 A.D., when he described the syndrome as, The patients urinate unceasingly..... they are

tortured by an unquenchable thirst; they never cease drinking and urinating..... the integuments of the abdomen become wrinkled and the whole body wastes away". (Hirsch, 60)

Horowitz (61) very aptly summarizes the beliefs as to the cause of diabetes in the early history of the disease up to the 17th Century. The causes were: 1. A specific poison, 2. Remainder of an acute disease, 3. Cold and wet temperature and little resistance power of the surface arteries, 4. Strain of night watches, drinking large quantities of water and 5. Sexual excesses.

From this time on physicians began to form more scientific ideas of disease, and we have the beginning of the acceptible possibilities involved in the causes of diabetes mellitus. For instance Dobson 1775 (39) first noticed that the sweet taste of diabetic urine, observed by Willis 1675, depended upon sugar, which he demonstrated by evaporating the urine and producing sugar crystals. He concluded that this characteristic distinguished it from all other diseases. Many theories were contributed then, but nothing concrete was offered until 1889, when von Mering and Minkowski (87) observed a syndrome identical to that of diabetes mellitus produced by removing the pancreas in dogs. They accidentally

came across this contribution while trying to see whether certain fats were absorbed in the absence of pancreatic ferments, but instead their animals produced hyperglycemia, glycosuria, ketonuria, polyuria, emaciation, and death.

Thus we have the beginning of the modern concept of diabetes as due to disturbances of the pancreas.

THE PANCREAS AND DIABETES

Since the great achievement of von Mering and Minkowski in 1889, association of the pancreas to the etiology of diabetes was appreciated and extensive investigation of this organ at once began.

It wasn't until 1903 that the old concept of the pancreas being made of single cellular characteristics was changed by the observation of Rennie, (108) when he found distinct islets in the pancreas of Teleostei fish which may usually be observed by the naked eye. He also demonstrated these to be functionally active. Four years later Lane (78), using special stains and technique, studied the cytological characteristics of these islets of Langerhans, named for the first observer of these islets in the human pancreas. Lane described two types of cells, calling them the alpha and beta cells. Each showed different granular content, and both appeared different from the zymogen cells making the acini of the pancreas. Bensley (13) also noted the independent types of cells making up the islands of Langerhans, and that they developed separately from pre-existing islet tissue or from duct epithelium and not out of acini. Recent investigation by Gomori (48) with the use of special stains has shown that the

pancreatic islets in normal human material shows a wide variation. The ratio of alpha cells to the beta cells varies from three to one, to eight to one. He could find no transitions from the acini cells to those of the islets.

The specific action of the islets of Langerhans was definitely shown by MacCallum (82) in 1909 when he separated a portion of the pancreas and ligated its duct. There was resulting atrophy, and the remaining tissue was composed of enlarged islands of Langerhans and the remnants of pancreatic ducts. Then if the rest of the pancreas is removed, this atrophied remnant is capable of warding off glycosuria even when considerable amounts of dextrose are ingessted. When it itself is also removed, glycosuria appears at once. Kirkbride (72) verified MacCallum's experiments. Clark (1916, 28) demonstrated that sugar consumption by the excised Mammalian heart is definitely increased when Lockes Solution has first been passed through the blood vessels of the pancreas, and then perfused through the heart.

One can assume from the above findings that the pancreas has more than one function and that each is independent of the other. The islets of Langerhans

have a specific action concerned with maintenance of the normal carbohydrate metabolism. Thus we have a direct relation between the pancreas and a possible cause of diabetes.

PATHOGENESIS

In the nineteen hundreds it was a hopeful idea that diabetes would be due to any destructive process of the pancreas. In fact, Opie (102) in 1903 cited two cases of interacinar pancreatitis in which there occurred diabetes. Microscopically hyaline deposits between the capillaries and the parenchymatous cells had so completely altered the islands of Langerhans that they were no longer recognizable. He describes another case in which diabetes accompanied pancreatic calculi, however the diabetes was very mild and the induration of the gland and destruction of its parenchyma were far advanced. Thus Opie (103) advanced the statement, with his cases for support, that more than half of all cases of diabetes are the result of destructive lesions of the pancreas.

Cecil (27) in 1909 made a study of the pathological anatomy of the pancreas in ninety cases of diabetes mellitus and he describes the finding of lesions of one sort or another in 88% of them. The lesions found

were those of fibrosis, hyaline degeneration, lymphocytic infiltration, and hypertrophy. He concluded also that diabetes was due to pathological destruction of the pancreas, however he recognized an inconsistency of lesions in each case.

Allen (5) in 1922 describes a hydropic degeneration of the islets of Langerhans which he believed to be a specific diabetic phenomena, produced solely by overstrain of the function of the islet cells by diets in excess of the weakened assimilative power. He observed that the rate of anatomic bhanges varies with clincal conditions, i.e., with a case of unchecked diabetes a period of four to seven days is required for development of vacuolization, and by one and one-half months the beta cells may have disappeared. This he believes to demonstrate purely a functional exhaustion, with a latent anatomical destruction of the cells due to the prolonged overstrain. These changes are absent when the diabetic symptoms are prevented by diet. In a study of 26 cases Warren and Root (121) found hyalinization of the islets to be a predominant finding in over 50% of the cases. However this pathology was found in the pancreas of older patients and usually a certain amount of hyalinization can be found in the

pancreas of aged non-diabetic patients. In another series (122) of ten cases of diabetic children studied, the predominant lesion was merely lymphocytic infiltration, which brings about discrepancies in the pathogenesis of diabetes in relation to the pancreas. Thus Warren concluded that actually there is little pathological change in either islands or acinous tissue, and that present does not appear sufficient to account for the marked disturbance in function. Root and Warren (121) let to admit that," No one distinctive lesion of the islands was found". In 1927 Warren's conclusions were supported by experimentation on the part of Allen (7) and Minkowski (89) which showed that as much as nine-tenths of the pancreas must be removed from dogs before the capacity of the organ is diminished enough to interfere with the metabolism of carbohydrates.

Thus after reviewing all the inconsistencies the universally accepted view that the islets of Langerhans are functionally deranged in pancreatic diabetes has not as yet found its anatomic counterpart that is satisfactory to explain the cause of diabetes.

INSULIN

At the same time of study of the pathogenesis in the pancreas, another group were interested in the study

of the internal secretion of the pancreas, isolating it and then correlating it with diabetes.

Based on the findings of von Mering and Minkowski, Lepine in 1891, (78) was the first to advance the view that diabetes was due to a failure of the pancreas to produce a glycolytic ferment, which it normally secretes and destroys sugar. This theoretical advancement was supported by many other men, but no attempt was made to isolate the secretion until 1903 when Rennie (108) found the isolated islets of the Teleostei fish to be functionally active. He prepared an extract from them but its effect was only slight se he abandoned it.

Success was almost attained when the German, Zuelzer (130) in 1908 prepared from the pancreas of recently fed animals an alcoholic extract which on intravenous injection was capable of diminishing the glycosuria resulting from the injection of epinephrin. He had previously ligated the veins of the pancreas from which the extract was prepared to produce congestion. Then using both dogs and human patients he produced lowering of their glycosuria; however, due to fevers and toxic reactions the advantages of the extract were over-balanced and thus the procedure was abandoned. It was later found that his extracts contained considerable

quantities of protein and these were responsible for the reactions.

Of especial interest was the experiment of Knowlton and Starling (73) who analyzed the isolated heart muscle of dogs fed with normal blood and found that it consumes about four milligrams of glucose per gram of heart muscle per hour. Then after complete excision of the pancreas of these dogs this power of consuming sugar is reduced to a minimum or disappears altogether in the heart muscle. Finally with the addition of boiled extract of the pancreas to the blood circulating through the heart of a diabetic animal, the power of utilizing the glucose from the circulating blood was restored to the heart muscle.

A year later the above findings were rather discredited by Murlin and Kramer (96) in 1913. True they showed that the intravenous infusion of pancreatic extract made from cow's pancreas produced a slight fall in hourly dextrose elimination in depancreatized dogs; also, that a mixed extract made of dogs' pancreas and stomach mucosa produced even a greater fall in urinary sugar. But, they also showed that a similar quantity of Ringer's Solution made alkaline to the same degree as the medium for the extract, produced an effect on the

glycosuria almost identical. They even went further to show that a 2% sodium carbonate solution produced a sharp decline in the excretion of sugar, and that a 2% solution of hydrochloric acid given by stomach tube produced a sharp increase in the excretion of sugar. They concluded from this that none of the extracts up to this time are yet a measure of any practical importance in restoring to the depancreatized dog the ability to burn sugar.

This problem was solved when Banting and Best (1921, 12) devised a means of producing an extract capable of controlling the sugar level of the blood. This work was based on the fact that there must be an internal secretion of the pancreas capable of controlling the carbohydrate metabolism of the body, and also on the work of MacCallum already cited on page five. They used dogs and first ligated the pancreatic ducts, with no hyperglycemia recorded in any for 7 to 10 weeks. The the degenerated pancreas was swiftly removed and sliced and macerated in a chilled mortar in Ringer's Solution. The solution was then filtered and injected intravenously after being raised to body temperature. They found that the injections exercised a reducing influence upon the blood sugar level in every case,

and that the extent and duration of the reduction caried directly with the amount used.

The work of Banting and Best ranks first as the most important contribution to our knowledge and relation to diabetes mellitus. Thus we have the beginning of a new era in the treatment and approach to the study of the etiology of diabetes.

THE ACTION OF INSULIN

Since Zuelzer's attempt in 1908 to employ an alcoholic extract, it was known for sure that insulin or at least some influence it had, diminished the glycosuria produced from injections of epinephrin. The manner in which this was produced was not known until Campbell and Macleod (1924, 24) based their study on the finding of Minkowski, who found the liver of the depancreatized dogs contained only traces if any glycogen. They used depancreatized dogs and determined the glycogen after they were given large quantities of sugar for some time before death. They found the liver to contain only traces of glycogen, despite the heavy feeding of sugar. This was contrasted to one being fed large quantities of sugar but also receiving insulin, here analysis of the liver showed it to contain over 20% glycogen. Thus it was concluded that insulin causes sugar to be deposited

in the liver as glycogen. They made another observation that in an existing case of diabetes the percentage of fat is high in both liver and blood, then after receiving insulin the levels were both lowered. The fat of the blood was reduced first and then that of the liver, which indicated to them that the fat of the liver was removed at a pace which is conditioned upon the rate at which it can be deposited in the fat depots or converted into other lipoid substances.

Laufberget (76) concluded from experiments on frogs and rabbits that insulin does not inhibit the formation of glycogen from glucose and dioxyacetone. It prevents the change of proteins and fats into glucose. These conclusions were more or less theoretical.

At the same time Cori (34) showed from a series of experiments on rabbits and mice that insulin produces glycogenesis whenever there is a certain excess of sugar available. Also, he verified that insulin in the starving animal shows no remarkable glycogenesis. This latter finding was also shown by Macleod. This could possibly suggest that the sugar level of the blood is a controlling factor in the amount of liver stores of glycogen. Cori and Cori (36) verified this

as a definite fact and also found that with insulin the liver stores are small because of the large utilization of sugars by the peripheral tissues, especially muscle. This utilization opened up all the question of how insulin was able to effect the blood sugar level. Best et al, (1926, 15) experimented on eviscerated spinal cats with muscles at rest, and showed that part of the glucose disappearing from the circulation under the action of insulin is deposited as glycogen in the muscles; and that the remaining glucose had been oxidized. Thus, the small level of sugar left in the blood or at least not accounted for in the liver and muscle was supposedly oxidized.

Macleod, (83) using the evidence that utilization of carbohydrates in the animal body is afforded by the behavior of the respiratory quotient, showed that when sugar is given to starving animals or those living on a fat and protein diet the quotient rises. Again in diabetic animals this quotient was lowered. One can see that it is likely insulin that casuses the increased oxidation of glucose in the body.

Cori and Cori (35) 1928 have shown the actions of insulin by comparing the assimilation of glucose before and after insulin, in a series of experiments run on

animals. They found that after insulin there was a 6% increase in glucose oxidized; a 12% decrease in the amount of glucose converted to liver glycogen; and a 12% increase in the amount of glucose converted to body glycogen, chiefly in the muscles.

Thus, we have convincing evidence that insulin in some manner promotes the oxidation of carbohydrates; it has a controlling effect on the conversion of body products to glucose; and lastly it causes the deposition of glucose of the blood in the muscle and liver as glycogen. These factors all contribute to the relief of diabetic symptoms when insulin is used.

Other factors of insulin might be discussed briefly which influence insulin action and production.

Through the investigations of both Evans (42) and Houssay (63) it has been shown that the anterior pituitary hormone is associated with carbohydrate metabolism. Its administration produces glycosuria and hyperglycemia and also renders the animals insensitive to insulin. Likewise the hypophysectomized animal has a low blood sugar with hypoglycemia and is abnormally sensitive to insulin. This opens the possibility of anterior pituiary as being a great factor in the etiology of diabetes, or at least derangements of the pituitary gland.

Each endocrine gland has its specific influence on carbohydrate metabolism which could be correlated with the actions insulin and will be discussed separately in the following pages.

Himsworth (57) made an interesting conclusion when he divided diabetic patients into the insulin-sensitive and the insulin-insensitive. Insulin-sensitive patients are those in which a small amount of insulin will bring the blood sugar down to normal and are due to a deficiency of insulin. While insulin-insensitive are those hard to control and the underlying cause is restriction of an insulin sensitizing factor. He further concluded that when carbohydrate is given to a normal person the body reacts by rendering itself more sensitive to insulin. Also, when carbohydrate is given to an insulin-sensitive diabetic, the insulin requirement does not increase and glycosuria does not appear. While if the same is given to insulin-insensitive patients they react by glycosuria, and consequent increased insulin requirement. Flaum (43) in 1938 demonstrated that blood sugar curves obtained in insulin-sensitive group of diabetics are similar in contour to those of normals, but occur at higher level, that their diabetes is due to lack of insulin. Also that patients

with acromegaly show diminished action of insulin in depressing the blood sugar level, thus showing the patients are insulin-insensitive. X-rays in both of the acromegalics showed tumors of the pituitary gland. These findings support the theory that diabetes mellitus can be present with a normal pancreas which secrets a normal amount of insulin. de Wesselow and Griffiths (125) carried out a series of the above tests but could find no evidence of these two distinct types of insulin sensitivity. This has also been doubted by other workers. In later studies Himsworth (54) found in a series of 13 healthy individuals ranging in age from eighteen to sixty-four years, that insulin insensitiveness occurred more frequently in the higher than in the lower age groups.

In giving insulin to the diabetic, it has been wondered whether it has any resting or regenerative effect on the pancreas. Some evidence has been contributed by Major and Mann (84) when they showed that five days after withdrawal of insulin in depancreatized dogs, they are capable of forming glycogen in both skeletal muscle and liver, although at a rate far below that of a normal dog, suggesting some revived condition of the pancreas. Haist and Best (52) believed the beta

cells of the pancreas are rested as shown by the fact that the insulin content of the pancreas is lowered by the feeding of fat, by fasting, and by insulin administration. Then there is the classical case cited by Boyd and Robinson (19) showing evidence of regeneration of the pancreas. This is the case of a nine year old boy, who had diabetes since the age of two. He had originally lived on an Allen diet, however began taking insulin in 1922. At this time he weighed thirty pounds, was thirty-nine inches long, was unable to utilize even 15 grams of glucose, and was very drowsy. After insulin was started he was also given an adequate diet for a boy his age. In one year his tolerance to carbohydrates had trebeled, being judged by the thirty units at the beginning, or without insulin he could metabolize forty-five grams of carbohydrates instead of the fifteen grams. Shortly from this time he was killed in an auto accident and died from skull fracture and an autopsy was performed in thirty minutes with emphasis on the pancreas. Microscopically the pancreas was normal except for an occasional pyknotic nucleus in some of the islets.

Evidence has been presented showing the logical mechanism of diabetes with respect to the panceas and

insulin, although not describing an actual trigger for the cause of diabetes it is apparent that the pancreas and insulin play a role in the irregularities of carbohydrate metabolism. Thus, I shall proceed to describe other factors in diabetes which might lend support to more logical theories of the etiology of diabetes.

THE PITUITARY AND DIABETES

Considerable interest has been shown in the relation of the pituitary and diabetes. First interest was centered around the posterior lobe. Burns in 1923 (20) showed that injections of extract of the posterior lobe of the pituitary gland given simultaneously with injections of insulin, diminish or abolish the fall of blood sugar produced by the latter; however, doses alone did not give a rise of blood sugar. He could not find this same action by any other gland or the anterior pituitary. Houssay and Biasotti (64) have shown that the posterior lobe extracts are antagonistic to hypoglycemia and insulin. Wislicki (127) went further and broke down the separate extracts of the posterior pituitary and qualified their degree of effect. He found that both pituitrin and pitressin in large doses cause a transitory hyperglycemia in the rabbit but that pitocin is ineffective. Also that large doses of pituitrin inhibit the hypoglycemia, which is caused by small doses of insulin subcutaneously. Fall in blood sugar after large insulin doses is not inhibited by pituitrin. Even insulin when given by vein is not antagonized by pituitrin, which he found to be the strongest in potency. Gurd (51) verifies these findings.

No clinical significance could be made from these scanty findings and especially when the effects in relation to later anterior pituitary findings are so minor, that interest was turned to the anterior pituitary actions.

This interest in the anterior pituitary and its effects was brought into focus by the extensive work of Houssay. It should be mentioned that prior to his findings, that the relation of acromegaly to diabetes had been appreciated. Evans (42) speculated that acromegaly was an expression of hyperfunction of the pituitary, the hyperglycemia and glycosuria must be the result of its overactivity, and they must be associated with oversecretion of the acidophilic cells of the pars anterior of the pituitary. Davidoff and Cushing (37) in a series of one-hundred cases of acromegaly found one out of four had glycosuria, and one out of eight proved to be clinical diabetes. They suggested this to be due to a hypophyseal tumor giving pressure against a predicated sugar center in the hypothalamus.

The investigations on the anterior pituitary by Houssay and Biasotti (64) extended from 1924 to 1930 with the following findings; first, following hypophysectomy they found dogs to have a greater tolerance

to sugar; in some there was a hypoglycemia with weakness, postural instability, abundandant salivation, convulsions, coma, decreased temperature and death; there was an increased sensitiveness to insulin. They showed an intense and specific diabetogenic activity by the subcutaneous implantation of anterior lobe in hypophysectomized-pancreatized toads. Another observation of importance was that 40% of their records of acromegalics had associated diabetes. Thus they contend that the following factors support the anterior lobe of the pituitary as being of importance in carbohydrate metabolism: 1.) The frequent occurrence of diabetes in acromegaly the etiology here being an acidophilic adenoma of the anterior pituitary. 2.) The fact that in hypophysectomized animals hypoglycemia occurs more readily and is less well tolerated, therefore, there is a greater sensitiveness to insulin, phloridzin, and fasting. They believed that the pituitary acts directly on the tissues or indirectly on the pancreas. Ham and Haist (1941, 53), also Campbell and Best (1938, 23) made interesting findings when they produced diabetes in dogs by anterior pituitary extracts. A dog was given injections of anterior pituitary extract for seventeen days during which he

excreted increasing quantities of glucose. Glycosuria continued fifty-eight days following cessation of injections. The glucose tolerance curve was that of diabetic type, and insulin caused a prompt fall in blood sugar. The pancreas was then removed with little effect on the insulin requirements. The islands of Langerhans showed extreme hydropic degeneration and insulin content was very low. This they believed suggested that permanent diabetes was produced by a degeneration of the islands and a consequent deficiency in the supply of insulin. This anterior pituitary extract was called Young's glycotropic factor of the anterior pituitary. Young (129) describes this as acting to inhibit the action of insulin, the inhibition of insulin secretion, stimulation of glycogen accumulation in the liver and muscles, depression of carbohydrate oxidation. Himsworth and Scott (59) studied the action of Young's glycotropic factor and found that in the peripheral tissues the glycotropic factor antagonizes the action of insulin, but does not effect the rate at which the tissues utilize glucose spontaneously. It influences the liver so that it responds to a decrease in blood sugar by an excessive outpouring of glucose.

The effect of anterior pituitary extract on the insulin content of the pancreas was studied by Best, Campbell, and Haist (16). They found that the subcutaneous administration of diabetogenic extracts of the anterior pituitary gland produces a prompt and extensive fall in the insulin content of the dog's pancreas. When after seven daily injections, the extract is discontinued, a rise in insulin content is noted and the normal value is regained within four days. When however, permanent diabetes is established in dogs the insulin content of the pancreas remains low and even in too small of amounts to estimate; no recovery was observed in any of these cases. Houssay et al (65) showed that the pancreas from six hypophysectomized dogs produced a normal insulin secretion, showing that an anterior pituitary hormone in not necessary for its production or maintenance. In fourteen normal dogs given anterior pituitary extract for three or more consecutive days and presenting diabetes the pancreas showed diminished insulin production. In those having permanent diabetes showed the pancreas to be markedly pathological and the insulin secretion was practically nil. They believed that the hypophyseal extract produces these histological changes in many tissues and

damages the islands of Langerhans. The coexistent high blood sugar probably exhausts the beta cells and exaggerates their injury. This pathological damage was definitely shown by Richardson and Young (110). They found that after a few daily injections of the pancreatic islets showed cellular proliferation and hydropic degeneration in the individual islet cells. In those that had been diabetic for ten months there were no normal detectable islet tissue, they were completely hyalinized. Other endocrine organs in the dog showed no striking histological changes. Ham and Haist (53) in similar studies on dogs showed that there was progressive degranulation, hydropic degeneration and death of the beta cells by stimulating these cells to excessive function. They proposed the conclusions that the anterior pituitary may act to cause the beta cells to work by acting on the tissues to increase the bodies need for insulin; the early stages being due to the increased need for insulin and the permanent diabetes being due to diminished production of insulin from actual cellular damage, of the islets. Graham (49) also supports this hypothesis.

Thus we have strong evidence for a direct cause of diabetes, however, this being so predominantly a

hormone mechanism I would lean toward a neurogenic factor which is the actual cause since the hormones are inter-controlled by the nervous centers.

Other interesting observations have been made on the anterior pituitary which should be briefly mentioned.

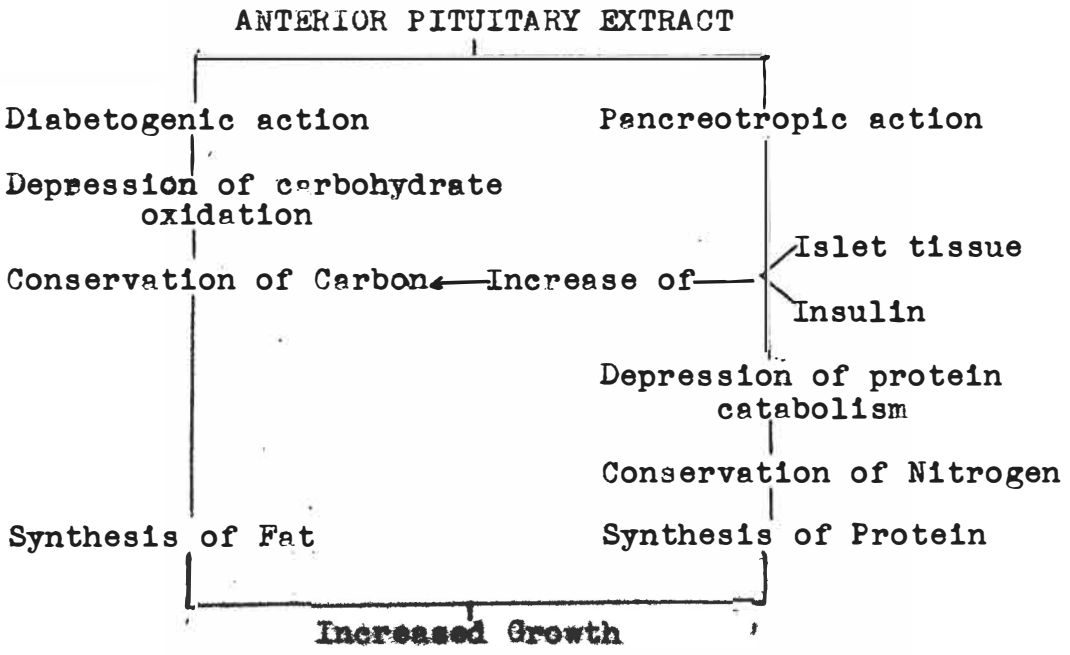
A very interesting one is that made by Himsworth and Scott based on the relation of the diet to the hypophysis and sugar metabolism. After removal of the hypophysis, the administration of a low carbohydrate diet no longer produces the impairment of sugar tolerance and of insulin sensitivity which occurs in normal animals subjected to this regime. Also injection of anterior pituitary extract into the hypophysectomized rabbit taking a high carbohydrate diet produces impairment of sugar tolerance and of insulin sensitivity similar to that produced in normal animals by a low carbohydrate diet. These findings they suggest to show a functional activity of the hypothesis is controlled by the carbohydrate content of the diet. The hypothesis acts to limit the amount of available carbohydrate by increasing its secretion of a substance similar to the glycotropic factor of the anterior pituitary. (1938, 58)

Other factors as pointed out by Davidoff and Cushing (37) are that the glycosuria of pregnancy is a frequent occurrence and is thought to be due to the pituitary, as the hypophyseal pars anterior enlarges and takes on additional activity. Then there is the glycosuria in the period of rapid growth in adolescence which is attributed to the active response of the pituitary. Joslin (68) informs us that a study of 100 diabetic children shows them to average 2.7 inches above the standard height at the onset of their disease. In regard to this growth Mirsky and Swadesh (91) found that the anterior pituitary extract exerts a dual actio on protein metabolism. One, of direct stimulation of protein catabolism in muscles, and two, indirect stimulation of the pancreas. They suggested that its influence on growth may be dependent upon a pancreatropic function.

Another observation in correlation with the presence of the pituitary hormone as causing glycosuria in growing children and its similar part in old people was born out by de Wesselow and Griffiths (124). The blood plasma of some elderly, obese, glycosuric patients when injected into rabbits was found to diminish the

hypoglycemic action of insulin in a manner closely resembling that observed by other workers with extracts of the anterior pituitary gland. Plasma of young diabetic patients or that of normal control subjects gave entirely negative results.

In summing up the importance of the pituitary one can impress its significance by showing its relation to the pancreas. Ogilvie (1944, 100) on discussing the etiology of diabetes presents the interrelation of the pituitary and the pancreas with a diagram.



"The diabetogenic action of the extract by depressing carbohydrate oxidation leads to a conservation of carbon, while its pancreotropic influence produces pan-

creatic islet hypertrophy and more insulin. This insulin, through inhibiting protein catabolism, effects a sparing of nitrogen and also synthesises the conserved carbon and nitrogen into fat and protein respectively. The resultant increase in body weight may consequently be interpreted as due to excessive diabetogenic action balanced by increased pancreatic istlet function induced through the pancreotropic action of the extract."

Thus exaggerated activity of the pituitary gland is neutralized by corresponding hyperfunction of the pancreatic islets; however, due to over-strain of the islets they give away to degeneration. This causes the nitrogen to no longer be retained and carbon which remained unoxidized as a result of excessive diabetogenic action is excreted in the urine as sugar. Failure of this pituitary-pancreatic balance expresses itself in diabetes mellitus.

THE ADRENALS AND DIABETES

The anatomical structure of the adrenal gland is that of two separate glands, the cortical portion and the medulla. Schafer in 1916 (115) recognized the latter part as being responsible for that well known hormone adrenaline, but the relation of the function of the cortex was more obscure. He theorized that since the blood supply runs directly from the cortex through medulla, then the cortex contains a precursor of the adrenaline of the medulla. However, more recently definite functions of the two divisions have been described.

Grollman (1938, 50) has shown that hypoglycemia is produced by adrenal insufficiency with also a diminution in the glycogen content of the muscles and liver. It was also shown that the diabetes produced by pancreatectomy was reduced in intensity by removal of the adrenal cortex. This suggests that the adrenals act to cause a marked rise in blood sugar and depletion of liver glycogen and muscle glycogen.

Cannon et al (25) observed that the cardiac acceleration in hypoglycemia is not due to direct action of the insulin on the heart or its effect on the adrenal gland, but that it was due to an increased adrenal discharge in response to nervous impulses. They further deseribed

this mechanism as that of protecting the body from dangerous hypoglycemia, and that it works in two stages: 1) Primary, where sympathetic activity with adrenal secretion occurs and mobilizes sugar from the liver; and 2) if the first step is inadequate then it is accentuated and intensified by stimulating convulsive seizures. The source of the glucose liberated by epinephrin was still a point of dispute. Bollman et al (18) showed in depancreatized dogs that epinephrin causes a marked decrease in the glycogen content of the muscles. The extra amount of glucose which appears in the urine corresponds to glycogen lost from the muscles, thus indicating the source. No evidence was obtained of additional excretion of glucose which could have been derived from fatty acids. They showed this to also be true in normal dogs. There was also indication of mobilization of the carbohydrate stores in the liver. Thus, this bears out the emergency theory of the adrenal function, discussed by Best and Taylor (17). Here then in the case of emergency, as a defense or flight, the hyperglycemia produced ensures an adequate supply of fuel to the active muscles. This also supports a nervous mechanism controlling the adrenal instead of insulin. In 1940 Rogoff and Nixon (112)

definitely proved in the laboratory that insulin does not detectably alter the rate of liberation of epinephrin from the adrenals.

Therefore, it is brought out that the secretion of the adrenal medulla has influence upon carbohydrate metabolism through some nervous mechanism. Joslin (68) points out that since this is a nervous mechanism and its influence is of a relative temporary nature and not fundamental in the sense that the anterior pituitary hormone is. Diabetes has never been produced by the continuous administration of epinephrin.

An interesting case was presented by Duncan et al (40). The case was that of a diabetic who had also high blood pressure. X-ray showed a definite shadow over the upper pole of the right kidney. Blood sugars were usually over 300 milligrams and very difficult to control. Operation revealed a medullary adrenal tumor (Pheochromocytoma). After removal the diabetes cleared up. This is interesting not only from the standpoint of etiology of diabetes, but also is a good clinical syndrome to remember; diabetes mellitus, hypertension, and hypermetabolism.

Thus far the discussion has dealt with the medullary portion of the adrenal, when actually a greater

influence can be demonstrated by the cortex of the adrenals. Long (79) showed that just removal of the medullary portions of both adrenals does not prevent an animal from developing typical diabetes when the pancreas is subsequently removed. However, after removal of the entire glands the diabetes produced by pancreatectomy was greatly ameliorated. This suggests the greater importance of the adrenal cortex. Lukens and Cohan (81) showed by experimentation that the administration of adrenal cortical extract is capable of restoring the diabetes of the adrenalectomized-depancreatized animals.

Long in 1940 (80) showed that in adrenalectomized mice and rats maintained on sodium salts could retain practically normal carbohydrate levels when fed; but on fasting, these levels decline more rapidly than normal controls. Then the administration of cortical extract or it active crystalline steroid to either fasted normal or adrenalectomized mice and rats is followed by large increases in liver glycogen and slight hyperglycemia. The muscle glycogen was not affected. There occurred increased nitrogen excretion of sufficient magnitude to suggest that the increased protein catabolism is the source of the newly formed carbohydrate.

It definitely exacerbates glycosuria of animals with intact adrenals or causes its reappearance in the adrenalectomized animals.

Sprague et al (119) present a case of a woman who had severe disturbance of carbohydrate metabolism with all characteristics of diabetes mellitus, without other obvious endocrine disturbances. This completely disappeared following removal of a large tumor arising from the cortex of the right adrenal.

Thus, it can be seen that adrenalin produces a temporary mobilization of sugar in the liver and utilization of glycogen in the muscles. Cortical extract on the other hand causes a gluconeogenesis which is supplied by the catabolism of proteins.

THE THYROID AND DIABETES MELLITUS

Another link is made between the thyroid gland and diabetes mellitus. Here again the exact mechanism of influence is not definitely known, but evidences of the present concepts will be presented.

Schafer (114) was one of the early men to observe the effect of the thyroid on liver glycogen. He found that glycogen disappeared from the liver when animals were fed thyroid. He found that there was no associated glycosuria, which he believed to be explained by the sugar being conveyed to the tissues and oxidized. Allen (6) also observed this glycogen reduction in the liver. He observed that a thyroid excess may aggravate the symptoms of an existing diabetes, but he could never demonstrate its excess as contributing to the actual causation of the diabetes. In 1936, Mirsky and Broh-Kahn (90) experimented on rabbits and produced hyperthyroidism; found that the extrahepatic tissues were able to remove glucose from the blood at a much greater rate than do those of the normal animal. This increased rate of removal is due to increased carbohydrate utilization. The muscles of these thyroid fed animals are characterized by a marked depletion of glycogen. Thus

they concluded that there is a marked acceleration in carbohydrate oxidation in the tissues. There is an accelerated hepatic glycogenolysis which is common in pancreatic diabetes.

Carmichael (26) showed case reports of hyperinsulinism associated with hypothyroidism and improvement of the hyperinsulinism is obtained by feeding dessicated thyroid. This supports the above findings that thyroid influences the release of glucose from the liver and in this way counteracts the action of insulin. Burns and Marks (21) showed similar results. After thyroidectomy there was diminution in the hyperglycemic reaction to adrenaline and also an increase in the hypoglycemic reaction of insulin. Then thyroid feeding again proved the opposite results. If the liver glycogen is low or absent then feeding is the same as thyroidectomy.

The incidence of diabetes with hyperthyroidism was studied by Foster and Lowrie (44). They found that the highest incidence occurred in patients 51 to 70 years of age with predominance in the females. There was 2.44% of the hyperthyroid admissions found to have diabetes, 64% of these had toxic adenomas. Then following thyroidectomy the carbohydrate metabolism of each

patient was improved. In another series of cases, Regan and Wilder (107) found the incidence of diabetes to occur with a frequency of 3.2% of all their cases of hyperthyroidism. Follow up studies showed marked improvement of the diabetes following thyroidectomy.

It seems that since a condition of hyperthyroidism is characterized by suggestive over-stimulation of the sympathetic nervous system, whic would give an increased basal metabolic rate, an exophthalmos, fine tremor of the hands, flushing of the skin, and etc. This oversensitivity would also stimulate the adrenal gland and thus cause a mobilization of sugar in the body with increased oxidation. One then would believe that the thyroid had no direct effect to cause diabetes and thus influences carbohydrate metabolism through a nervous mechanism.

OVARIAN INFLUENCES ON DIABETES MELLITUS

The influence of the ovary on diabetes mellitus has been studied very little or at least little is known, even though one would expect it to have some influence because it is one of the endocrine glands and is interrelated to them.

In 1940 Spiegelman (118) made a study of nine diabetic women. He followed them for a one year period in trying to determine the effect of estrogen on their diabetes. He observed them four months before beginning estrogen; five months during administration; and then three months after withdrawal of estrogen... Estrogen was administered by the intra-muscular route in doses of 10,000 International Units given twice a week for the four month period. Their regular insulin dosage was kept at the lowest compatible level. He found that the daily insulin requirement was cut from an average of 48 Units to 18 Units, a decrease of 63%. This was in the premenopausal patients, however, the postmenopausal patient's requirement of insulin fell only 41% or from an average of 101 Units to 63 Units.

Thus one must bear in mind this evidence of another factor in the variable sugar level of the body.

THE LIVER AND DIABETES MELLITUS

The one organ in the body which plays the most important part in carbohydrate metabolism is the liver. Although it has many functions, each in themselves being very important, we are only going to discuss the one function in regard to sugar metabolism and diabetes mellitus.

Mann and Magath (85) showed that following total removal of the liver there was an immediate and progressive decrease in the sugar content of the blood. The glycogen content of the muscles also decreases. They believed this to show that the liver is the key carbohydrate station of metabolism and storage.

It is the modern concept today as described by Best and Taylor (17) and Soskin et al (117), that the liver forms glycogen from blood glucose and other sugars; converts products as the amino acids, lactic acid, and products of fat metabolism into glucose and thus into glycogen. It is also the site of glycogen breakdown into glucose thus supplying it to the blood stream the mechanism being regulated by the blood level or other factors; and lastly for storage of glycogen.

Why then wouldn't liver disease or liver dysfunction be a logical source for the production of diabetes in

that the liver could no longer be a depot for storage of glycogen and thus must be maintained in the blood?

Ravidin (106) attempted to answer this when he experimented on dogs and observed a definite deficiency in carbohydrate metabolism in hepatic disease. There was a decreased ability of the injured liver cells to synthesize and store glycogen. Althansen and Thoenes (9) found a similar condition when they showed that in animals during the stage of liver necrosis and fatty degeneration, which follows poisoning with chloroform, there is a subnormal tolerance to a combined test of insulin and oral glucose; but during the stage of liver regeneration when the organ is full of young cells, there is supernormal tolerance to the test.

A more definite experiment was run by Conn and Newburgh (31) on obese middle-aged patients with glycosuria. They found no deficiency of oxidation of glucose, but there is a disturbance in the mechanism which removes glucose from the blood stream and deposits it as glycogen. Control patients were placed in a respiratory chamber after imbibing 100 grams of glucose solution for a four hour period. They were checked by the open circuit method of indirect calorimetry. These subjects disposed of 40 to 50 grams of

glucose by oxidation. Since in a normal individual the fasting level has returned to normal in three hours, it is evident that 50 to 60 grams of the ingested glucose were disposed of by deposition of glycogen in the liver. There was no glycosuria in these normal cases. Using the same procedure on five obese patients with glycosuria who were being treated for diabetes mellitus, they were found to oxidize normal amounts of glucose but their urine contained 4 to 17.5 grams of glucose. It should be mentioned that their curves prior to the study were of the typical diabetic type. The glycosuria, of course, was accounted for by their inability to lay down glucose as glycogen. Then these obese patients were put on a restricted diet and each showed a gradual return to normal of the glucose tolerance curve, which was attained in all cases when a normal weight was reached. This clearly indicates that a true hyperglycemia and diabetic glucose tolerance curves simulating milder forms of true diabetes mellitus may be produced by disturbances within the liver which are associated with obesity.

Another interesting aspect of this liver dysfunction and the effect on the sugar level of the blood was presented by Mirsky (92) in a discussion of the

etiology of diabetic acidosis. From his experimentation he concluded that the most important cause of the development of diabetic ketosis and the consequent acidosis and coma is the impoverishment of the liver with respect to glycogen. Deprivation of insulin produces such an effect but excessive carbohydrate intake does not produce such an effect. In fact, he found that any other similar phenomena which will accelerate the depletion of glycogen in the liver as hyperthyroidism, hyperpituitarism, hepatitis, infection, surgical procedures, gastro-intestinal disturbances, vomiting and etc., will result in secondary acceleration of fat oxidation and the consequent secretion of acetone bodies into the blood stream in excessive amounts.

Cope, (32) using hypophysectomized rabbits which should create a hypoglycemic state, found that as long as the liver glycogen was present the animal is able to maintain the blood sugar level. However, when the store was depleted a rapid decline in the sugar level occurs.

Thus in attempting to associate trauma and disease to the etiology of diabetes it would seem more logical to me, to consider trauma and disease of the liver as a major factor rather than that of the pancreas, since it has already been shown that the pancreas can supply

sufficient insulin to carry on normal carbohydrate metabolism when it is only nine-tenths present.

Before leaving the subject of the liver an interesting theory first suggested by Markowitz et al (86) should be mentioned. They suggested that the action of insulin requires a third factor other than the sugar level of the blood. It was found that immediately following removal of the liver from a dog insulin exerts its usual activity, but that several hours or so afterward, large doses of insulin may exert no action on the blood sugar. Himsworth (54) also made similar observations. It was frequently observed that a diabetic taking three equal meals a day, required more insulin to prevent glycosuria after the morning meal. Another example of decreased efficiency is seen in those cases of diabetes which become resistant to insulin even when administered in large doses. He concluded that insulin is secreted continously and the time up to point A must represent the time taken for it to develop demonstrable activity. The reaction of activation must develop with increasing velocity. Therefore, he believes that insulin as we know it and as it is secreted by the pancreas is an inactive material which requires activating by some unknown substance

tenatively called insulin kinase. As he points out, the reported cases of insulin-resistant diabetics are now numerous and in practically every case an abnormal state of the liver exists. The pancreas has been found normal, thus suggesting the source of this insulin kinase as being in the liver.

PHLORHIZIN DIABETES

It was the desire to find a way to produce diabetes in animals so a more complete study could be made of the characteristics of the disease. True, they could give injections of pituitary extracts or could take out the pancreas but these were rather difficult, so they wanted a simple drug that could be given and would produce the disease.

As pointed out by Nash (98) this drug was unknowingly found by de Konick in 1835 but he didn't appreciate the physiological effects of the substance which was called phlorhizin. Von Mering was the first to observe that the drug produced glycosuria in animals.

The mechanism of this believed diabetes was shown by Nash and Benedict (97). They showed that dextrose ingested in sufficient amounts to induce protracted hyperglycemia in phlorhizinized dogs is recovered quant tatively in the urine, indicating that no sugar is burn ed. Phlorhizin affects the permeability of the kidney to absorb blood sugar. They believe that phlorhizin produces an intrinsic impairment of utilization of sugar by the tissues. Deuel et al (38) support this renal contention. They used the respiratory quotient as an index to glucose utilization and found that there is

no impairment in the ability of the tissues to oxidize glucose when present in normal quantities. Therefore the ability of the tubular cells to reabsorb the glucose normally present in glomerular urine is decreased.

Insulin in the phlorhizinized animals causes a depression in the output of sugar in the urine as shown by Colwell (29). Hwever, Cori (53) found that despite this diminution in the sugar excretion, there was no lost power of blood sugar regulation.

Thus we can see that phlorhizin although producing a glucosuria does not exert the same mechanisms that we know to be present in diabetes mellitus. Therefore its importance has diminished as a method of producing a laboratory diabetes for experimental purposes.

ALLOXAN DIABETES

A new and interesting field in the study of the etiology of diabetes has been opened by the discovery of Alloxan. The original discovery was an accidental one, as Dunn et al (1943, 41) employed alloxan in an endeavor to reproduce in the kidney the picture of the crush syndrome, but the most striking effect observed was a complete necrosis of the islet tissue of the pancreas. The acinar cells were unaffected. There was a marked and fatal hypoglycemia. These findings were found by Bailey and Bailey (1943, 10), Goldner and Gomori (47), and other workers. After giving it in large amounts to animals there is an initial hypoglycemia followed by a hyperglycemia which is much prolonged. The reason for the hypoglycemia as shown by Kennedy and Luken (71) was due to the liberation of insulin from the cells of the islets damaged by the alloxan poisoning.

Goldner and Gomori (46) found also fatty degeneration of the liver which developed a few days following the initial injection. They very accurately describe the histological changes of the islets as complete degranulation of the beta cells with shrinkage of the

entire cell body. The number of the agranular cells gradually disappeared. Most conspicuous feature was extreme vacuolization of the epithelium of all the intralobular ducts in later stages of the disease.

Alloxan being a derivative of the purines and thus uric acid has led Joslin (70) to speculate as to a new etiological factor in diabetes connected with an upset in the bodies uric acid metabolism. Alloxan is the ureide of mesoxalic acid and is very active chemically because of its four carbonyl groups. Joslin points out that alloxan may act as an oxidizer and thus can act as hydrogen acceptor which gives it affinity for the sulfhydryl groups which he believes to be of particular biological significance. It is obtained by oxidation of uric acid with nitric acid. In connection with the uric acid in the body it might be said that uric acid originates both exogenous and endogenous. It is excreted in the urine. The excretion of uric acid increases with muscle exercise, which is not only the greatest consumer of sugar but is also the chief source of endogenous uric acid.

Jones and Friedgood (67) found that the diabetes produced by alloxan in rats completely disappeared or there was a marked reduction of symptoms after

adrenalectomy. This shows a similar response to adrenalectomy as that shown by pancreatectomized animals.

Bailey et al (11) obtained peculiar results in their diabetic induced rabbits and rats. They found that after four to six weeks there developed bilateral cataracts. This is very difficult to explain but in the future it might contribute a possible mechanism in the development of the diabetic eye changes so often seen today in human diabetics.

The only other chemical to cause islet necrosis has been demonstrated by Sheenan, Dunn, and McLetchie (116). The substance is called Styryl-quinoline No.90. It produced acute necrosis of the islet tissue of the pancreas after intra-peritoneal innoculation.

This chemical, alloxan, presents a new challenge to men of science to go into its field of study and possibly discover a more basic cause of diabetes. The association of alloxan to uric acid metabolism adds support to liver dysfunction as being the cause of diabetes. The liver is the chief organ in uric acid metabolism.

HEREDITARY ASPECTS OF DIABETES

Since the advent of insulin the more thorough study of hereditary factors in diabetes has been possible. In discussing hereditary factors I shall place emphasis on racial differences, the family, and sex.

Probably the first analysis of a group of diabetics was made by Mitchell (93) in 1921. He used 229 cases, 116 of them being diabetic and the others were used for controls. Of the families of the diabetics 46.6% of them were found to have other members with diabetes. It was also interesting that of all 116 diabetics there were 111 obese relatives as against 20 of the 112 non-diabetics. A later survey conducted by Pincus and White (104) of 523 family histories of diabetic patients with 153 control histories, obtained from non-diabetics, shows a significantly higher incidence of diabetes in families of diabetics. In diabetics it was 25% positive while in non-diabetics, it was 10%. They believe this on the basis of Mendalian inheritance suggests a single recessive gene. They tried to find some correlation by studying the incidence in twins. In a series 48 pairs, 19 similar in type and 29 dissimilar, showed that 63% of the similar twins were diabetic and only

7% of the dissimilar. Similar reports have been made by other workers.

Despite the cited evidence and that found by many other workers, it doesn't prove it. Joslin (68) states that a pattern of the mode of inheritance must be demonstrated. Without going into review of the Mendelian hypothesis, it is Joslin's belief that the predisposition to develop diabetes is inherited as a recessive trait, thus off-spring inherit the potentiality or are capable of transmitting it. However all in all too many sources of error exist which at the present time discredit a valid basis for hereditary as causing diabetes. We can only accept the fact that family history of diabetes is found more commonly in diabetic patients and so must keep it in mind.

Colwell in 1942 (30) presented an interesting correlation between possible inheritance and onset of the diabetes. A group of patients treated under uniform conditions was analyzed to determine the relation between the need for insulin and the duration of the existing diabetes at various ages. He assumed that there was increased severity if insulin dosage was increased. This group of 166 cases were judged from three points: first, the age at which the diabetes was

recognized; second, length of time it existed up to time of study; three, daily dose of insulin necessary for a satisfactory control. He found that using the insulin dosage as the abscissa and the years of existence the ordinate, that the earlier in life the diabetes appeared the more rapidly the need for insulin increased, and the longer the diabetes existed greater was the need for insulin at all ages. He concluded that the course of diabetes begins at the time of birth, regardless of how late in life it is recognized. Should these insulin curves be extended backward they tend to converge at an approximate point of birth, indicating that diabetes of a predetermined type is inherited. Thus diabetes begins its course at birth and progresses through an unrecognized phase at a rate which continues after its discovery.

Thus I believe that familial inheritance must play a minor part in the cause of diabetes, in that it has predisposed the individual to diabetes.

RACE

It is a well known fact that the incidence of diabetes among the Jewish race is greater than that of any other race. Mills (88), who resided in the far East for several years, observed that the incidence of

diabetes was relatively infrequent among the Chinese, Japanese, and the peoples of the Philippines, India, the Sudan, West Africa and Venezuela. Where it did exist it was most frequent among the wealthy and leisure classes.

Joslin (68) found from the Jewish Communal Survey of Greater New York that the rate of diabetes in Jews is 50% higher than that of the general city rate. At ages above forty-five years the rates for Jews are higher and in old age are double the general rate. In his own cases of diabetes in Jews the disease was found to develop relatively early. Although various sets of figures give different findings it is apparent that there is a greater tendency for diabetes among Jewish patients.

SEX

In the first ten-thousand patients of Joslin there was found to be 64% of them females. In England and Wales the diabetes death rate of females of all ages is 25% higher than the male rate. In general all sections of the world show a preponderance of diabetes in females. It has been speculated that the reason is the fact that they have a tendency to be obese, their average age of death is higher than that of the males, and their medical supervision is the closest.

THE DIET, OBESITY AND DIABETES

On discussing the diet in diabetic etiology it will not be the purpose to evaluate the various diets that have developed for the treatment of a case of diabetes. Thus certain evidences will be presented of the dietary factors influencing the onset of diabetes.

An early hypothesis was contributed by Allen (1) in 1914 which he called the Amboceptor hypothesis. He contended that the pancreas furnishes some definite substance used by the cells of the body for metabolism of carbohydrates and in diabetes the substance was used up in the metabolism. He based this on the finding that removal of nine-tenths of the pancreas produces a lowering of the sugar tolerance and gives severe diabetes, but if the remnant is one-eighth of the pancreas then you get only a very mild diabetes. On feeding a meat diet to these with one-eighth remnants no traces of diabetes could be found, however a high carbohydrate diet produced a glycosuria immediately. Thus he believed that restricting the diet an otherwise insufficient amount of 'amboceptor', may become sufficient when metabolism diminished. He later showed (3) that the feeding of a low carbohydrate diet to

dogs produced a gain in their tolerance. The intact state of the islands of Langerhans furnished evidence that no injurious change was in progress, and that the same condition of health could have been maintained indefinitely. One of the rather interesting criticism of this dietary restriction was made by Wohl (128), and not without support. He points out that the many complications and symptoms found in diabetes were due to an avitaminosis as a result of this unbalanced diet. Such symptoms as constipation and asthenia he believed were caused by this. He cites reported cases of diabetic patients developing conditions like beriberi and eye lesions not unlike those of xerophthalmia.

Today since the use of insulin in the treatment of diabetes the importance of the diet as a causative factor has died down.

However the association of obesity to diabetic patients has led many investigators to study the role of fat in carbohydrate metabolism. The role of fat has been partially discussed in the section on the liver and diabetes, where it was found that obese persons had a decreased tolerance to carbohydrates and after a restricted diet the patients' weight had returned to normal, their tolerance to carbohydrates was also

normal. Allison (8) made observations of 121 cases of obesity occuring in adult life and arising from extrinsic causes, such as over-eating, lack of adequate exercise, or both. He found glycosuria present in 14% of the cases. Their sugar tolerance was also found decreased and likewise returned to normal on reducing weight. This is rather strong evidence that fat has a definite influence if not causation on diabetes and must be seriously considered.

Striking figures were presented by Newburgh et al (99) on diabetes mellitus in the obese. They reported that obese glycosuric hitherto diagnosed and treated as true diabetics, comprise over 60% of all the diabetics of middle age and 44% of all diabetics.

Data are presented by Himsworth (56) showing the different diets eaten by different races, nations, and social classes throughout the world and a correlation has been demonstrated between dietary preference and the incidence of diabetes mellitus. Countries in which the incidence of diabetes mellitus is high are those in which diets containing a relatively low proportion of carbohydrate and high proportion of fat are chose. While those of low incidence take diets opposite. Himsworth further points out that the rise in

the incidence of diabetes which has occurred in the countries of the Western Civilizations during the last thirty years has occurred concurrently with a change in dietary preference by which a progressively greater proportion of fat and smaller proportion of carbohydrate has been chosen. During the World War I there was observed a fall in diabetes mortality, thought to be related to the restriction of food supplied. There was marked reduction of fat and an increase in the carbohydrates.

Himsworth and Marshall (55) also considered the diet of diabetics prior to the onset of their disease. The study involved 143 cases of proved diabetes. Both qualitative and quantitative studies show that prior to the onset of diabetes the patients desired diets containing an excessive portion of fat and a very small number preferred a diet high in carbohydrates. Similar diets impair sugar tolerance and insulin sensitization in non-diabetic patients. This suggested that the habitual ingestion of a diet containing a diminished proportion of carbohydrate may cause progressive permanent impairment of sugar tolerance and insulin sensitivity so that in the course of time, diabetes results.

NEUROGENIC ETIOLOGY OF DIABETES

Since the production of diabetes in dogs by Claude Bernard's piqure of the medulla, association of a neurogenic mechanism to the cause of diabetes has been attempted.

Allen (1922, '4) rather discredited any nervous basis for the cause of diabetes. From his experiments he found that no influence of emotion upon the production of diabetes could be demonstrated in dogs and cats. He questioned the findings of Claude Bernard. Then he further showed that complete separation of a pancreas remnant from its original nerve supply fails to give rise to diabetes or even any lowering of assimilation. Olmsted and Logan (1923, 101) showed that hypoglycemia is produced by insulin even if the brain has been removed. Houssay et al (1925, 66) obtained the same results as Olmsted. They further found that section of the splanchnics considerably increased the sensitiveness to insulin. Splanchnics oppose insulin action by their function of liberating glucose directly through the liver, and indirectly through the adrenals If both vagi are cut above the diaphragm insulin produces a less marked hypoglycemia and recovery is more

rapid. Thus there is some suggestion of nervous control of the sugar level of the blood.

Houssay (1925, 62) showed on animals that drugs stimulating the sympathetic nervous system or organs of its innervation tend to counteract insulin hypoglycemia, such as adrenaline. Drugs inhibiting the sympathetic nervous system increase the insulin hypoglycemia, such as ergotamine. Likewise the stimulation of the parasympathetics increase the effects of insulin,as eserin and miotin. Houssay and Biasotti (1930, 64) in summing up their investigations extending from 1924 to 1930, emphasize the regulation of the internal secretion of the pancreas is through the nervous system. This was supported by the effect psychic factors had in diabetics and that lesions in the vicinity of the diencephalon frequently produce diabetes.

Since 1930 the conception of the diencephalon as being the center of cause has come to the foreground. LaBarre (1930, 74) using dogs and transfusing hyperglycemic blood through their isolated heads, showed that there is an increase of insulin secretion consequent to the hyperglycemia and thus was due to central stimulation. In another series the same experiment was run with isolated head minus its cerebral hemi-

spheres and thalamic region with no effect on insulin secretion, while after the thalamic portions were separated the increase in insulin secretion is abolished.

Morgan and Johnson (1930, 94) showed that the transient rise in blood sugar following experimental lesions in the posterior part of the hypothalamus was apparently associated with hyperactivity of the adrenal glands and resulted in a depletion of the glycogen reserves of the liver. This has not been shown by other workers.

Morgan et al (1937, 95) presented some very interesting evidences of the pathological changes in the hypothalamus in cases of diabetes mellitus. They investigated the clinical records, including complete gross and microscopic pathological studies including the internal secreting glands. In the diencephalon definite pathology was found in all of fifteen cases of diabetic patients studied. The primary change was in the nucleus paraventricularis and involved diffuse changes in the nerve cells.

Thus most of the research done on the hypothalamus indicates that there is a center concerned with carbohydrate metabolism. The definite center is thought to be in the posterior hypothalamus. The fact that we seem to have the regulation of sugar metabolism

controlled by the adrenals, pituitary, and hypothalamus; a neurogenic basis for diabetes is quite logical.

Byrom and Russell (1932, 22) report a case of a 49 year old woman with an ependymal cyst of the roof of the third ventricle. Necropsy showed a normal pancreas, however a progressive clinical diabetes was present. This suggested to them that the mechanical irritation of the hypothalamus by the cystic tumor in the third ventricle caused a chronic sympathetic hyperglycemia.

INFECTION AND DIABETES

Infection has been dealt with in the discussion of the pathology found in the pancreas, but here general body infection will be discussed.

In 1920 Wishart and Pritchett (126) produced infection in dogs using pure cultures of gas bacillus, bacillus aerogenes capsulatus. They showed that there was a lowering of tolerance to sugar demonstrable both by feeding and by intravenous glucose tests.

Allen at the same time (2) concluded from experiments he made on dogs that the aggravation of human diabetes is a reaction to intoxication rather than to fever, as shown by its occurrence in the afebrile stage of Tuberculosis. He believed that no specific aggravation of diabetes or lowering of tolerance results from metabolic alteration attendent upon elevation of body temperature in experimental animals.

Referring to specific evidences of infection, Renshaw and Fairbrother (1922, 109) isolated from the stools of diabetics a new organism which they believed to be specific for diabetes. The organism was capable of splitting up starchy foods, forming oxybutyric acid, diacetic acid, butyl alcohol, and acetone. Sugar is also formed during this fermentation. It is their

theory that in diabetes, carbohydrate fermentation occurs in the alimentary canal, forming abnormal products which probably so affect the glycogenic function of the liver, as to lead to improper storage therein of the glucose from the alimentary canal. They termed it the Bacillus amyloclasticus intestinalis. This finding has received little support from other men, however.

Bergey (1926, 14) presented another tangent of demonstrating specific infectious origin of diabetes. He made experiments on rabbits with urine of diabetic patients. The urine was injected into the rabbits and curiously enough produced a glycosuria. This he believed laid the cause of diabetes to a filterable virus. (He had filtered the urine.) This again did not receive support since it could not be demonstrated by other investigators.

Thus attention turned back to focal infections and tumors. Richardson (1927, 111) presented two cases whereby local infection, when cleared relieved the patient of diabetic symptoms and they were then able to assume a full diet three times a day without spilling sugar.

Warfield (1927, 120) reports four cases of acute

pancreatitis, which were followed by diabetes. The lesions were in the tail of the pancreas. Two of the cases give no history of predisposition to diabetes. Then again one can cite cases of tumors of the pancreas which produce diabetes, as the case presented by Sano (1941, 113) where the patient had a duct carcinoma of the tail of the pancreas with invasion of the jejunum, left adrenal, and spleen. It was an ideal experiment of gradual and mechanical suppression of the islands of Langerhans. The incidence of cancer of the pancreas among malignant tumors is about 2.1%. Those arising in the tail make up about one-fifth of all pancreatic tumors. However despite these isolated pieces of evidence and as I have already discussed more thoroughly the inconsistencies of pancreatic pathology, it would be logical to only consider infection as a factor influencing the course of diabetes.

Warren and Root (1925, 121) in studying 26 cases with great scrutiny found that the variation and inconsistency argue against an infectious origin and lesions present did not suggest invasion by organisms. They did suggest a toxic origin believing that the infection acted as an injurious agent over a long period of time. They have shown evidences of islet regenera-

tion in acute infections which might account for the transient glycosuria sometimes met with, in acute infections. In hemochromatosis there is evidence of both acinar and islet tissue of the pancreas. This type of diabetes is the same as that of diabetes mellitus. Thus the long continued action of an injurious agent causes a gradual destruction of island and at times acinar cells. Regeneration takes place to replace those destroyed only to be exposed to the injurious influence with further pathological change. Eventually the destructive process wears down the regenerative powers thus explaining the unfavorable course of the diaease.

The incidence of vascular disease in diabetic patients should be mentioned here under infection. It is the belief that this is the result rather than the cause of diabetes. Warren and Root (1925, 121) noted the high frequency of severe myocardial damage and of sclerosis of the coronary arteries and of the aorta. They cite the case of a sixteen year old boy, in whom they found at autopsy atheromatous plaques on the aorta. He had a high blood fat. They also noted the frequency of chronic vascular nephritis was somewhat higher in our series than that encountered in non-

diabetic patients, reinforcing the evidences of vascular disease in diabetic patients.

This vascular disturbance is believed due to disturbed carbohydrate metabolism giving rise to abnormal fat or protein metabolites.

TRAUMA AND DIABETES

In dealing with trauma I believe it has been indicated sufficiently in the discussion of infection and pathology of the pancreas that it does not play a direct role in the production. Nevertheless, it was interesting to me the number of cases of diabetes that followed severe trauma and have been presented in the literature. I should like to present a few of these from the interest standpoint.

Wells (1922, 123) presented the case of a teamster aged 32, who was run over by his wagon. Four and a half months after injury he was brought to the hospital stuporous, seriously ill and emaciated. Since the accident he had developed polydipsia and pruritus. He was too moribund for blood and urine tests. At autopsy the pancreas weighed 122 grams, was irregular, and felt as though filled with small stones. On microscopic examination over 95% of the pancreatic tissue had been replaced by fibrosis and calcified areas. Here there was actually enough anatomical destruction to account for the diabetes. Then Pollack (1933, 105) demonstrated that the fracture of bones results in altered carbohydrat tolerance where the glucose tolerance curves assume the diabetic type. He presents a case of a forty year old

man having multiple fractures of long bones and possible skull fracture without previous history of diabetes, developed typical symptoms and was treated by insulin and diet. In 1940 Geiger and Bensom (45) cite two cases. One of a 26 year old female who developed diabetes following trauma and shock; however, it must be accepted that the obesity which she had and also a family history of diabetes predisposed her to diabetes. Thus this might be considered only the exciting cause. The second case was that of a 14 year old boy who had received two different blows to the head at the ages of five and nine, who developed diabetes. He was not obese and there was no family history of diabetes.

Of late, many investigators are leaning to the fact that trauma is an exciting factor in the onset of diabetes. Leinoff (1938, 77) summarized two cases in which both were free of signs and symptoms of diabetes before injury. Following they suffered from physical as well as mental shock. The signs and symptoms of diabetes showed up within forty-eight hours and remained. He speculates that these however were simply precipitating or exciting factors in the cases.

A rather conclusive statement was made by Joslin

(1943, 69) when we pointed out that out of 200 cases in which the onset of diabetes was sudden, he recognized none with a traumatic basis.

The fact that one always mentions physical and mental shock following trauma would suggest a definite upset of the nervous system which refers support to a neurogenic cause for diabetes mellitus.

SUMMARY AND CONCLUSIONS

The importance of the diabetic problem has been stressed, emphasizing the already present number of 660,000 diabetics in the United States. Despite the history of diabetes being known back to time B.C. our knowledge of the actual cause of diabetes mellitus is yet lacking; the knowledge is made up only of factors.

Our first concrete knowledge of the characteristics of the mechanism of deabetes mellitus was formed due to the experimentation of von Mering and Minkowski in 1889. They produced diabetes by extirpation of the pancreas.

THE PANCREAS AND DIABETES Development of our present concept of the pancreas from its anatomical and physiological aspects was presented. The islands of Langerhans were found to be the producers of insulin and this secretion directly influenced the body carbohydrate metabolism. Here it was hopeful that the cause of diabetes would be due to any destructive lesion of the pancreas. However, despite the many cases of diabetes found associated with pathology of the pancreas, no consistent lesion could be found. Rather conclusive evidence was cited of Allen and Minkowski, who demonstrated that nine-

tenths of the pancreas must be removed before the capacity of the organ is diminished enough to interfere with the metabolism of carbohydrates.

A brief discussion was made of the discovery of insulin and its action. It was interesting how close the Frenchman, Lepine, and the German, Zuelzer, came to isolating extracts comparable to insulin, but discontinued, because of the bad effects or they felt the action was not appreciable enough. However, the second great advancement in diabetes was made by the discovery of insulin by Banting and Best in 1921. This contribution made possible the more accurate studies of diabetes, however, it has created a lag between knowing the cause and treating the disease. The actions of insulin as described by Campbell and Macleod were those of glycogenesis, the glycogen being stored in the liver and muscle and oxidation of glucose. It also has an inhibiting affect on the formation of glucose from protein and lactic acid.

The work of Himsworth and his theory of sensitive and insensitive insulin patients was recorded. He believes that the insulin-sensitive patients are those in whom there is an insulin deficiency and the insulin-insensitive patients are those deficient in insulin

sensitizing factor.

Speculation has been that the diabetic pancreas undergoes certain regeneration after treatment. The evidence presented by Haist and Best; Major and Mann; and Boyd and Robinson suggests regeneration. This could be interpreted as some outside mechanism which creates a greater demand of insulin and thus overstrain on the pancreas.

THE PITUITARY AND DIABETES Little significance could be associated with the posterior pituitary and its influence on diabetes, despite the fact that injections of posterior pituitary extracts when given simultaneouly with insulin diminish or abolish the fall of blood sugar produced by the latter.

The anterior pituitary received thorough investigation by Houssay, and its importance is established by his work. Hypophysectomy produced increased sensitivity to insulin and hypoglycemia, this being abolished by the subcutaneous implantation of anterior lobe substance. Campbell and Best produced diabetes in normal dogs by injecting anterior pituitary extract. Anterior pituitary causes a marked diminution in the insulin content of the pancreas and if permanent diabetes is produced the pancreas is markedly pathological.

The relation of the glycosurias of pregnancy, adolescence; and growth factors have been associated with pituitary function.

ADRENALS AND DIABETES Hypoglycemia is produced by adrenal insufficiency. This suggests the action of it affecting the release of glucose into the blood stream in response to a low blood sugar or to the emergency sympathetic phenomena. It prevents a hypoglycemia to some extent and also supplies glucose to the muscles for energy for greater demands placed upon them. This is a nervous mechanism as pointed out by Joslin, and the influence is temporary so its importance is not great.

The cortex of the adrenal has more effect by producing a pronounced glycosuria or at least promotes gluconeogenesis. Long demonstrated the source of the gluconeogenesis as being due to a protein catabolism caused by the adrenal cortical substance.

THYROID AND DIABETES Allen observed the aggravation of symptoms of existing diabetes with thyroid excess. The greatest effect seemed to be influenced by an increased release of glucose from the liver. The incidence of diabetes with hyperthyroidism was stressed, however since the symptoms of hyper-

thyroidism simulate the over-activity of the sympathetic nervous system. Thus the thyroid could exert its influence on carbohydrate metabolism through action on the adrenal.

OVARIAN INFLUENCE ON DIABETES Evidence as presented by Spiegelman showed that estrogen when given to diabetic patients decreased the insulin requirement 63% in premenopausal cases and only 41% in postmenopausal patients. This demonstrates another factor in the variable sugar level of the body, but it would not suggest a cause for diabetes in my opinion.

LIVER AND DIABETES The importance of the liver in carbohydrate metabolism has been definitely shown. The liver forms glycogen from blood glucose and other sugars; converts products as the amino acids, lactic acid, and products of fat metabolism into glucose thus into glycogen. It likewise serves as a chief reserve source of glucose from the breakdown of glycogen. The effect of a high fat level in the blood has shown displacement of the sugar stores of the liver. Actually this with other factors mentioned explains the variations in the glucose tolerance curve and the production of the diabetic tolerance curve.

Thus it is my opinion that trauma and disease of the liver play a major role in the production of diabetes mellitus.

PHLORHIZIN DIABETES The mechanism of phlorhizin diabetes is impairment of the permeability of the kidneys to prevent reabsorption of glucose and thus produces a glycosuria. The sugar control of the blood however is not effected.

ALLOXAN DIABETES This has been shown to be a uric acid derivative. It caused the symptoms of diabetes following injections. The pathogenesis is a specific destruction of the islets of the pancreas and certain liver changes. This presents the latest challenge to the explanation of diabetes. It emphasized that the liver would be the source of trouble due to its role in uric acid metabolism.

Styryl-quinoline No.90, a drug discovered by Dunn et al, produces diabetic symptoms by necrosis, also.

HEREDITY The figures for the incidence of diabetes in families of diabetics shows 25%. In the families of non-diabetics the incidence was 10%. No pattern of the mode of inheritance could be demonstrated and thus we can only conclude that at the present time no valid basis can be

given for a hereditary cause of diabetes.

Facts presented indicate a greater incidence of diabetes in the Jewish race.

All sections of the world show a preponderance of diabetes in the female sex.

DIET AND DIABETES Allen demonstrates that the glucose tolerance increased on a low carbohydrate diet. Insulin has minimized the importance of the restricted diet.

Obese people show a decreased tolerance to sugar. On decreasing their weight to normal by restricted diet, their tolerance to carbohydrates also returned to normal. Himsworth presented diets of various sections of the world and correlated their dietary preferences to the incidences of diabetes. The high incidence of diabetes was associated with a low carbohydrate and high fat diet.

It is my conclusion that the dietary factors are direct results of liver dysfunction in relation to fat and glycogen stores.

EUROGENIC CAUSES OF DIABETES It is the modern conception that the diencephalon is the center which gives the cause of diabetes. More specifically it is the posterior hypothalamus. If both

vagi are cut above diaphragm insulin produces a less marked hypoglycemia. Drugs inhibiting the sympathetic nervous system also counteract insulin hypoglycemia. Likewise stimulation of parasympathetics increases the effect of insulin.

Thus a nervous mechanism disturbed by pathology of the hypothalamus, emotional upset, or mental and physical shock cause development of a diabetic condition.

TRAUMA AND INFECTION Despite isolated pieces of evidence, it can only be concluded that infection is a factor influencing the course of diabetes.

Trauma effects the onset and course through its influence on the nervous system as a result of physical and mental shock.

In conclusion I believe the etiology of diabetes mellitus is found in the liver and is due to pathology or nervous influences on its function.

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