Pathology of Diabetes Mellitus

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To the pathologist whose principal concern is morbid anatomy, diabetes mellitus is not a clear cut entity. The histologic changes which are specific for this disease are strikingly few, and in fact, the only one which so far appears to be associated solely with diabetes mellitus is intercapillary glomerulosclerosis. The pancreas, which is the organ most directly concerned, shows variable and non specific lesions, whereas in other organs and tissues histologic alterations are not outstanding and are most easily interpreted as due to the metabolic disturbances related to insulin deficiency.

THE PANCREAS

As mentioned above, no specific lesions are uniformly encountered in the islets of Langerhans. In fact, one does not invariably find histologic abnormalities. Of those which do occur, however, hyalinization of the islets is the most typical. Although this same change may occur in nondiabetics, it is much less extensive, and much less common. The nature of this substance, and its manner of development remain obscure. It is always found in association with the capillaries of the islet, and makes its appearance first in association with the vessel wall. The nature of this substance is unknown, and it does not bear any relation to the similar appearing hyaline material found in intercapillary glomerulosclerosis, in that there is no parallel in the incidence of the two lesions. One striking feature of islet hyalinization is its prevalence in diabetics over 40 years of age. Despite the fact that the hyaline is found more commonly in diabetes of long duration and in individuals over 40 years of age, Shields Warren[1] makes the statement that it is a cause of diabetes and not a result. In my opinion this is a debatable statement.

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A second lesion, found in about one quarter of diabetics, is fibrosis of islets. This again is found in older diabetics and is often associated with hyaline. In its earliest stages it appears to begin as reduplication of the capillary wall. This has been described by Hartroft.[2]

Most of the textbooks describe hydropic degeneration of islet cells as a common finding. This lesion has recently stimulated great interest as Toreson[3] showed that the vacuolation represented in fact glycogen infiltration. This work has not been repeated by others, and awaits confirmation. The significance of glycogen infiltration of the islets is difficult to evaluate. Experimentally it can be shown to be an exhaustion phenomenon related to hyperglycemia. Furthermore it is reversible in its early stages at least.

At the beginning it was stated that diabetics with histologically unaltered islets are occasionally encountered. It is our experience that differential stains in these cases sometimes reveal a deficiency of beta cells.[4]

CHANGES ASSOCIATED WITH ABNORMAL CARBOHYDRATE METABOLISM

It is not surprising, in view of the profound disturbance in carbohydrate metabolism, that glycogen infiltrations are found in many tissues. Most commonly these are seen in liver and kidney. In the liver, it occurs in either nucleus or cytoplasm in the form of droplets. Strangely enough, it is not found in both sites at the same time. The large glassy appearing nucleus, greatly distended, is an expected finding at autopsy in the diabetic, but it also occurs in other unrelated conditions. In the kidney vacuolation due to glycogen droplets is seen in Henle's loop and in convoluted tubules. In other locations similar infiltrations are found, for example in myocardial muscle fibres, in the stratum corneum, and epithelium of hair follicles, and sweat glands in skin, and in the pigmented epithelium of the iris.

These depositions are reversible and are significant in the skin, which is thereby rendered much more suscepti-

ble to infection, and possibly in the pancreas, where such infiltration may be an indication of cellular injury.

CHANGES ASSOCIATED WITH ABNORMAL FAT METABOLISM

The single most important result of abnormality of fat metabolism in diabetes is the development of atherosclerosis at an earlier age, and to a greater extent, than in nondiabetics. Other results of disturbed fat metabolism are found in spleen, where lipid filled reticulum cells are seen; in skin, where xanthomata may develop; in gall bladder, where the incidence of stones and cholecystitis is increased; sometimes in liver, which may show fatty metamorphosis; and in the kidney showing intercapillary glomerulosclerosis. These latter changes are most probably directly related to hyperlipemia.

In considering atherosclerosis, diabetics do not show any differences of distribution from nondiabetics, although the involvement of small muscular arteries of lower extremities may be more marked. The lesions in the intima are identical in both groups of cases. Not only is the diabetic predisposed to atherosclerosis, but also to the development of medial calcification, or Monckeberg's sclerosis. These two lesions are not necessarily associated with one another. The reason for the diabetic's enhanced susceptibility to arteriosclerosis remains obscure. Theories as to the etiology of atherosclerosis have been numerous over the years, and the fashion changes frequently. First regarded as a process natural to aging, later investigators turned to injury to the vessel wall as a predisposing factor. In more recent years, as more has been learned of fat metabolism, and the frequent association of hyperlipemia with the development of atherosclerosis noted in diabetes, myxedema and other entities, an extensive investigation of blood lipids has been undertaken by many investigators.[5, 5-a] As Warren[1] has stated, these investigations have been directed towards answering two questions: a) Is the level of serum cholesterol related to the degree of atherosclerosis in a given individual, and b) Is the level of serum cholesterol related to the dietary intake of this substance?

Conflicting evidence has been produced in answer to both questions. There is some support for the belief that hypercholesteremia is related to atherosclerosis, but little relationship between dietary cholesterol and blood cholesterol levels can be established. The work of Gofman[6] and his associates, in revealing an abnormal lipid pattern in atherosclerosis, gives considerable support to those who believe in the importance of blood lipid level, in that there appears to be an association of abnormally large lipoprotein molecules in plasma with the development of atherosclerosis. For the past few years, however, despite the most detailed clinical and experimental investigations, it has become increasingly apparent that abnormal blood lipid patterns are not the sole cause, nor even possibly the principal cause of atheroma. Recently a different approach to the problem has been made, and this goes back to first principles.

For many years, and in fact still, there has been much dispute concerning the pathogenesis of atheroma. Is the fat, which is in the intima of the blood vessel wall, located, in the earliest stages, in cells, or in intercellular substance? Is the fat carried into the wall by lipophages, or does it reach the intima by imbibition? Part of the solution to these problems has been given by Duff and McMillan,[7] who have shown that in the rabbit the earliest detectable change in the vessel wall is an alteration in intercellular ground substance, followed by the development of fat droplets in the intercellular material. The subsequent development of the atheroma obscures this, in that fat accumulates in lipophages, and in intercellular substance, with surrounding fibrous tissue proliferation and later necrosis, calcification and ulceration. The importance of these observations lies in the emphasis placed on the alteration in intercellular ground substance as a change preceding the appearance of fat.

If we now consider those entities characterized by marked atherosclerosis we find a possible connecting link in the altered ground substance, or intercellular material. This consists of complex mucopolysaccharides, whose integrity is dependent upon a variety of hormones, such as cortisone, thyroxin, and estrogens, and upon vitamin C.[8] We find, too, that in older individuals, this ground substance in some situations, such as the wall of the aorta, increases in amount and shows some histologic alteration in character. Here, then, is the most recent, and certainly the most promising hypothesis regarding the etiology of atheroma, that the fundamental disturbance leading to accumulation of fat and lipoid in the vessel wall is an alteration in intercellular ground substance. This is hypothesis only, at present. When one attempts to extend this theory to the atherosclerosis of diabetes mellitus, there is some relation, in that the mucopolysaccharides of intercellular substance must conceivably be affected by the profound disturbance in carbohydrate metabolism. In fact, Shields Warren[1] and others[9] have described alterations in intercellular ground substance in the skin of diabetics.

In summary, one may say that although elevation of blood lipids and possibly alteration in blood lipid pattern play an important role in the etiology of atherosclerosis, of equal if not greater significance may be alterations in the vessel wall, and especially in the intercellular ground substance. In reaching this conclusion we have gone a full circle, and are back to Virchow's original hypothesis, as enlarged and modified by Aschoff,[10] that local loosening of intercellular cement substance, due to mechanical stress, is followed by imbibition of lipid-containing fluid from the blood plasma into the vessel wall.

THE KIDNEY

As part of the complicating arteriosclerosis, renal changes, such as benign nephrosclerosis, are common. Less commonly pyelonephritis develops, and acute necrotizing papillitis, a complication of pyelonephritis with an obscure pathogenesis. Of great interest, but of debatable incidence, is the intercapillary glomerulosclerosis first described by Kimmelstiel and Wilson.[11] In this complication there is the deposition of hyaline-like material, in nodular pattern, in the central part of the glomerular lobule. Usually an intact capillary is seen at the periphery of the hyaline mass. Frequently the efferent arteriole as well as the afferent, show similar hyaline thickening of their walls. This lesion is apparently specific for diabetes mellitus, and has not been described in any other condition. Tubules may show varying degrees of degenerative change secondary to obstruction of blood flow through the glomerulus, as often the whole glomerular tuft becomes converted into a functionless hyaline mass. The nature of this lesion is obscure, as pathologists disagree about its pathogenesis. Whether the hyaline material has its origin in the capillary wall, in the connective tissue of the glomerular stalk, or is deposited in the intercapillary space remains unsettled. In view of the theory advanced earlier, that there is a disturbance in mucopolysaccharide metabolism, one is inclined to favor the glomerular lesion as originating in the capillary wall, the basement membrane of which is composed of mucopolysaccharides. Support for this belief is found in the capillary lesions of the retina.

A second form of hyalinization of glomerulus is seen in diabetics. This has a diffuse distribution, but is non specific and is seen in essential hypertension, and in chronic glomerulonephritis of both the human and experimental types.

THE EYE

The last group of lesions to be mentioned are those occurring in the eye. It is difficult to dissociate retinal changes in diabetics from associated hypertension, and renal disease. It is apparent, however, that there is a retinopathy seen only in diabetics. This is due chiefly to the development of microaneurysms of capillaries. The incidence of these lesions parallels closely that of intercapillary glomerulosclerosis. One finds small spherical outpouchings of the capillary wall, often with dilated retinal veins, and small hard white exudates composed of protein. These have been well described by Friedenwald.[12] The capillary aneurysms are of great interest, because these lesions lend support to the theory of disturbed mucopolysaccharide metabolism resulting in weakening of capillary wall, with aneurysm formation.

Other eye changes, such as retinitis proliferans, are the result of organization of hemorrhages.

Lens opacities are commonly associated with diabetes mellitus, even in the younger age group, but statistical evidence that the incidence of such opacities is higher in diabetics is conflicting.

SUMMARY

In diabetes mellitus the commonest lesion in the pancreas is hyalinization of islets of Langerhans. Fibrosis, and glycogen infiltration are found less commonly. Occasionally no histologic alteration can be seen.

Glycogen infiltrations in liver and kidney are not significant, but in the epithelium of hair follicles, and sweat glands of skin enhance the susceptibility to infection.

Disturbance in lipid metabolism results in premature development of atherosclerosis, in cholelithiasis and cholecystitis and possibly in intercapillary glomerulosclerosis of kidney.

The importance of disturbance of mucopolysaccharide metabolism is discussed as a predisposing factor in the development of the atherosclerosis, the intercapillary glomerulosclerosis, and microaneurysms of the retina.

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The Undernutrition Treatment of Diabetes

Just at my entrance into the war in 1918 I wrote the following sentences in a paper planned for delivery before the Johns Hopkins Medical Society and presented for me by Dr. Sidney Miller. "At the beginning of 1914, the outlook for diabetic patients was depressing. The statistics of the Massachusetts General Hospital showed that in the preceding 16 years for each 100 diabetics submitted 28 were discharged dead, a record which duplicated the experience of the hospital between 1824 and 1898. Physicians dreaded to place their patients in an institution lest the treatment there prescribed prove more disastrous than that adopted by the patient's fancy. Surgeons dodged the diabetic, while the obstetrician was out and out afraid of diabetes and urged pregnant women to have abortions. The neurologist, dermatologist would throw up their hands at complications within their respective spheres and exclaim, 'Cure the diabetes and then we will help the patient.' It is hard to realize that these conditions prevailed over four brief years ago.

"As so often happens when the clouds are darkest, light unexpectedly appears, and I recognized its approach one afternoon while talking with Dr. Allen. It happened in this way: We were discussing one of my several cases (Case No. 344) and I pointed out how the type of diabetes in this instance changed from severe to mild as tuberculosis came on and the patient progressively became weaker and lost weight. I remember telling Doctor Allen that if he could explain why this change took place the problem of diabetic treatment would be greatly advanced. The next day I heard from him that he felt he could explain the reason for the improvement, and furthermore believed that he would be able to demonstrate the cause for it by experiments on animals, and soon after I was gratified to learn how doctors could give their diabetic patients renewed hope. You are familiar with his experiments by which he showed that dogs made artificially diabetic and then forced to lose weight gained in tolerance for carbohydrate.

"This striking improvement in diabetic treatment belongs to the first year of the disease, the year which I call the diabetic's danger zone. This is important, for it is the most useful year to the diabetic and to the community. The first year of the disease is preeminently the year of coma. Eighty-seven per cent of all diabetics who have come under my care and have later died during the first year of the disease have succumbed to it. And yet today everyone will agree that diabetic coma during the first year of the disease should be considered an accident which can and should be avoided not only in adults but in the youngest child."

From *Diabetes Yesterday, Today, and Tomorrow,* by Elliott P. Joslin, M.D., in *Proceedings* of the American Diabetes Association 1:124-125, 1941.