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VASCULAR COMPLICATIONS OF DIABETES MELLITUS*

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VASCULAR disease is by far the most serious complication of clinical diabetes mellitus. Atherosclerosis of the medium-sized arteries, according to Warren and LeCompte,[1] is the largest single cause of death among diabetic persons. The most alarming feature is the high incidence of serious vascular degeneration in relatively young people who have had diabetes for a long time. Coronary thrombosis is the cause of death in diabetics less than 40 years of age ten times as frequently as in nondiabetics of the same age.[2] Patients in this age group who have had diabetes mellitus for more than 20 years almost never escape the development of intercapillary glomerulosclerosis.

Clinical and Pathologic Manifestations

The most important clinical effects are caused by involvement of the coronary and the cerebral arteries, the arteries of the legs, the arterioles of the kidneys, and the capillaries of the glomeruli and the retinas. The atherosclerotic lesion is characterized by focal thickening of the intima with the deposition first of lipid and later of calcium. Renal arteriosclerosis associated with chronic glomerulonephritis and hypertension is much more frequent and severe in patients with long-standing diabetes, particularly young patients.

Intercapillary glomerulosclerosis is the name used originally by Kimmelstiel and Wilson to describe the hyaline masses between the glomerular tufts in diabetes. They formerly were thought to originate between the capillaries. Recently, Bergstrand and Bucht,[3] using the electron microscope, have demonstrated that

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the early lesions are in the capillary basement membrane and in the basement membrane of Bowman's capsule. The disease may be either diffuse or nodular. In the diffuse form the thickening extends rather evenly along the course of the glomerular capillaries. In the nodular form there are masses of clear, acellular material deposited between the capillary tufts. The diffuse form is seen fairly commonly in glomerulonephritis and in old age. The nodular form, on the other hand, particularly when severe, is almost exclusively a change typically associated with diabetes.

The exact nature of the material forming the nodules is not known. When stained by hematoxylin and eosin, it looks like hyalin, but the fact that it takes a periodic acid—Schiff reagent suggests a content of carbohydrate, perhaps of mucopolysaccharide.[4] Many such nodules also accept stains for lipids. Muirhead, Montgomery, and Booth[5] recognize two types of lesions: one is due to a collection of collagen-like material in the capillary wall, and the other is due to an intercapillary collection of fibrinoid-like substance. It seems likely from the work of Lynch and Raphael[6] that the accumulated material arises from erythrocytes.

Lonergan and Robbins[7] report that among 62 autopsies of patients with hemochromatosis and diabetes, no intercapillary glomerulosclerosis was found. Twenty-one of the group had diabetes for five years or longer, and in three it existed for more than 15 years. In patients having diabetes only, approximately 15 per cent would be expected to have the lesions of intercapillary glomerulosclerosis. Estimates of the frequency of the disease vary greatly, probably because of differences in criteria used. Laipply, Eitzen, and Dutra[8] estimated from autopsy material an incidence of 64 per cent.

The usual progress of the disease appears to be slow;[9] it is associated with arteriosclerosis, and frequently with pyelonephritis. In the early stages the condition may be suspected because of albuminuria, but not until it is moderately advanced can an assured diagnosis be made without renal biopsy or autopsy. It causes about 30 per cent of the total number of deaths of young diabetic patients who have had the disease for more than 15 years.[10,11]

The clinical manifestations of the disease include diabetes of long duration, albuminuria, edema of the legs, arterial hypertension, and anemia. Diabetic retinopathy is an almost invariable accompaniment. The serum albumin content is less than normal, and generally there are an increased amount of beta-globulin and concentrations of cholesterol and lipoprotein in the blood. There are doubly refractile bodies in the urine. In the terminal phase there may be a great reduction in insulin requirement. It frequently is difficult to decide how much of this is a feature of the disease or the result of the inevitable low food intake of an ill patient.

Diabetic retinopathy is a degenerative disease also of the capillaries. Its frequency has greatly increased in the past 20 years because of the longer duration of the diabetes as compared to its frequently short course formerly. The first manifestation

of the disease is the appearance of minute, circumscribed, saccular dilatations of the capillaries, said to be chiefly on the venous side of the capillary beds. These formerly were called punctate hemorrhages, and it may be difficult to distinguish between the two types of lesions, especially since small true hemorrhages may be contiguous with the dilatations. The walls of the capillaries in some sections appear to be thin and in others to be thickened from the deposition of a hyaline material. The veins are irregularly dilated and tortuous. Minute or massive hemorrhages arise from the capillaries and veins. Yellowish-white, so-called "hard" exudates appear, and eventually extensive formation of new vessels may result in retinal detachment.

Microaneurysms are not exclusively associated with diabetes; they occur with hypertension, glaucoma, and with occlusion of the central retinal vein. Although, according to pathologic studies,[12,13] retinopathy invariably occurs in patients with intercapillary glomerulosclerosis, only 58 per cent of diabetic patients with retinopathy had intercapillary glomerulosclerosis.

The course of the disease varies greatly. It may cause blindness within a few months or it may remain relatively inactive for years; it is only in the unusual instance that temporary improvement occurs. Fagerberg[14-17] connects neuropathy closely with vascular disease. In a study of biopsy specimens of nerves in 150 cases of diabetic neuropathy he has shown that this lesion may be largely vascular in origin. The specific lesion appears to be one of ischemic degeneration of the myelin sheath, the vasae nervorum being occluded with polysaccharide deposits. It is easy for me to accept the idea that vascular disease often is a factor in diabetic neuropathy, but it is difficult to understand how a lesion of this type could be solely responsible for the most common diabetic neuropathy that disappears completely and permanently within a few days or a few weeks during good diabetic control—the neuropathy commonly accepted in the past to be "metabolic."

Factors Influencing the Frequency and Severity of Vascular Lesions

Duration of diabetes is the most important single factor in the etiopathogenesis of vascular degeneration. This correlation has been demonstrated strikingly by White and Waskow[4]: among 200 patients in whom diabetes developed before the age of 15 years and who survived more than 20 years with the disease, nephropathy was present in 50 per cent, calcified arteries in 75 per cent, and retinal hemorrhages in 80 per cent. Paul and Presley[18] found retinopathy in 45 per cent of patients who had juvenile diabetes of 15 or more years' duration. Others[19-21] reported vascular degeneration in long-standing diabetes to vary from 60 to 83 per cent of patients. Complications seldom occur before the tenth year of the disease, but are almost always present after the twentieth year.

The difference between the frequency both of coronary occlusion and of nephropathy in diabetic persons as compared with that in normal persons is much more notable in those less than 40 years of age than it is in elderly persons.

Bell[22] in a report based on 1,559 necropsies on diabetic subjects observed that nephropathy was present in all less than 40 years of age who had had the disease for 20 years; whereas, in persons who died at the age of 60 years or older who had had the disease for 20 years, the incidence fell to about 40 per cent.

The prognosis is not altogether unfavorable. Although vascular lesions almost always are present in persons who have had diabetes for a long time, they are not always severe. Bell's[22] necropsy findings indicate that 30 per cent of 93 patients who lived more than 20 years with diabetes did not have serious vascular disease.

Severity of the disease and its control. Most clinicians who treat diabetes extensively believe that there is a relationship between both the severity and the degree of control of diabetes to vascular degeneration, but there is not complete unanimity concerning either factor. Both severity and degree of control are difficult, if not impossible, to define accurately. The severity of the disease cannot be measured well on the basis of insulin requirements. I agree with Ricketts[23] that "The true test of severity is the behavior of the disease when insulin is withheld." In many young diabetics taking no more than 30 units of insulin per day, acidosis develops promptly when insulin is omitted; it is chiefly in this group that vascular disease occurs with the greatest frequency and severity. Yet, there are some young diabetics who by any criteria have severe diabetes, who will escape vascular disease for more than 25 years; and other young adults who have been almost aglycosuric and have had normal blood sugar values for years and have not required insulin, in whom retinopathy develops. The fact that mild or potential diabetes may be associated intimately with vascular disease was demonstrated by Bartels and Rullo,[24] who showed that in glucose tolerance tests of 100 unselected patients with peripheral vascular disease, there were 59 for whom the glucose tolerance curve was abnormally high.

There is even sharper disagreement about the importance of good control of diabetes in the prevention of vascular disease. Wagener, Dry, and Wilder[25] presented data on 200 patients seen frequently during periods as long as 25 years. Not one escaped retinopathy, regardless of the age at onset or the severity of the diabetes or the type of treatment used. On the other hand, Root, Pote, and Frehner[26] reported that in 451 patients with diabetes of from 10 to 34 years' duration, nephropathy occurred in less than 2 per cent of those with good control, while 67 per cent of those with poor control had moderate or severe retinopathy. It is just as important and much more difficult to explain why one fourth of the patients with good control had severe retinopathy and one third of the patients with poor control had none. We recently studied 101 patients who have had diabetes for 15 years or longer. Twenty-two of these patients have had their disease for more than 25 years; five (23 per cent) had no evidence of degenerative disease, and seven (32 per cent) had no evidence of retinopathy in dilated pupils observed by one of our consultants in ophthalmology.

Mucopolysaccharides. Because mucopolysaccharides are deposited in excess in

the affected tissues in both the nephropathy and the retinopathy of diabetes, investigators have examined the possible relationship of glucose, glucosamine, and carbohydrate bound to alpha-2-globulin in the blood. There has been little to suggest that high concentration of blood sugar is harmful in itself, but some evidence indicates that great fluctuations may be harmful. Góth, Lengyel, Nádasdi, and Sávely,[27] by using glucose and insulin in rats to cause notable fluctuations in blood sugar content, produced renal lesions that simulated intercapillary glomerulosclerosis. It has been clinically demonstrated that blood content of protein-bound mucopolysaccharides is higher in the presence of evident vascular disease than in its absence.[28] Lerman, Pogell, and Lieb[29] observed an increase in alpha-2-globulin in patients with retinopathy, but the values were identical in patients without retinopathy and in normal persons tested. The serum glucosamine content was high in diabetic patients with or without retinopathy. Because it is known that the concentration of serum mucopolysaccharides is increased in conditions characterized by destruction of tissue, it is suspected that the increase in these substances may be the result, and not the cause, of vascular damage. Neilsen and Poulsen,[30] however, found increased concentrations of similar substances in the blood of diabetic patients without complications as well as in those with renal disease.

Serum cholesterol and lipoproteins. Much has been written in recent years about the relationship of elevated concentrations of cholesterol and lipoprotein in the blood in atherosclerosis in diabetic patients, and in those without diabetes. A causal relationship has been implied or claimed, but none has been proved to exist; also there is no proof that high concentrations of blood lipids are the cause of diabetic retinopathy or nephropathy.

Pomeranze and Kunkel[31] studied 273 diabetic patients. Total blood lipid contents were above normal average in half of the patients, and below in the other half. Barach and Lowy[32] studied 614 diabetic patients and found the blood cholesterol concentration elevated in 58 per cent, and normal in 42 per cent. These authors found blood lipoprotein values elevated in less than half of their diabetic patients; others[33] have found no significant differences between these values in diabetic patients and in normal persons.

In general, it appears that the lipoprotein and cholesterol values tend to be elevated in poorly controlled diabetes more frequently than in the well controlled. In diabetic patients who have renal disease, the blood lipoprotein values almost always are elevated, probably caused by the renal lesions and not the cause of them. In retinopathy without measurable renal disease the lipoprotein concentration usually is normal.

Pituitary and adrenal influence. Since Poulsen[34] published the record of a patient in whom diabetic retinopathy disappeared over a period of years after Sheehan's syndrome due to pituitary failure developed, considerable interest has been aroused as to the relationship of pituitary and adrenal factors as to cause or aggravation

of diabetic vascular disease. Treatment with ACTH has been reported to cause microaneurysms as well as renal lesions similar to the intercapillary glomerulosclerotic type in alloxan diabetic rabbits,[35] and glomerulosclerosis associated with an increase in alpha-2-globulin has followed treatment with cortisone under similar circumstances.[29]

Such laboratory findings are not readily correlated with clinical data. Most diabetic patients do not have any signs suggestive of Cushing's disease; furthermore, most patients with acromegaly or Cushing's syndrome, even those with diabetes, do not have retinopathy. However, in most of these patients, diabetes has not been known to exist for 15 years. In our own experience with 22 acromegalic patients with diabetes, four had retinopathy. Diabetes had been known to exist no longer than eight years. Of 21 patients with diabetes and Cushing's syndrome, two had retinopathy after diabetes of eight or nine years' duration. It seems likely, therefore, that underlying factors that are a part of diabetes, or intimately connected with it, are the chief causes of such lesions, and that pituitary-adrenal hyperactivity may under some circumstances be an aggravating factor. One of our patients with acromegaly and diabetes of four years' duration died and autopsy was performed. Proliferative retinitis was present and yet there was no evidence of intercapillary glomerulosclerosis. In another similar instance[36] in which proteinuria also was present, retinopathy was observed but there also were no signs of intercapillary glomerulosclerosis.

Heredity. Although there is little in the way of factual data available to implicate heredity as a cause of vascular degeneration, this possibility is gaining consideration. It is clear that when the diabetes is mild and the vascular disease is severe, or where in contrast the diabetes is severe and the vascular disease is absent, other factors must be at work. Such factors may be constitutional and perhaps hereditary.

Treatment

The cause of vascular degeneration associated with diabetes is incompletely understood. Vascular degeneration appears to be an almost integral part of the disease, although in general, the more severe or poorly controlled the disorder, the greater is the component of vascular degeneration. If this is true, then it must follow that until diabetes is prevented, diabetic vascular damage will occur. Because prevention is not foreseeable in the near future, our aims must be: (1) reduction of the incidence by combating those factors known to be associated with the development of diabetes, (2) early detection of vascular involvement, and (3) as complete control of the diabetes as is possible. It is believed, although it remains to be proved, that detection and treatment of diabetes mellitus early in its course prevent complications. One of the best tests for early detection is the postprandial blood sugar test. It can be performed by physicians as part of the standard procedure of the initial examination of all patients. Special attention

must be given to patients with strong family histories of diabetes, and especially to obese patients.

If it is worthwhile to detect diabetes early, it is logical that it should be treated and controlled with meticulous care. The best possible diabetic control should be applied to all patients. The blood cholesterol content should be maintained at normal if possible. If this does not follow control of sugar in the blood and the urine by ordinary means, a low-fat diet may be prescribed; if that is unsuccessful, a diet in which unsaturated fats are allowed, so that the total daily intake of fat is from 60 to 90 gm., may be effective.

Vitamins in excess of normal requirements, hesperidin and rutin have not been proved to be of value in preventing or reversing retinopathy or nephropathy.

It is important to avoid all urinary infections, and for their detection urine cultures are useful. For men, mid-voided specimens may be used, and for women, clean voided specimens can be obtained with meticulous attention to cleanliness, thereby avoiding the risk of introducing harmful bacteria by catheter. The use of properly selected antibiotics will control most lesions of pyelonephritis.

For retinopathy, radiation therapy to the pituitary and to the eyes has proved to be of little or no value.

Hypophysectomy is drastic, and there have been few if any unequivocally and permanently beneficial results. For the amelioration or reversal of diabetic retinal and renal lesions the operation has been performed in a total of about 30 patients reported in the studies of Luft and Olivecrona,[37] and Kinsell, Lawrence, Balch, and Weyland[38]; in seven patients adrenalectomy was done.[39] The results have not been strikingly favorable. The paradox here seems to be in the facts that pituitary-adrenal hyperactivity was not known to be present before surgery, and that in addition these patients required postoperative support indefinitely with hydrocortisone or cortisone—the very substances supposedly pathogenically responsible.

In the uremia of intercapillary glomerulosclerosis, a low-sodium diet and diuretics will control most of the edema, and a high caloric intake will spare the body's protein. In extreme renal failure, a daily protein intake of less than 40 gm. may be necessary to reduce azotemia. Transfusions of packed erythrocytes, sodium-free albumin, or dialysis are measures of limited value and only to be used under extreme circumstances.

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