Present-day Concept of Diabetic Retinopathy

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The interpretation of the pathogenesis of diabetic retinopathy has changed so much in the past twenty-five years that it is of interest to consider how and why this evolution has occurred. In part the method of sectioning retinas on the flat and the newer staining and injection procedures have given a better picture of the vascular changes. In addition, ophthalmologists have always tried to determine whether findings in related specialties have an application to their problems, and thus advances made in pathology in general have suggested to thinkers in ophthalmology the possibility of applying such knowledge to their own field. We are indebted for much of our present-day concept of diabetic retinopathy to Friedenwald, Becker, Rich, McManus, Ballantyne, Loewenstein, and Ashton.

In recent years diabetic retinopathy has been on the increase, and if we are to get at the basic cause we must seek the reasons for the vascular involvement that is the basis of its development. The lengthening in life expectancy and the stress of present-day living probably do contribute to the increased incidence of visual loss, but if we are to gain in the prevention of blindness from diabetes we must try to remove or neutralize the fundamental pathology; namely, the involvement of the capillaries and venules which is the beginning of the trouble.

The characteristic vascular lesion of diabetic retinopathy consists of great numbers of minute saccular aneurysms in the retinal capillaries. Often the aneurysms are hyalinized. Two possibilities come to mind in regard to their formation: increased capillary pressure or histochemical changes that allow for the development of these aneurysms. In regard to the former, Friedenwald[1] noted in studying histologic specimens of diabetic retinopathy that localized retinal venous occlusions were associated with abundant newly formed capillary collaterals. Aneurysms were not seen in these newly formed vessels, suggesting that increased capillary pressure is not in itself sufficient to cause the aneurysmal dilations. Some abnormal weakness of the wall appears to be essential. Day[2] in a study of polysaccharides in ocular tissue concluded that in diabetic retinopathy the normal polysaccharide pattern of the capillary bed is disturbed and is unlike that of other diseases of the retinal vessels. McManus[3] suggested that the retinal capillary lesions might be the result of a disturbance in mucoid metabolism. It seems possible that some defect in the basement membrane of the capillary may be the immediate cause of the aneurysm. In studies of capillary fragility Barnes[4] found that in 80 patients with diabetic retinopathy, 85 per cent had abnormal fragility. But 48.5 per cent of diabetics with no retinal pathology showed abnormally weak capillaries, indicating that diabetes in itself is associated with increasing capillary fragility. Rutin reversed fragility in only 25 per cent of the cases even if given for eighteen months and longer, and some patients had vitreous hemorrhages while the capillary fragility was normal and they were taking rutin. We still have been unable to define capillary fragility pathologically.

Today it is finally accepted that the picture of diabetic retinopathy is not dependent on hypertension, arteriosclerosis, or atherosclerosis. In keeping with this concept are the findings in the ocular examinations of 286 juvenile diabetics that I have done at Camp NYDA in a two-year study. In no case was there ophthalmoscopic evidence of retinal blood vessel disease, yet nine patients had hemorrhages or pinpoint aneurysmal dilations —1.5 per cent positive findings in patients having no visual complaints. Incidentally, 0.69 per cent (four patients) gave evidence of cataract formation. The absence of exudates or vessel changes other than those observed in the capillaries emphasizes the latter as the earliest change. Friedenwald[1] finds the intraretinal capillary aneurysms, mostly spherical, to be 20 to 30 microns in diameter and hence just at the limit of ophthalmoscopic visibility. Of course the larger ones of 80 to 100 microns are easily seen.

The retinal lesions of the diabetic are closely related to the renal lesions described by Kimmelsteil and Wilson. The latter are often associated with capillary aneurysms in the kidney glomerulus, and the typical globular hyalin, glomerular nodule of Kimmelsteil and Wilson

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may be in fact a hyalinized saccular capillary aneurysm, showing the retinal and renal lesions to be joint manifestations of the same vascular disease. Ashton and Friedenwald[1] found no distinguishing features in staining and histochemistry between hyaline of the Kimmelsteil-Wilson nodule and the thickened walls of the retinal capillary aneurysm. Both have well developed membranes. No other organs have as yet shown these hyaline nodules other than a rare one that has been seen in the brain.

A case of rubeosa iridis diabeticora, seen through the courtesy of Dr. Henry Marks, that came to complete autopsy is worthy of review in this connection.

R. B., age ten, began to have polyuria and diabetes was then recognized. He was put on insulin but was careless with his diet. Twelve years later he was first noted to have capillary retinal microaneurysms, retinal hemorrhages, and exudate. Pulmonary tuberculosis made its appearance. One year later marked vitreous hemorrhage of the left eye was noted. Rubeosa iridis diabeticora followed soon thereafter, associated with glaucoma in each eye. A filtering operation controlled the tension, but recurrent hemorrhages and retinal detachment followed a retinitis proliferans. At the age of twenty-six with a blood pressure of 195/120 the patient went rapidly downhill and died shortly thereafter.

Postmortem examination revealed pulmonary tuberculosis and diffuse glomerulonephritis, with the cortex reduced in thickness. Histologically Kimmelsteil-Wilson disease was diagnosed by Lisa. The pancreas revealed atrophy of the islands of Langerhans.

Patients seen by Lawrence[5] and others have developed diabetic retinopathy during pregnancy, which cleared following delivery. These observations suggested that the increased corticotropin during pregnancy might play a role in the pathogenesis of diabetic retinopathy. Rabbits given cortisone or compound F alone developed Kimmelsteil-Wilson-like lesions, but no retinal lesions were apparent.

Friedenwald and Becker[6] have found, however, that alloxan diabetes in rabbits predisposes these animals to the capillary lesions elicited by cortisone and corticotropin and have in this way produced an ophthalmoscopic picture resembling early diabetic retinopathy. They have therefore suggested that the retinopathy and nephropathy of the diabetic may be the consequence of an increased secretion of cortisone (or related substances) by the adrenals. Their working hypothesis suggests that both the pancreatic lesions and the action of corticotropin in amounts that are excessive for a diabetic are factors in the development of both the diabetic retinopathy and the Kimmelsteil-Wilson lesions in the kidney.

Hoover, Becker, and Winter found that all the diabetics exhibiting adrenal hypofunction were free of retinopathy, and diabetics with retinopathy exhibited more adrenal activity than did the average diabetic without retinopathy.

Further clinical evidences for excessive adrenocortical function in diabetics with retinopathy is suggested by the worsening of diabetic retinopathy by infection and administration of corticotropin, both of which are associated with increased adrenocortical activity.

Patients with diabetic retinopathy also have increased excretion of oxysteroids, indicative of excessive secretory activity of the zona fasciculata of the adrenal cortex. Improvement of diabetic retinopathy has been reported following decreased adrenocortical function induced by adrenalectomy, pituitary necrosis, and testosterone administration.

Becker[6] reported that at autopsy diabetics with retinopathy and Kimmelsteil-Wilson disease, in contrast to patients with uncomplicated diabetes, had 24 per cent heavier adrenals with excessive lipoid vacuolization of the zona fasciculata and an abnormally high incidence of adrenal cortex adenomas.

Experimentally, when corticotropin or cortisone is administered to alloxan-diabetic rabbits the incidence of renal lesions is increased.

Zubrod[7] and his co-workers noted a marked clinical difference between groups of diabetics with and without Kimmelsteil-Wilson lesions. The Kimmelsteil-Wilson group showed a remarkable absence of acidosis even in the presence of marked hyperglycemia. This Becker explains by a relative excess of certain adrenocortical secretions in the Kimmelsteil-Wilson group. The thesis of Zubrod has been disputed by Wilson, Root, and Marble.[8]

Thorn and his co-workers noted the close interdependence between the function of the adrenal cortex and that of the beta cells of the pancreas in man. They pointed out that primary dysfunction of either of these tissues is often correlated with compensatory functional changes in the other. Thus, they described islet atrophy in Addison's disease and decreased adrenocortical activity in some diabetics.

Becker and Hoover performed adrenocortical function tests in living diabetics. The diabetics with diabetic retinopathy had an adrenal cortex responsive to exogenous corticotropin as measured by eosinophil counts, whereas the adrenal cortex of some diabetics without retinopathy responded less readily or not at all to the corticotropin test. This failure to respond, they believe,

must be related to defective function of the adrenal cortex, since the same patients have a fall in eosinophils following injection of cortisone.

In regard to the possible interrelationship of the glands of internal secretion in the production of diabetic retinopathy, one should note the use of testosterone by Saskin and his co-workers,[9] who found improvement in the fundi of some diabetics to whom they administered it. Even though this improvement has not been substantiated in many cases by others, it is a fact that testosterone has been shown to produce atrophy of the hypophysis and diminished adrenal activity in animals. Occasionally diabetics treated with testosterone have diminished daily insulin requirements as would be expected if they were experiencing diminished adrenal activity.

Dysfunction of both the pancreas and the adrenals has effects on the utilization of several of the B vitamins. Insulin is required for the formation of high-energy phosphate compounds and hence indirectly for the conversion of most of the B vitamins into their phosphorylated functionally active forms.

Becker pointed out the interrelationship of vitamin B_{12}, diabetes, and adrenocortical hormones. Vitamin B_{12} labeled with cobalt 60 was found in relatively high concentrations in the pancreas, kidney, and adrenals of experimental rats. Becker's interest was therefore aroused in the relationship of vitamin B_{12} to diabetic retinopathy and the Kimmelsteil-Wilson lesion.

Experimental chronic alloxan diabetes in rats was noted to induce vitamin B_{12} deficiencies and cause excessive retention of a test dose of the vitamin. Cortisone administration to rats mobilized vitamin B_{12} from all tissues and increased its excretion in the urine. This occurred even in the presence of a marked vitamin B_{12} deficiency, thus aggravating the deficiency state.

Symptoms of vitamin B_{12} deficiency are markedly exacerbated by cortisone, and the turnover of this vitamin is greatly accelerated in adrenal hyperfunction. Chow and Becker state that both cortisone-treated animals and human beings excrete far larger fractions of a test dose of vitamin B_{12} than do normals. Some of the symptoms of cortisone intoxication—for instance, thymus atrophy—are reversed by administration of this vitamin. Chow and Becker have tested the capacity of diabetics with and without retinopathy to retain a test dose of vitamin B_{12}. Diabetics without retinopathy excreted in their urine a smaller fraction of the test dose than did normals. Chow and Becker interpreted this as indicating vitamin B_{12} deficiency.

Diabetics with retinopathy excreted as much as or more of the test dose than did normals. This might indicate that these patients were saturated with vitamin B_{12} or that they were unable to retain the test dose because of adrenal hyperfunction. To test this, these patients were treated with testosterone and retested for vitamin B_{12} excretion. In every case greater retention of the vitamin occurred after testosterone than before it. The increased retention was most marked in those patients who showed increased insulin sensitivity after the testosterone; that is, evidence of diminished adrenal function.

Becker, Winter, and Friedenwald[10] tested the influence of vitamin B_{12} deficiency in rabbits on the renal lesions produced by cortisone. Nondiabetic animals on a vitamin B_{12}-deficient diet which were given 7.5 mg. of cortisone daily for two weeks had a much higher incidence of renal lesions resembling the Kimmelsteil-Wilson nephropathy than did animals on a normal diet containing aureomycin and vitamin B_{12} subjected to the same cortisone treatment. The lesions were in fact more severe and abundant than those produced in alloxan-diabetic animals on a vitamin B_{12} supplement diet given the same cortisone treatment. "It would appear, therefore," says Friedenwald, "that one of the convergent metabolic pathways leading to the production of the vascular lesion may be B_{12} deficiency induced by diabetes and exacerbated by adrenal hyperfunction." Becker concludes that deficiency of vitamin B_{12} does not appear to be the sole defect in the pathogenesis of diabetic retinopathy and Kimmelsteil-Wilson lesions, for four reasons:

(1) Although it prevented cortisone-induced renal lesions in some rabbits it failed to do so in others.

(2) Severe deficiency of vitamin B_{12} in rats did not produce renal lesions resembling those described by Kimmelsteil and Wilson.

(3) Intense vitamin B_{12} therapy failed to alter the clinical course of patients with diabetic retinopathy.

(4) Vitamin B_{12} deficiency in pernicious anemia is not usually associated with Kimmelsteil-Wilson lesions or diabetic retinopathy. "There is ample evidence," says Becker, "that B_{12} deficiency cannot be the sole cause of the retinal and kidney lesions." It seems to him more likely that adrenocortical hormones, diabetes, and vitamin B_{12} deficiency act together in producing the lesion by means of their effect on some other deficiency or metabolic disorder.

The diabetic exhibits an increase in plasma lipids. Lipemia is common in alloxan-diabetic rabbits. Increased blood lipids can also be produced by cortisone, and this effect is found in experimental rabbits. In rats, on the other hand, lipemia is not readily elicited either by alloxan diabetes or by cortisone administration, and the

species does not develop retinal or renal capillary aneurysms under the experimental conditions that produce these lesions in rabbits. Pellerman, working on "complement" in the blood, isolated a new serum protein that he and his co-workers named properdin. The properdin levels given in biologic units of the new protein for each milliliter of blood serum were 25 to 50 in rats, 4 to 8 in human beings, and 4 to 8 in rabbits. Of all the warm-blooded animals tested, the rat had the highest level of properdin, and it is well known that this animal is extremely resistant to infection. It is suggested that properdin plays a part in natural immunity. May we not hope that the future will show other chemical differences that can explain pathologic as well as physiologic difference of man as well as animal and show why human beings develop disease? Some believe that a disturbance of fat metabolism may be related to diabetic retinopathy and nephropathy. Renard and Dhermy[11] emphasize the lipotropic factor of the pancreas as important in the development of diabetic retinopathy.

In conclusion, it is stimulating to be working in an era when diabetic retinopathy has been taken out of the category of irreversible pathologic entities and is being approached as an error in metabolism that may be in our day retarded, stabilized, or even prevented.

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DISCUSSION

HENRY DOLGER, M.D., (*New York*): It has been mentioned several times today that the use of corticotropin and cortisone, experimentally or clinically, might be instrumental in the production of diabetic retinopathy. I cannot recall any diabetic patient who received cortisone or corticotropin in whom diabetic retinopathy subsequently appeared. Similarly, I do not believe that diabetic pregnancy is uniformly associated with retinopathy. It is a fact that there is frequently amelioration of retinopathy during pregnancy.

Dr. Leiter mentioned amelioration of diabetes as the Kimmelsteil-Wilson syndrome progresses. Although such patients have been reported as presenting poor glomerular function so that glycosuria could not be detected, he thought it possibly had to do with deficiency factors. Twenty years ago Keith of the Mayo Clinic, in a report on chronic renal disease, mentioned a patient who died of uremia whose pancreas revealed a total absence of beta cells. There was no record of diabetes in the history. This patient might have had diabetes which had become latent. Recently certain patients who had had diabetes twenty-seven years or more lost all clinical evidence of diabetes in the course of terminal uremia; their glucose tolerance tests were also fairly normal. Thus, one must invoke some other factor. It has been postulated that uremia is associated with the breakdown of ground substance, mucoproteins, and the like, substances which might be the factors in the amelioration of diabetes. In other words, materials released from mucoprotein degradation may be the inhibitors of insulinase which according to Mirsky is destroying insulin activity. With this in mind, two years ago I thought of using glucosamine to inhibit insulinase, but the results of the trial were negative. Diabetic patients were given glucosamine in doses of 50 gm. a day. None of them exhibited any improvement in diabetes.

In conclusion, it is possibly in this particular group that we may find the rationale for a new treatment of diabetes. In other words, the patient with Kimmelsteil-Wilson lesions whose glycosuria and glycemia disappear may be manufacturing the material that makes exogenous insulin unnecessary.

GEORGE WISE, M.D., (*New York*): The first point that I wish to emphasize is the reversibility of diabetic retinopathy, particularly in its early stages. I am sure all ophthalmologists have seen this occur spontaneously. While this enhances our hope for an eventual cure, it also necessitates considerable caution in interpreting any clinical therapeutic result.

Young diabetics with early fundus lesions of pure

diabetic retinopathy should be selected in any clinical research. The fundus picture in these individuals is usually purely diabetic and sufficiently simple for accurate determinations of any change from visit to visit. If older patients with more extensive retinopathy complicated by aging vessels, sclerosis, hypertensive changes, and venous thrombosis are used, the picture becomes much too complicated to judge accurately small changes from visit to visit, and thus the data are less reliable.

The second point I wish to emphasize is the importance of the venous changes in diabetic retinopathy as compared with the capillary aneurysm. The latter is the more dramatic recent discovery and has occupied much of our discussion today, but venous changes are far more important from the standpoint of visual prognosis. Most loss of vision in diabetics is due to the venous changes and their sequellae.

Clinically, diabetic venous changes due to endothelial thickening first appear as narrowing or enlargement of the venous blood column. Unless carefully looked for they can be easily missed. Any fundus vein or its branch may be involved, and the phenomenon is often scattered. As the venous lumen narrows and the wall thickens, thin white sheathing may be seen. This can become very marked. Eventually the lumen is occluded and the typical fundus picture of venous obstruction distal to the point of involvement occurs. Retinitis proliferans and vitreous hemorrhage, the causes of the loss of vision in most diabetics, are intimately associated with and secondary to such venous obstruction. Neovascularization or retinitis proliferans occurs in diabetes, nondiabetic venous destruction, Eales' disease, migratory retinal venous thrombosis, and some traumatic cases. The common denominator of all of these conditions is venous obstruction. Thus, the underlying cause of the visual loss in the diabetic does not seem to be quite so much the diabetes in itself as the blockage of the vein. It is of interest to realize how long we went without recognizing the importance of these venous changes. Only very recently has attention been called to them.

The third and last point is in the realm of biochemistry. Two of the common findings in disseminated lupus erythematosus are the "wire loops" of the kidney and the so-called fibrinoid around the smaller arteries. Fibrinoid apparently got its name because, although known not to be fibrin, it was morphologically like fibrin. It was thought originally to be due to a breakdown of the collagen fibers of the vessel wall.

Klemperer and Baer have presented evidence that both fibrinoid and the thickened arterial basement membrane of the kidney glomerulus, the "wire loop," are depositions of protein residue due to the depolymerization of desoxyribonucleic acid protein. The latter is a very important constituent of the nuclear protein and chromatin material of cell nuclei.

I was particularly interested in hearing Dr. Berkman's discussion, because I think that a good deal of very important information is going to come from further work on the ground substance and the derangements in these protein-bound complex mucopolysaccharides.

LEOPOLD G. KOSS, M.D., (*New York*): In advanced diabetic nephropathy the glomerulus occasionally displays not one lesion but two different lesions. One lesion is the conventional Kimmelsteil-Wilson lesion, which is round and takes silver stain very well. The other one stains red in trichrome, is of crescentic form, and frequently surrounds the round lesions of Kimmelsteil-Wilson. This red-stained lesion is in all respects comparable to hyaline arteriolarsclerosis, and the deposits of this material arranged in this fashion are found only in diabetic kidneys. I have named this renal lesion the "hyaline-fibrinoid" material, because it does take all the stains of fibrinoid, yet it displays, in hematoxylin and eosin, the appearance of homogeneous hyaline. It is possible that this material plays a significant role in the rapid downhill course of diabetics with advanced nephropathy. (Arch. Path. *54*:528-47, 1953)

I have been interested in the discussion pertaining to protein polysaccharide complex on one hand and the permeability of the basement membranes in diabetes in general. I have examined about 180 autopsies on diabetics and have found the hyaline-fibrinoid material in a fairly large number of cases. My findings are that this material is found not only in the glomerular location and not only in the markedly altered arterioles, but also—it is not shown in the picture—in the Bowman's capsule and in the basement membrane of the tubules of the kidney, and that it is undoubtedly a polysaccharide protein complex.

In addition, this material is in all respects similar to inspissated tubular casts which may be found in distal renal tubules. Therefore, on morphologic grounds, it is fair to assume that this is the same material. How did it get into the wall of the glomerular loops? Possibly, the permeability of the capillary loop in the kidney is so altered that the protein which comes from the circulating blood has some way of penetrating through the internal limiting membrane and forms this sort of deposit. This, incidentally, is very closely related to some of the findings found in the eyes of diabetics.

A word about lipids in the kidney of diabetics. In diabetic kidneys, the deposits of fat and lipids, as I

have found, are actually a late phenomenon and not an early one. Therefore, the deeply altered kidneys do contain lipids, and thus the diagnosis can be made on examination of urine. In early diabetic lesions of people who died of intercurrent diseases or accidents, and so forth, there is no evidence of lipid in the glomerulus.

SUMMARIO IN INTERLINGUA

Le Concepto Hodierne de Retinopathia Diabetic

Le autor revide observationes clinic e experimental in relation al cambiamentos ocular associate con diabete, le quales currentemente recipe multe attention.

Le lesion vascular que es characteristic de retinopathia diabetic consiste in grande numeros de minute aneurysmas saccular in le capillares retinal. Il es generalmente acceptate que retinopathia diabetic non depende de hypertension, arteriosclerosis, o atherosclerosis. Le lesiones retinal es multo affin al lesiones renal describite per Kimmelsteil e Wilson. Datos es presentate que suggere que le cambiamentos e retinal e renal pote resultar de un augmentate production de hormones adrenocortical. Un interrelation de vitamina B_{12} e le hormones adrenocortical in diabete ha etiam essite postulate, sed il es clar que un deficientia de vitamina B_{12} non pote esser le sol causa de retinopathia diabetic.

Le autor sublinea le potential reversibilitate de retinopathia diabetic, le qual es nunc studiate como un falta metabolic que probabilemente un die on va succeder a retardar, stabilisar, o mesmo prevenir.