Special Article

Conference on Microcirculation and Diabetic Retinopathy

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A conference on microcirculation and diabetic retinopathy, sponsored by the National Society for the Prevention of Blindness, was held at the O'Hare Inn on May 6 to 8, 1962. The participants gathered at the motel, which is adjacent to the O'Hare International Airport near Chicago, for dinner on Sunday evening, met all day Monday and Monday evening, and concluded their sessions at noon on Tuesday so that nearly all could catch afternoon planes to return to their home cities.

The meeting was opened by Leopold of Philadelphia who discussed the 1960 symposium on diabetes which had been supported by the United States Public Health Service (*Survey of Ophthalmology* 6:483-612, 1961). At this symposium the histology and ultrastructure of normal retinal blood vessels in man and experimental animals were discussed. The lack of information concerning vessels of the retina was most apparent. Since that time studies with the electron microscope and the development of the trypsin digestion technic have yielded a much clearer picture of these vessels.

Cogan of Boston, on the basis of trypsin digestion of the human retina, differentiated two types of cells in the retinal capillary wall: (1) endothelial cells that are pale staining and sausage shaped, and (2) round cells which are darker staining and appear in certain magnifications to be outside the wall. However, since the basement membrane surrounds these cells on both sides, he called them mural cells and believes that they are unique to the retinal blood vessels and that they are not capillary pericytes.

Hausler of Toronto presented studies of retinal vessels stained by means of the silver perfusion technic. He believes that the trypsin digestion technic is superior in many respects.

Patz of Baltimore found no cytologic difference in mural and endothelial cells with electron microscopy. Bloodworth of Madison believed that the so-called mural cells were pericytes and he felt that it was not necessary to coin a new term to describe them. Miss Feeney of San Francisco presented electron microscopic studies of the retinal vessels in the rat, monkey, a five-month human fetus, and six humans ranging in age from forty-seven to sixty-nine years. No significant morphologic difference was found between the rat and the monkey arteries. The rat capillary has all the components of the human and monkey capillary but is more delicate in configuration. She believes that man does not show a distinctive anatomic pattern of the retinal blood vessels to account for diabetic retinopathy.

In the second session the histology, ultrastructure and physiopathology of the capillaries in man and experimental animals were considered. Spargo of Chicago summarized some of his previously published reports and pointed out that there are two main groups of capillaries from the viewpoint of the electron microscopist: (1) those with definite pores and (2) those with no pores. He stated that there was another intermediate group that might be thought to be pores but there was a membrane over the area containing such pores. He showed electron microscopic pictures of heart and lung capillaries which, like those of the retina, have no pores but do have basement membrane. However, unlike the retina, these capillaries are without mural cells or anything that could be considered mural cells. The liver capillaries were interesting in that they had no basement membrane. The kidney capillaries had a complex relationship with the adjacent epithelial cells.

Spargo also showed human renal biopsy studies, using the electron microscope, of four different human diseases characterized by thickening of the basement membrane, including the Kimmelstiel-Wilson lesion and the diffuse glomerulosclerosis of diabetes. He called attention to the possible use of the electron microscope as a sensitive and specific way to detect chemical elements to obtain definite information concerning concentration changes taking place in minute areas of the basement membrane.

Rees of Boston emphasized the occurrence of a basement membrane disorder in chemical diabetes. He presented ten patients who had been treated by means of

pituitary stalk resection with resultant clearing of the vitreous and no further retinal hemorrhage in four, death in one, and initial clearing but further hemorrhages in the remaining five. He emphasized insulin binding in clinical diabetes and stated that it deserved particular attention because it provided a theoretic approach to therapy by releasing the bound insulin.

Lazarow of Minneapolis presented chemical analysis of the basement membrane of glomeruli in the diabetic and nondiabetic human. The chemical data bear out the early electron microscopic data in terms of primary thickening of the basement membrane as being an intimately associated phenomenon of diabetic complications. He stated that a fundamental change of the basement membrane occurred in association with the complications of diabetes, and this occurs not only in the kidney and retina but also in the blood vessels of the skin, muscles and mammary gland.

In the third session, the histology and ultrastructure of the blood vessels in spontaneous and induced diabetes in man and experimental animal were discussed. Kuwabara of Boston presented material derived from a study of over 200 human diabetic eyes, using the trypsin digestion of the retina. He showed that there were three types of change in the diabetic retina: (1) aneurysm formation with ghost mural cells in which the mural cell described by Cogan lost its nucleus; (2) diffuse capillary changes with proliferation of the endothelial cells and dilatation of the capillaries, and (3) capillaries containing no blood but containing endothelial and mural cells. He felt that ghost mural cells are nearly 100 per cent specific for diabetic retinopathy, whereas loss of mural cells may occur in other conditions. He presented electron microscopic pictures showing in one instance thickening of the basement membrane outside a mural cell.

Wolter of Ann Arbor illustrated human retinal microaneurysms by means of silver impregnation. He particularly emphasized intravascular strands and their connection with outpouchings of blood vessels. He believed that lipid deposits in the retina were probably degenerated ganglion cells and mural elements that were later phagocytosed by microglial cells. Hausler, using a silver preparation, thought that the basement membrane of microaneurysms of the retina might be up to forty times normal thickness. He studied vessels to learn if there were points of weakness and, by increasing pressure, found that there was no blow-out in the aneurysm area or points of obvious leaking. He reported a fourteen-year-old dog made diabetic by injection of growth hormone twelve years earlier. The retina showed many aneurysms and what Cogan believed was loss of mural cells but there were no ghost mural cells. The fundus could not be studied before death because of cataracts. Study of the kidney had not been completed.

Patz of Baltimore reported on a twelve-year-old dog with spontaneous diabetes treated for two years by the owner with insulin. The retina showed microaneurysms, ghost mural cells, areas of loss of endothelium and exudate, all of which were thought to be characteristic of diabetic retinopathy. The eyes of twenty-three normal dogs which were more than ten years of age showed no changes.

The renal lesion in the dog with retinopathy aroused much discussion as to whether it was the same type of lesion as is seen in the human. There was diffuse glomerulosclerosis in each glomerulus examined, but it was felt that to prove it was a true diabetic change electron microscopic study would have to be done.

Bloodworth presented the electron microscopic pictures of the retinal capillaries of two dogs with diabetes and renal changes. He believed they showed thickening of the basement membrane. The fundus changes in these animals were not as obvious as those of Patz and Hausler.

Levine of New York presented three pancreatectomized rats studied a year after operation. There were minimal changes in the retina, which included thickening of the arterioles and increased PAS staining of the arterioles and capillaries.

Yerganian of Boston presented work with Chinese hamsters with hereditary diabetes. He believes there is a great need for thorough study of these animals by people interested in diabetes. Diffuse glomerular changes were noted in the animals. Kuwabara showed trypsin preparations of the retina of the Chinese hamsters with diabetes. There were areas of loss of endothelial cells and questionable loss of mural cells which Cogan believed to be related to the age of the animal rather than to diabetes.

Becker of St. Louis, using fluorescent antibody stain, has shown marked concentration of bound insulin in microaneurysms of the retinal capillaries and in Kimmelstiel-Wilson disease there was similar binding of fluorescein-labeled insulin in the diabetic kidney. This binding may be antigen-antibody in type and may indicate an immunogenic component of the complications and perhaps of the metabolic disease itself.

Graef of New York briefly presented material relating to hormonal interrelationships in diabetes, particularly pituitary and adrenal. Marble of Boston emphasized the role of good control in the prophylaxis of vascular defects.

The question was brought up whether diabetes is primarily a carbohydrate disease which goes on to produce changes in the vessels or whether it is a vascular disease in which one aspect is the carbohydrate defect.

In general, the meeting emphasized the important role of the basement membrane in current studies of the complications of diabetes and the important amount of work done on the retinal blood vessels since the meeting in 1960.

It was agreed in advance that a verbatim account of the meeting would not be published. A more extensive account of the discussions appeared in the January 1963 issue of the *American Journal of Ophthalmology* (55: 156-72, 1963).

Special Article

Statement on Emergency Medical Care

The American Diabetes Association's original Committee on Emergency Medical Care was formed in 1950 to consider the problems of the diabetic in event of a disaster. Its comprehensive report, which was published in *The Journal of the American Medical Association* Dec. 1, 1951, pages 1350-54, has been reviewed from time to time. The Committee was reconstituted with the approval of the Council of the Association meeting in Detroit, Michigan, January 1962, and now makes the following recommendations which differ in certain important respects from those originally adopted. These changes have been made in order to meet conditions which might result from nuclear warfare.

Insulin. The manufacturers of insulin currently have adequate reserve supplies, in addition to which it is estimated that there is a sixty- to ninety-day supply widely distributed in wholesale areas and in local drug stores. The average diabetic also keeps approximately a three-week supply on hand. It is *recommended,* for purposes of the present emergency, that diabetics should store supplies of insulin necessary to maintain them for a minimum of two months.

Ideally, and by Food and Drug Administration regulation, insulin should be refrigerated (below 59° F. and above freezing) while being kept in reserve. However, it does maintain almost full strength for a long while under ordinary conditions, and should not, even if unrefrigerated, be discarded on expiration date during times of emergency. It is important, however, that the older vials should be used first, in order to keep the supply currently as fresh as possible. The diabetic who might be caught in a disaster while at work away from home should also arrange to store a supply of insulin at his place of work.

Oral Drugs. The oral hypoglycemic compounds for diabetics are much less perishable than insulin. It is therefore *recommended* that the diabetic arrange to store enough of these drugs to provide for his therapeutic needs for two months at least during the period of emergency.

Testing materials, syringes and needles, and isopropyl alcohol. All these supplies should be stored in amounts sufficient to last for two months. Among testing agents, Benedict's solution is the most stable, but requires a heat source. Where no heat is likely to be available, the other testing materials requiring no heat must be used. However, it should be remembered that the newer reagents are subject to deterioration by heat and moisture. These reagents, which include copper sulfate tablets, bismuth-containing powders, and glucose oxidase tapes or sticks, should all be stored in their original containers with seals still intact. Those that have been on hand longest should be used first. As for syringes and needles, they should also be stored in as dry a place as possible, in their original sealed containers to protect them from damage due to moisture or other contaminants in the atmosphere. Bottles of alcohol should be sealed to reduce evaporation losses to a minimum.

All diabetics should take their medical supplies and equipment with them if it becomes necessary to go to a community shelter since such items will not be available in shelters.

Food supplies. In a national atomic emergency, the diabetic will, like the general public, be required to follow government regulations as to how much food and what kinds of food may be made available in community shelters. For supplies placed in reserve at home, it is *recommended* that diabetics store a large enough quantity