EDITORIAL

CAPILLARY SHUNTS IN THE PATHOGENESIS OF DIABETIC RETINOPATHY

In the present issue, Cogan and Kuwabara suggest a relationship between the ghost appearance and absence of mural cells in the walls of the retinal capillaries and the presence of microaneurysms. With the development of a new trypsin digest method and subsequent staining by suitable dyes, these investigators have identified two types of cells associated with the capillary wall.[1] One type is the endothelial cell lining the lumen; the other type they have called the mural cell[2] because it is encased within the vessel wall and covered on both its inner and outer surfaces by basement membrane. They have not been able to find these mural cells on capillaries elsewhere, e.g. connective tissue, conjunctiva or choroid. They also could not find these mural cells in vessels that proliferate pathologically into the vitreous of man. Cogan and Kuwabara have distinguished the mural cell, which they initially identified as a perivascular glial cell, from the pericyte, limiting the term of pericyte to cells outside the wall in contradistinction to the term (mural cell) which refers to cells within the substance of the wall. Pericytes as defined, unprotected by the wall of the capillary if present, would be digested away by the trypsin prior to making the whole mount of the retina and would not be seen in their preparations. It has been suggested that these so-called mural cells may be similar, if not identical, to the so-called undifferentiated cell of the other body capillaries described by Bloom and Fawcett.[3] Although the vessels which pathologically develop into the vitreous in the human eye do not show mural cells, Mutlu and Leopold[4] have seen them lining the capillaries that make up the normal hyaloid circulation of the eye of the human fetus. These have been observed in specimens as early as sixteen weeks of age.

Cogan and Kuwabara have assumed that the mural cells play a significant role in the retinal capillary function because of their widespread occurrence and abundance in all mammalian retinas studied, e.g. man, monkey, cat, dog, hamster, mouse and rat.

In 1961, Cogan, Touissant and Kuwabara[5] postulated that focal degeneration of the mural cells may be the initial lesion in diabetic retinopathy. Most investigators suspect that capillary degeneration is the initial incident in diabetic retinopathy and speculate that the retinal capillary disease is part of a body-wide microangiopathy of diabetes mellitus.[6] The observation of Cogan et al. could explain the focal involvement of the capillaries, particularly those of the eye. Basement membrane changes have been described in many body capillaries of patients with diabetes mellitus. The basement membrane is definitely thickened in the retinal and renal capillaries, also in the muscle and skin capillaries. This has been evident by both light and electron microscopy. Yamashita and Becker[7] have reported a similar thickening of the basement membrane of the ciliary processes of the human eye of patients with diabetes mellitus. Perhaps the initial lesion of the capillary microangiopathy is, as suggested by Bloodworth and others, the thickening of the basement membrane in the capillaries of the retina, of the glomerulus, of muscle and subcutaneous tissue. This observation has been made in patients before the establishment of clinical diabetes. Perhaps the endothelial cell is responsible for this overproduction of basement membrane.

The function of the so-called mural cell or pericyte lying within the confines of the cell wall and within the thickening basement membrane is not known. The absence of mural cells in the large capillary channels associated with microaneurysms may be secondary to the basement membrane changes. The sequence of events is not certain.

Information is available on the light and electron microscopic appearance of these cells. Cytoplasmic contents of the mural cells are similar but much scantier than that of the endothelial cells. The endothelial cells are continuous with each other and the mural cells are discontinuous. Both appear to arise from the same anlage but the endothelial cells arise earlier. Histochemical stains have demonstrated dehydrogenase activity for lactate DPN and little, if any, phosphatase, cholinesterase or succinic dehydrogenase activity.[8] The mural cells may have the function of excluding red blood cells from most of the capillaries and Cogan and Kuwabara also suggest that inhibition of neovasculariza-

tion may be another function of the mural cell. They were unable to find any evidence of phagocytosis for these cells nor any ability of these cells to produce basement membrane.

It appears that the mural cells are less susceptible to aging and ischemia than the endothelial cells. The crux of the Cogan and Kuwabara thesis is that the loss of the mural cells in diabetes mellitus may in turn result in pathologic shunting of whole blood to some of the capillaries and a total ischemia of the adjacent capillaries. It is the shunt vessels that develop the microaneurysms and show endothelial proliferation. Shunts without microaneurysms but with endothelial proliferation have been observed in the retinas of nondiabetics. Shunts are not new vessels but arteriovenular dilatations of preformed capillaries accompanied by varying degrees of endothelial proliferation.

This observation may help to throw light on the manner of development of retinal capillary aneurysms in diabetes mellitus. A number of questions remain to be answered, however. Does the loss of mural cells follow or predate the basement membrane thickening? Is the loss of mural cells primary or secondary to the basement changes? Could the mural-cell loss be due to changes in surrounding tissue outside the vessel wall? Could changes in the surrounding tissue or in the wall of the vessel allow trypsin digestion to affect mural cells and produce the ghost appearance and loss as seen in the preparations? Perhaps the initial fault lies in the endothelial cells that contribute to the excess basement membrane. If the mural cells were derived from endothelial cells it would not be difficult to explain the sparsity and later absence of mural cells in the presence of a thickened basement membrane as well as the piling up of endothelial cells as due to the inability to penetrate to the outer areas of the wall because of the increased basement membrane material. It is even possible that mural cells might differentiate and become additional endothelial cells, thus accounting for the local loss of mural cells. The observation of ghost cells would argue against this impression. The function as well as the metabolism and reaction of the mural cells merit further investigation. One wonders why ghost appearance is not accompanied by karyorrhexis as well as karyolysis. It is not clear why the brain capillaries fail to show similar lesions. Is the failure due to technical difficulties in preparing trypsin digested material of brain cortex? Rare microaneurysms of the brain were described by Friedenwald[9] several years ago.

There is no doubt that this suggestion of Cogan and Kuwabara is a stimulating, speculative concept and one which is based on careful histologic study.

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BOOK REVIEWS

THE CHEMISTRY AND CHEMOTHERAPY OF DIABETES MELLITUS. *By Alexander Marble, M.D., and George F. Cahill, Jr., M.D. $7.75, pp. 204. Charles C Thomas, Springfield, Illinois, 1962.*

This small text, one of the "Living Chemistry Series," is written in two parts: Part I, dealing with current concepts of the physiology and derangements in the diabetic state, is by George F. Cahill, Jr., M.D.; Part II, dealing with the agents used in the treatment of the diabetic patient, is by Alexander Marble, M.D. Both authors are extraordinarily well-equipped to deal with their respective material. The subjects in general are timely and current and are discussed in a clear, simple, and straightforward manner.

Part I reviews briefly and logically the mechanism of insulin action, its structure, synthesis, storage, release, transport, and destruction. The section dealing with the intermediary metabolism of carbohydrate and its relationship to lipids is perhaps less effective—no doubt since it deals with such a highly complex area. The differences in tissue behavior with regard to insulin and nutrition are diagrammatically shown. The references are well-chosen from an enormous literature.

Part II provides information with regard to insulin and oral hypoglycemic agents useful to students and physicians interested in a brief, clinical consideration of these subjects.

This book is highly recommended with the one reservation that Part I may well be out of date within a short time in view of the rapidity of development of new research in this field.