COMMUNICATIONS

NOMENCLATURE OF PERICYTES* INTRAMURAL AND EXTRAMURAL

BY

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The cellular structure of the retinal vessels as revealed by the digest technique recently introduced by Kuwabara and Cogan (1960) has aroused widespread interest and speculation, especially concerning the nature and function of the cells to be found embedded in the walls of the retinal capillaries. Cogan and his colleagues at first thought that these were the nuclei of perivascular glia, but later concluded that they were special cells confined to the retinal circulation (Kuwabara and Cogan, 1963), wherein they were probably concerned in the control of capillary blood flow, and, being selectively injured in diabetic retinopathy, were of significance in its pathogenesis (Cogan, Toussaint, and Kuwabara, 1961). Believing that these cells were an entity not previously described they gave them the special name of "mural cells", a term which is already becoming established in the literature as a specific component of the retinal capillaries.

From our own observations and from a review of the literature, it has since become clear that this cell is not in fact unique to the retina, but corresponds to one type of cell found throughout the vascular system, and long classified under the confusing term of "pericyte". It has now become essential, not only in ophthalmological work, but also in general vascular studies, to clarify the nomenclature and select a term that accurately describes these cells wherever they may be found.

Evidence from Light Microscopy

Almost all authors from the earliest studies agree that there are two kinds of cell related to the capillary structure: those which form the endothelium and others in close relation to the outer wall, which have been discussed for almost a century. Rouget (1873, 1874, 1879) called the latter cells "non-pigmented adventitial cells" or "cells with ramified protoplasmic processes" and attributed to them a specific contractile function. His study was a careful and extensive one carried out on a wide range of specimens including frogs, rabbit and sheep embryos, kittens, puppies,

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adult sheep, and the meningeal vessels of embryo calves. He demonstrated these cells in all tissues studied and, in the present context, it is interesting that he illustrated them in the hyaloid and capsulo-pupillary membranes of sheep embryos, and in human and rabbit retinala. From his illustrations (see Figure) it is clear that these cells are morphologically identical with the “mural cells” of Kuwabara, Carroll, and Cogan (1961).

Figure.—Reproduction of Plate 24 from the classical work of Rouget (1873) showing adventitial cells (intramural pericytes) in various vessels. Fig. 2, in the capsulo-pupillary vessels of the hyaloid system of sheep embryo (note also retraction of vessel); Fig. 3, in new-formed capillaries of sheep embryo; Fig. 4, in the yolk sac of rabbit embryo; Fig. 6, in a retinal capillary of rabbit; and Figs 7 and 8, in adipose tissue of rabbit.

(By courtesy of the British Museum.)
NOMENCLATURE OF PERICYTES

Vimtrup (1922) named them "Rouget cells", agreeing that they had a contractile function (it may be noted in passing that this view was subsequently vigorously denied by others, while today it is the general consensus of opinion that capillaries are non-contractile (Wiedeman, 1963)). The term "pericyte" was applied to these cells by Zimmermann (1923). Without electron microscopy, however, none of these authors could have appreciated the exact location of these cells, and the name "pericyte" has subsequently caused considerable confusion, having been applied not only to cells with the morphological and topographical characteristics described by Rouget, but also to many different types of pericapillary cells.

Evidence from Electron Microscopy

With the advent of the electron microscope the true structure of the capillary was gradually revealed, so that capillaries are now known to be formed by a continuous layer of endothelial cells surrounded externally by basement membrane. Inside this membrane there are situated, at intervals, cells with ramifying protoplasmic processes, which surround the capillary and protrude from its outer wall. Farquhar and Hartmann (1956) reported them for the first time in electron microscopy of rat brain and called them "intramembranous pericapillary cells", and shortly afterwards they were described, again in the rat brain, by Maynard, Schultz, and Pease (1957). Maeda (1958, 1959) first described them in an electron microscopical study of the human retinal vessels, and referred to them as "pericytes". Since that time similar cells, described as "Rouget cells", "pericytes", "pericapillary cells", "perivascular cells", "adventitial cells" or "undifferentiated cells", have been demonstrated by the electron microscope in the retina (Bernstein, 1961; Bloodworth, 1962; Missotten, 1962; Hogan and Feeney, 1963; Ishikawa, 1963; Kuwabara and Cogan, 1963; and others); in the iris (Ikui, Mimatsu, Maeda, and Tomita, 1960; Tomita, 1960; Missotten, 1964); in the human corneal limbus (Iwamoto and Smelser, 1965); in the brain of human embryos (Dahl, 1963); in the rat and dog brain (Donahue and Pappas, 1961; Hills, 1964; Freeman, 1964); in rat muscle (Majno and Palade, 1961; Freeman, 1964); in human and rabbit connective tissue (Movat and Fernando, 1964); and in the capillaries of rat pancreas, lamina propria of the guinea-pig epididymis, choroid rete of fish eyes, and in capillaries from Amia and rete mirabile of the fish swim bladder (Fawcett, 1963).

Identity with "Mural Cells"

That these cells reported by electron microscopists are the same as those described by Kuwabara and Cogan (1960); Kuwabara, Carroll, and Cogan (1961); Cogan, Toussaint, and Kuwabara (1961); and Kuwabara and Cogan (1963) can hardly be doubted, for their location and ultrastructure are identical. Moreover, in our own studies in collaboration with Dr. M. Shakib we have seen them by electron microscopy in the iris, conjunctiva, retina, and brain, and by light microscopy in the retina, optic nerve, conjunctiva, brain, meninges, skin, and peritoneum, and can confirm their essential morphological identity.

With regard to the distribution of these cells we have found that in capillaries shaken free from the human brain, the structure and cellular components are almost identical with those in the retina (Ashton, 1963; Ashton, Kok, and Foulds, 1963);
indeed, in a study of capillaries of the cerebral cortex, isolated by an acid–water technique, it was found that a slightly greater number of "mural cells" exist in these capillaries than in the retina (Oliveira, 1964, 1965); their shape, staining properties, and regular distribution, however, were exactly similar. The same is true of these cells in the capillaries of the optic nerve and spinal cord, and they have recently been demonstrated in comparable numbers in the tunica vasculosa lentis of the human foetus (Mutlu and Leopold, 1964), and in the hyaloid system of the ratling (Agrawal, 1964). Capillaries cannot so effectively be studied in other tissues, but in flat preparations of conjunctiva, dermal and peritoneal connective tissue we have found similar cells; here, however, they were less regularly disposed than in the nervous system and showed some variation in shape. The very definite encapsulation of these cells within the basement membrane of the capillaries of the central nervous system is probably related to the fact that here the basement membrane is a well-defined entity, being delineated internally by the plasma membrane of the endothelial cells, and externally by the plasma membrane of the glia, whereas in other tissues with an ample extracellular space, the basement membrane may fade diffusely into the perivascular tissue depriving the "mural cell" of a compact outer envelope. It is thus possible that some cells of the same nature may be tenuously covered or even uncovered by basement membrane. This may explain why these cells are relatively poorly developed in the rabbit retina (Mutlu and Leopold, 1964) where most of the vessels are on the surface of the retina and possess a poorly defined basement membrane. By definition one would not, of course, expect to find "mural cells" in vessels devoid of basement membrane—as in the hepatic sinusoids (Hampton, 1958) or in developing vessels.

The statement by Kuwabara and Cogan (1963)—"we are unable to state whether or not mural cells comparable to those in the retinal capillaries exist elsewhere in the body"—can now, therefore, be answered in the affirmative, and all the evidence suggests that these cells are those originally described by Rouget in 1873 as "non-pigmented adventitial cells".

Nomenclature

We are not concerned in this paper with the derivation, function, or pathology of these cells, but only with their nomenclature. In previous papers we continued to use the non-committal term "pericyte" and deferred the adoption of "mural cell" until we were convinced that it was a new entity, but now that it is abundantly evident that it is not peculiar to the retina, the nomenclature of these cells as a whole needs revising.

In the light of the evidence provided by electron microscopy we can no longer continue to call these cells within the basement membrane "pericytes", "peri-capillary", or "perivascular cells", not only because these names confuse them with cells outside the capillary, but also because they are not sufficiently descriptive. Nor do we feel that the name "mural cell" is ideal, because it has erroneously come to mean a special retinal entity.

A nomenclature is required which accurately describes the situation of these cells wherever they may be found in the circulation, yet retains an association with retinal
studies and is not so completely new as to confuse the situation further. We consider that the terms “intramural pericyte” (encircling cell within the wall) for “mural cell”, and “extramural pericyte” (encircling cell outside the wall) for pericytes outside the vessel, provide the best nomenclature yet introduced (Rees and others, 1964). The name “pericyte” could then be used as a general term for both types. This nomenclature will therefore be used in all our subsequent papers on this subject, and we trust that others engaged in cognate work, whether ocular or extra-ocular, will consider it worthy of adoption.

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—— (1879). Ibid., 88, 916.
Nomenclature of pericytes: Intramural and extramural.

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