ULTRASTRUCTURE AND METABOLISM OF THE NERVOUS SYSTEM

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PREFACE

Investigators today have great opportunities for advancing their sciences. Unusually precise and penetrating technics are now available, and investigations are reasonably well supported. Such limitations as are imposed upon scientists by virtue of their administrative roles will be eased by further and more general types of support. Institutions will be built so that biologists and physical and social scientists will be able to concentrate their efforts, as well as extend their work into special types of research. The number of young, talented men being trained is growing. The future promises to be a productive one.

In the forefront of the compelling and complex issues to be faced are those relating to the mechanisms of the nervous system in health and disease. Not only are they intriguing in themselves, but they have personal as well as social significance. The way in which the nervous system operates biophysically, and how behavior which emerges from a single nervous system becomes adapted to and modified by the circumstances of social interaction, are scientific problems of magnitude.

This volume deals with two disciplines—chemistry and morphology—which are both involved in studies of the nervous system. We are interested in each separately and how they serve as different parameters of the same biologic events. This is a theme running through much of current inquiry. We need to know not only the chemical and physical reactions, but also where in the cell they occur and what their relation is in time and space to others. This is a particularly familiar problem to neurologists and psychiatrists, each with their own methods of examination and analysis of neural activities and behavior, each focused on a single aspect of the many functions of the same fundamental unit—the nervous system.

It would seem that the scientists whose contributions appear in this volume, while dealing with their own fields, support the simple thesis expressed in the title of this meeting, since they gave so willingly and fully of their time and effort. To them, as well as to Dr. Alfred Pope and Dr. Eli Robins, to Mrs. Natalie Friedheim who gave the volume structure, and to the publishers, I express my gratitude.

SAUL R. KOREY

CONTENTS

Chapter I

ULTRASTRUCTURE OF THE BRAIN AND ITS RELATION TO TRANSPORT OF METABOLITES[1, 2]

SARAH A. LUSE, M.D.

The central nervous system is set apart from other organs by its greatly restricted extracellular space. Cell touches cell, and the interstices between cells are filled by their closely packed intertwined processes, so that a residual extracellular space of only 150 to 200 Å separates any two plasma membranes. Horstmann and Meves (1) have calculated that this total interstitial space is only 3 to 5 per cent of the total volume in contrast to the 20 per cent calculated for skeletal muscle (2, 3). No perivascular connective tissue sheath surrounds the CNS capillary (fig. I.1) but rather, astrocytic and oligodendroglial processes completely invest the capillary basement membrane. A Virchow-Robin space exists only about large vessels, not capillaries. This arrangement in the CNS is in sharp contrast to that occurring in other organs, where large and small vessels course in an abundant extracellular space such as that evident in skeletal muscle (fig. I.2).

The question arises about the relation of the blood–brain barrier to this extraordinary lack of extracellular space around capillaries in the brain. Although the exact anatomic site of the barrier as well as the mechanism through which it operates are still equivocal, it has been clearly demonstrated that those areas of the brain in which the hematoencephalic barrier is deficient present a different vascular arrangement. Wherever the blood–brain barrier is absent (posterior pituitary, pineal gland, choroid plexus, area postrema, intercolumnar tubercle, subcommissural organ and, to some extent, the hypothalamus), the capillaries have the same morphologic arrangement as in non-neural organs. They are enclosed by an interstitial space bounded on each side by a basement membrane. The presence of a pericapillary extracellular space is particularly well demonstrated in argyria (fig. I.3) since the silver grains outline both basement membranes (4, 5) and there is no silver around capillaries of the brain proper.

[1] From the Departments of Pathology and Anatomy, and the Beaumont-May Institute of Neurology, Washington University School of Medicine, St. Louis, Missouri.

[2] Supported in part by U. S. Public Health Service grants B-1539 and B-425.

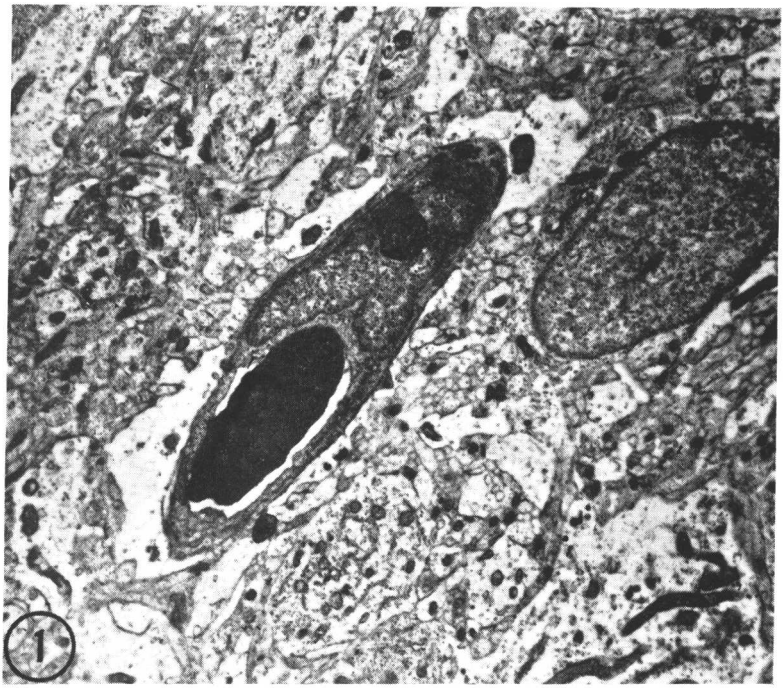

Fig. I.1. In the CNS, glial processes completely invest the capillary. ×10,000

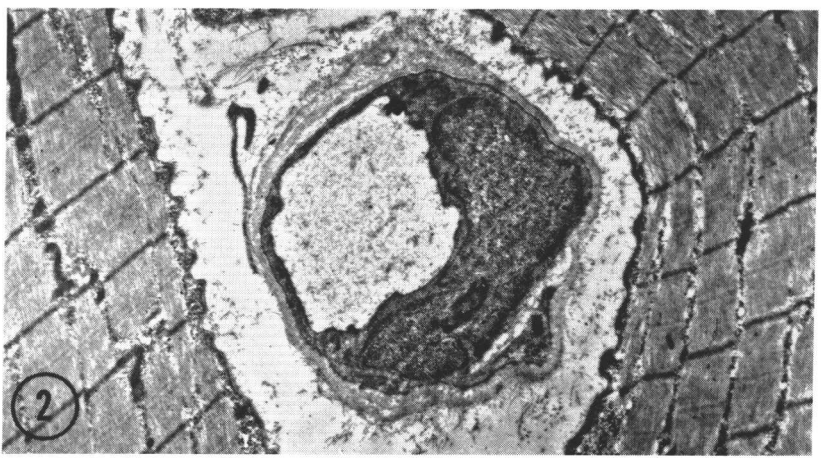

Fig. I.2. In skeletal muscle, capillary is surrounded by abundant extracellular connective tissue space. ×10,000.

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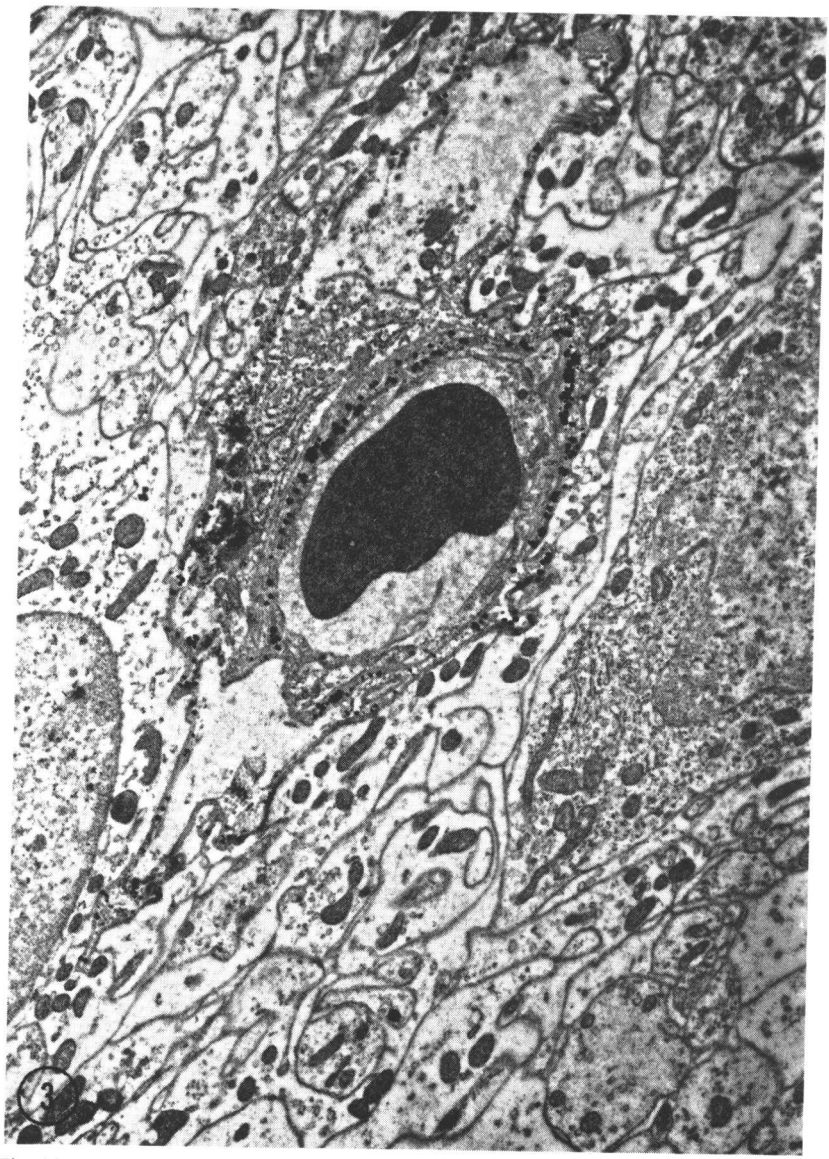

Fig. 1.3. Pericapillary connective tissue space exists in the parts of brain lacking blood–brain barrier. Experimental argyria in mouse; silver outlines extracellular space around vessel in hypothalamus. ×10,000.

IDENTIFICATION OF GLIAL CELLS

The ultrastructural histology of the CNS is yet to be thoroughly explored. It is still in a state of flux and our criteria for cellular identification need to be clarified before we can properly evaluate either the physiologic or the pathologic alterations of glia.

The oligodendroglial cells, as classically depicted by del Río-Hortega (6, 7), are arranged in rows in the white matter; as satellites to neurons; and as satellites to blood vesels. In contrast to them are the astrocytes, first clearly demonstrated by Ramon y Cajal (8). The protoplasmic astrocytes occur principally in the gray matter and fibrous astrocytes in the white matter and at the pia-glial membrane. As both Hortega and Cajal have shown, the astrocytic foot process forms a firm attachment to the capillary wall (fig. I.4) but does not invest the entire surface of the vessel as some have incorrectly believed. Rather, the firm astrocytic capillary attachment

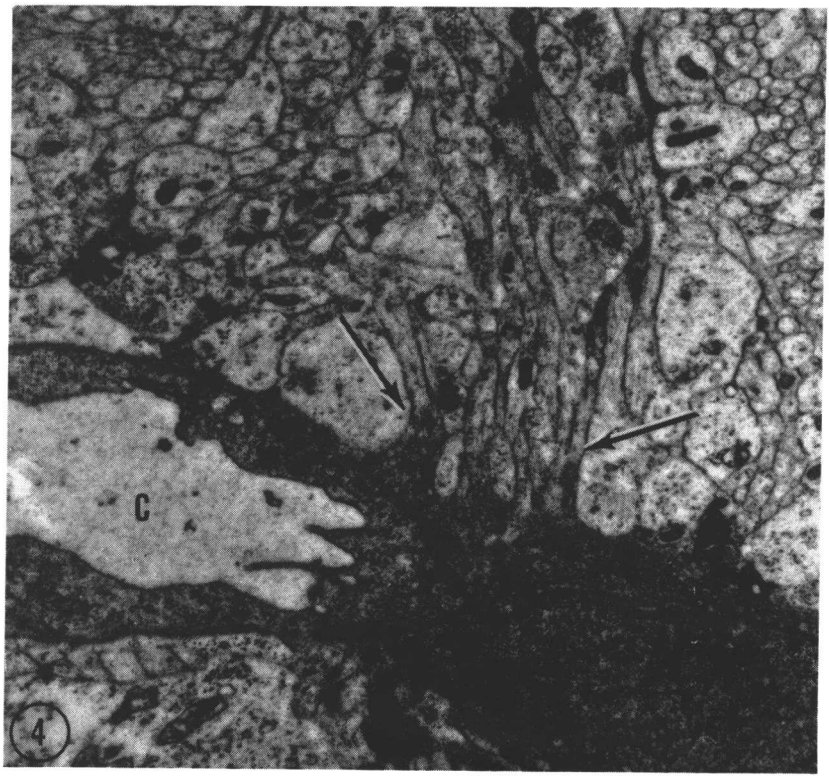

Fig. I.4. Electron micrograph showing astrocytic foot (*arrows*) inserted into wall of a capillary (*C*). ×10,000.

is interspaced between other glial or even neuronal contacts. del Río-Hortega (6) in 1922, and again in 1928 (7), clearly demonstrated oligodendroglial perivascular contacts. Either the oligodendrocyte itself or its processes may contact the vessel wall. This relation is well shown in figure I.5 from del Río-Hortega (6). It is of interest that here, in a gold chloride-sub-

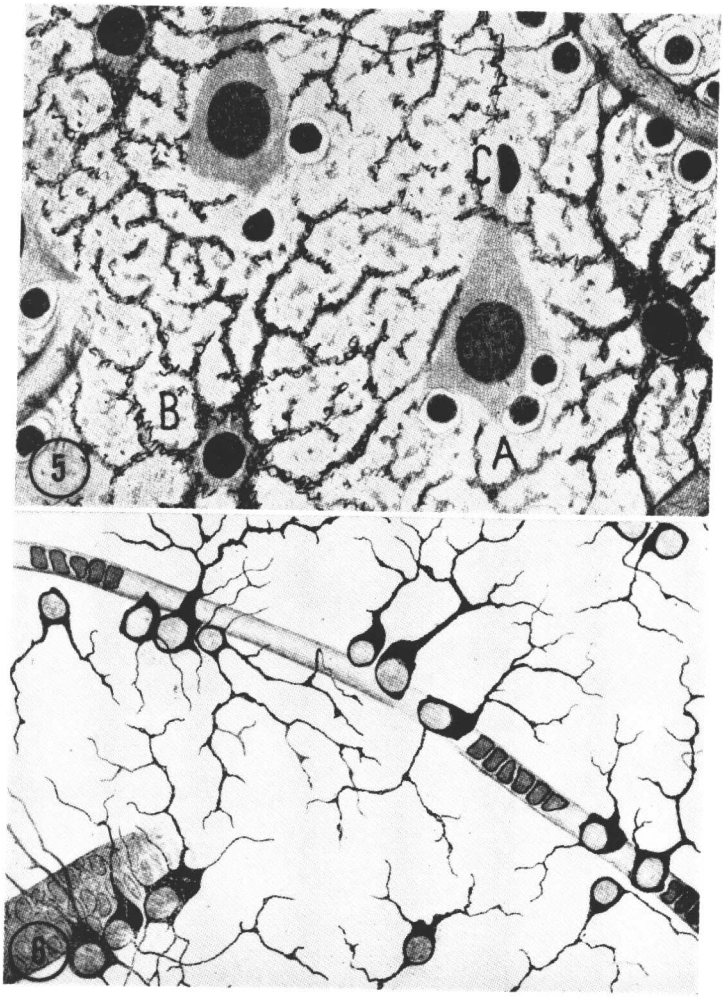

Fig. I.5. Copy of figure 1 from del Río-Hortega (6). Neuroglia of human cerebral cortex, stained by gold method of Ramon y Cajal. *A*, oligodendroglia; *B*, protoplasmic glial cell with short processes; *C*, microglial nucleus.

Fig. I.6. Copy of figure 66 from del Río-Hortega (6). White matter of a cerebellar folium of monkey. Many glial cells adjoin the vessels, with some quite large and branched processes. This demonstrates the difference in staining with silver carbonate.

limate impregnation, the oligodendroglial cell has a dark nucleus and pale cytoplasm, whereas when impregnated with silver carbonate (fig. I.6), it presents a mirror image with a pale nucleus and dark cytoplasm. Occasional microglial cells may also be perivascular satellites.

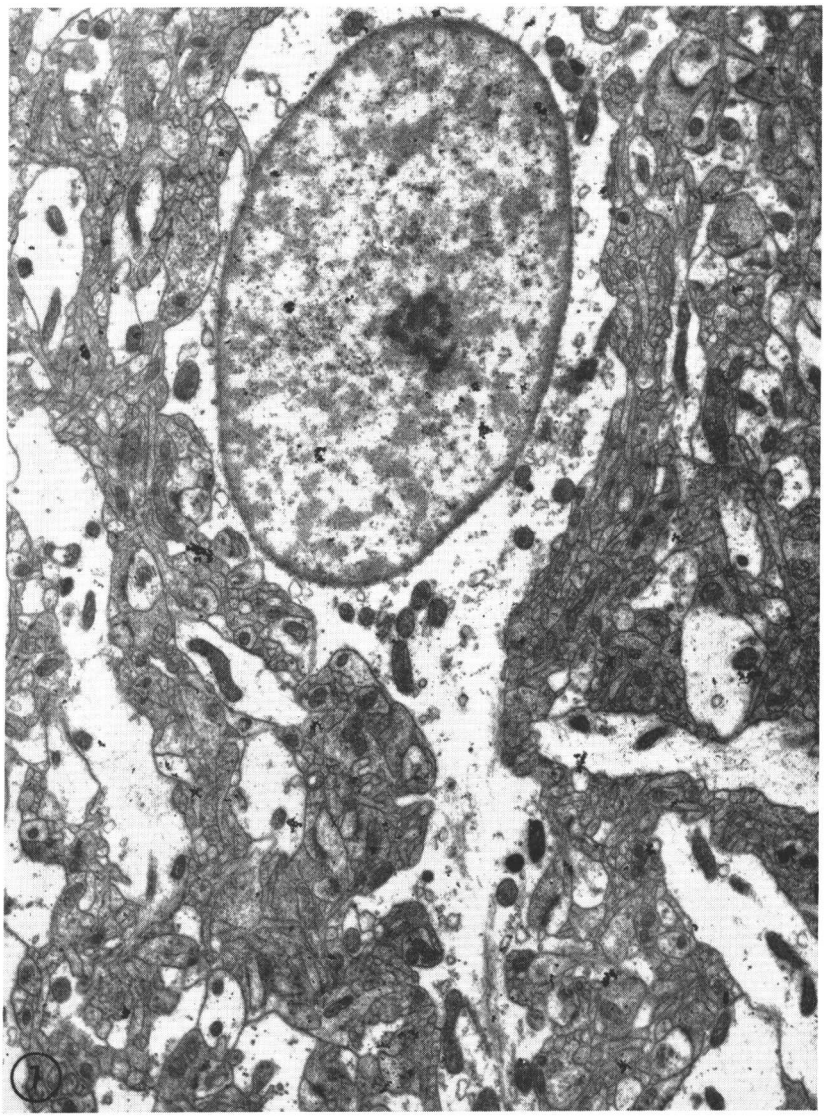

Fig. I.7. Oligodendrocyte in cortex, with abundant cytoplasm containing scant ergastoplasm. A single stout process extends downward; processes from other glial and neuronal cells form the neuropil surrounding oligodendrocyte. ×12,000.

In electron micrographs, the cortical oligodendrocyte is a cell with a round or ovoid nucleus and abundant pale cytoplasm containing little ergastoplasm, few mitochondria, and forming a few broad processes which often branch dichotomously (fig. I.7). The oligodendrocyte of the white matter (fig. I.8) is equally rotund but its cytoplasm usually is more dense, due to an abundant, finely dispersed endoplasmic reticulum associated with numerous fine punctate Palade particles (12). In contrast to it is the astrocyte, a cell with scant perinuclear cytoplasm extending out into a multiplicity of delicately branched and refolded processes. The astrocytic nucleus is ovoid or reniform. In the protoplasmic astrocyte (fig. I.9), the ergastoplasm is finely dispersed and the plasma membrane covering the plicated processes is more prominent than the protoplasm it encloses. The fibrous astrocyte, however, is simpler, with somewhat broader processes which contain abundant protoplasm filled with delicate tonofibrils as is demonstrated in figure I.10, an astrocyte at the surface of the cerebral cortex. Here the astrocytic processes can be delineated as they proceed to the pia to form the glial portion of the pia-glial membrane.

A controversy has arisen over identification of the glial cells. Palay (9) and Luse (10–14) have identified the pale cells as oligodendrocytes, and the cells with scant perinuclear cytoplasm and plicated processes as proto-

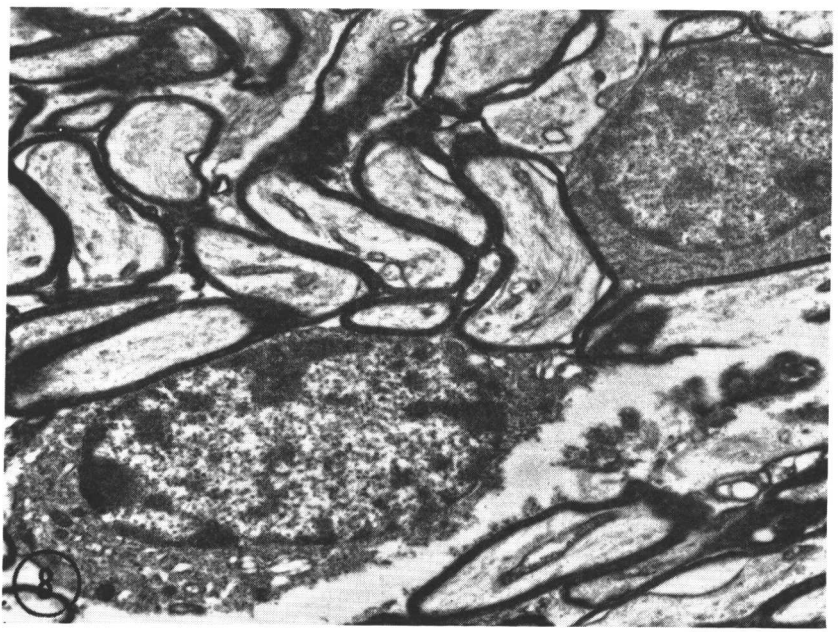

Fig. I.8. Two oligodendrocytes in a row in white matter. Their cytoplasm is as smooth in outline but denser than that of their counterparts in the cortex. ×7000.

Fig. 1.9. Electron micrograph of protoplasmic astrocyte in olfactory bulb. Perinuclear cytoplasm is scant and extends out into numerous delicate plicated processes (*arrows*). ×12,000.

plasmic astrocytes. Farquhar and Hartmann (15), Schultz and associates (16), and Gerschenfeld and co-workers (17) have equated them in the reverse, and the last mentioned thus have described the astrocyte as the cell that swells in cerebral edema. Our contention that the often pale cell with abundant cytoplasm equals the oligodendrocyte is based on: (*1*) their similarity to the cells occurring in the six human oligodendrogliomas that we have examined; (*2*) their position as satellites to neurons; (*3*) their organization into rows in the white matter; and (*4*) their association with myelinating axons in the CNS. Likewise, the cells present in gliosis (secondary either to stab wounds or to the presence of alumina gel on the surface of the cortex) are identical to those identified by us as fibrous astrocytes; similar cells occur in low-grade fibrous astrocytomas of the optic nerve, of the cerebellum and of the cerebrum; and their presence at the pia-glial membrane in the human being and in the cat has been used as a criterion for identifying astrocytes. In addition, in gliosis and astrocytic tumors impregnation of adjacent pieces of tissue by Ramon y Cajal's gold

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