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INTRODUCTION

PERSPECTIVES ON THE CELL BIOLOGY OF GLIA

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From the vantage point of 1981, advances in our understanding of glial cells over the last 20 years seem at once significant, provocative and high in promise. It is sobering to remember that at that time speculation about their role included a spectrum of romantic possibilities, from blood–brain barrier to memory, from constituting the total extracellular space of the brain to playing a key role in learning, from being essential for the neuronal action potential to producing impulses themselves, from ferrying vital materials into and out of neurones to having no function at all other than support. Unfortunately, the ratio of speculation to sound experimental observations was so high that, apart from continuing contributions from anatomists, to be interested in glia was almost disreputable, somewhat akin to dabbling in parapsychology or memory transfer.

A major change in emphasis was the approach of Stephen Kuffler and David Potter which dealt with the cell biology of glia. The starting point for their experiments in about 1961 was the frustration of trying to teach medical students neurobiology without mentioning the cells that made up the bulk of the brain. After an extensive search for a suitable preparation they chose a simple invertebrate, the leech, to ask questions such as: how did the membranes of glial cells compare to those of neurones, did they have resting potentials and give impulses, what ions were their membranes permeable to, what ions did they contain, were they required for neurones to give impulses, and what electrical and ionic interactions did take place between the two types of cell? These and similar down-to-earth experiments set the stage for Sidney Goldring's studies of glial cells in the mammalian brain, where they turned out to be strikingly similar in their membrane properties to those in the lowly leech. In its own way the paper by Kuffler and Potter in 1964 therefore served as watershed, changing dramatically the nature of the work on glia.

The papers at this symposium cover a far broader scope, showing progress in novel, unexpected directions, but again with emphasis on glial and Schwann cells as cells, with characteristic structures, junctions, relationships and interactions with neurones, in the normal nervous system, during development and in disease.

One key problem today concerns the morphology of membrane specializations and the distinctions between the various types of glial cells and Schwann cells. Freeze fracture has now revealed membrane particles distinctive for astrocytic glial cells located at specific sites in relation to blood vessels (p. 35). Immunological (p. 215) and enzymological techniques also offer high promise for establishing how oligodendrocytes, astrocytes and Schwann cells and invertebrate satellite cells can be distinguished chemically. It will be of considerable interest to understand the functional

roles played by the various marker proteins (p. 167) as well as the fundamental inter-relationships between the various types of glial cells. In spite of much additional information about the various junctions that may allow for coupling and for barrier functions (p. 7), it is somewhat surprising that we do not yet know just what part is played by electrical coupling between glial cells or even whether oligodendrocytes are coupled to astrocytes. And, apart from paranodal regions in myelinated nerve, what specialized structures or junctions (if any) occur between neurones and glia?

Since the 1960s, major progress has been made in our knowledge of the fluid environment of the CNS (p. 129) and the contribution of glial cells. Their membranes have now been shown to pump potassium (p. 49) and in insects to play a crucial role in determining the ionic environment of the neurones (p. 61). This homeostatic function is reinforced by glial blood–brain systems in the insect nervous system (pp. 7, 61) and (as described at the meeting by Joan Abbott) in animals such as the cuttlefish (*Sepia*) it is the glia rather than endothelial cells which constitute the barrier that limits exchange of large molecules (such as peroxidase) between the blood and extracellular fluid. A major incentive for studying glial properties has been the interest in potassium accumulation caused by physiological stimuli. As Kelly and Van Essen first showed, an oligodendrocyte situated in a column of the cat visual cortex can 'respond' selectively to a bar of light shone on to one particular part of the visual field with one particular orientation. Thus, it recognizes one specific visual stimulus. But what then? In certain instances there is evidence that the potassium acts as a trigger for metabolic effects (pp. 49, 75) and it has also been shown that potassium accumulation can affect synaptic transmission (p. 93) or such phenomena as spreading depression (p. 111). Yet even today there is still no conclusive quantitative answer to the question of how important the role of glia is in redistributing potassium at various sites within the brain that contain different populations of glial cells and neurones with different geometry.

Closely related are the findings of Kelly and Currie, David Brown and others on transmitters. Non-neuronal cells clearly need to be considered in relation to transmitter uptake in which they could play a quantitatively important part (p. 181). In the case of the squid giant axon acetylcholine has been implicated by Villegas in a series of events as a factor released by Schwann cells (p. 135). as at degenerated neuromuscular junctions of the frog. There, Miledi and his colleagues demonstrated that release of acetylcholine from Schwann cells gives rise to miniature endplate potentials in the denervated muscle.

In this same system of squid giant axon and Schwann cells the transfer of specific proteins including actin has been clearly demonstrated (p. 153). Indeed, such protein transfer can also occur between various types of neurones, as for example in the mammalian visual system after radioactive amino acids have been injected into the eye. A tantalizing question is whether sufficient quantities are transferred for those proteins to play a role in normal neuronal function.

It is perhaps in relation to development that among the most provocative new vistas have been opened. Starting with Mains and Patterson's work, it is now known that non-neuronal cells, including glia, can in culture release factors that profoundly influence the type of transmitter to be synthesized by a neurone (p. 195). Specific

factors within the brain regulate the division of Schwann cells and astrocytes (p. 215); and in *Aplysia* during development glial cells may play a role in regulating division by neurones (p. 205).

The extensive series of experiments by Aguayo (p. 231) and his colleagues bear on two other important properties of glial cells and Schwann cells. One, not represented at this meeting, is the importance of myelin in speeding conduction; the other concerns the role of Schwann cells and glial cells in regeneration. That glial cells in the developing mammalian brain can act as guides for neurones to grow to their destination has been shown by Rakic and his colleagues. The use of nerve transplants and grafts by Aguayo now indicates that regeneration of the adult CNS may be far more practicable and extensive than had previously been thought. Conduits can be formed by Schwann cells that allow damaged central neurones to grow for long distances. It will be of considerable interest to know whether such neurones form synaptic connexions and, if so, whether they can be used to restore function. Other work by Aguayo and by Brockes and their colleagues bears on the key problem of the signals required for myelination to occur (pp. 215, 231).

From these considerations, one is struck by the new avenues that have been explored, the hard evidence now available about aspects of glial and Schwann cell properties and the testable new speculations that have evolved. At the same time there is the challenge of certain major unanswered questions. We are still quite ignorant about glial cells in demyelinating diseases such as multiple sclerosis; it is still not yet known whether the primary lesion is in the neurones or the oligodendrocytes. What does seem appealing is that highly complex problems may now become more approachable with the advent of structural, immunological and biochemical techniques, together with the extensive basic information about the cell biology of glial cells and Schwann cells.