from active neurones, so buffering the extracellular space from increases in potassium, which might depolarize neurones or nerve terminals. They have also been implicated in CO_2 and H-ion regulation, in fluid transport, in the mechanism of the 'blood-brain barrier', in the inactivation or the formation of neuro-transmitters, and in the supply of energy-rich compounds (such as polymerized RNA and amino acids) to neurones. The role of astrocytes in maintaining the neuronal environment in a steady state now seems inescapable.

There is good evidence that the interfascicular oligodendrocytes are responsible for making and maintaining myelin in the CNS, though the function of the group of oligodendrocytes that are arranged as perineuronal satellites remains obscure. Like the normal Schwann cell, the peripheral equivalent that produces the peripheral-nerve myelin, the normal oligodendrocyte shows no propensity for division.

As for the microglia, these cells act as phagocytes in pathological states, though there is little indication that they have a function in the normal brain; because of the absence of regional lymph nodes and lymphatics from the CNS, microglia may turn out to have an as yet undefined immunological role, distinct from conventional phagocytosis.

It is clear that the interstitial cells participate in a wide range of normal activities and it is, in particular, the effect of disease on these normal activities that will be considered. Just as there are indications of intercellular regulatory and feedback systems between normal neurones and normal interstitial cells, so also there is an interrelationship between their normal and pathological reactions: knowledge of the normal can be amplified by study of the abnormal and vice versa.

Dr P D Lewis
(Royal Postgraduate Medical School, London W12)

Glial Reactions to Cerebral Injury

In recent years, research interest has centred on the cell kinetics of the reactive supporting elements in damaged nervous tissue rather than on those events – removal of myelin and other cellular debris, vascular proliferation and fibrous gliosis – which produce the healed, end-stage lesion. To a certain extent, these pathological cell kinetics can be related to normal cytogenesis, and a review of current ideas of cellular reactions to brain damage should consider the biology of the major glial cell types.

Microglia – part of the mesodermal 'third element' of Cajal – were separated from oligodendroglia by del Rio Hortega, who worked out their origin and distribution within the brain using metallic impregnation techniques. Hortega believed that they arose at the end of fetal life from blood-borne 'lymphocytoid' cells whose staining characteristics changed on entry into the central nervous system. Entry occurred predominantly through the choroid plexuses and basal leptomeninges.

Autoradiographic and electron microscope evidence suggests that a number of cells continue to follow this pathway in adult life. Thus, after injecting labelled marrow cells from one closely inbred animal into the blood stream of another, labelled microglia-like nuclei are found in the brain, sometimes beneath the cerebral meninges but more often beneath the ependymal lining of the ventricular system. Dividing cells with features of microglia are well recognized in this subependymal zone, while similar cells – some synthesizing DNA – can be seen lying on the ependyma, and both on and within the choroid plexus. In the latter site, these cells (Kolmer cells) have ultrastructural features of macrophages and appear to come from the blood.

It seems possible, therefore, that blood-borne mononuclear cells may enter the brain through the choroid plexuses, begin to synthesize DNA in their new environment, divide in or near the ventricular lining, and then migrate into the brain parenchyma. With autoradiography, it seems that a sizeable proportion of such cells leaves the brain – through blood vessels – within two weeks, though there is evidence that some remain for much longer. Though circulating monocytes are normally nonproliferative, whether or not they synthesize DNA is determined by their environment, and a possible counterpart to this system is found in the lung.

The reactions of microglia have been well studied both in response to the chemical change occurring in motor neurones after nerve transection and after the production of gross traumatic lesions. Changes in cell populations seen under these conditions can be related to physiological events, for control data from these experiments suggest that dividing – or DNA synthesizing – microglia are present in the normal adult brain and are renewed, persisting for a period of weeks. After production of a lesion, various observations indicate entry of monocytes from the blood in the first three days, as well as increased proliferation of *in situ* elements, and the number of reactive cells falls in the ensuing two to three weeks.

The reactions of other cell types can be considered briefly. Oligodendrocytes do not synthe-

size genetic DNA under normal conditions, have only a limited capacity for repair, and may in fact lose their differentiation when made to react. In contrast, astrocytes – small numbers of which may possibly be replenished in young animals from the subependymal layer – respond to adequate trauma by mitosis. The time relations of this process have been well worked out, maximal division occurring after two to three days, but the factors which induce mitosis in astrocytes are still obscure.

Dr E L Jones
(*Department of Pathology, Medical School, Birmingham B15 2TJ*)

The Interstitial Cell Reactions to Nitrosamide Carcinogens

Though it has long been possible to induce experimental brain tumours in animals using topical application or indirect implantation of carcinogenic polycyclic hydrocarbons, tumours of the central and peripheral nervous system can now be obtained much more readily by the systemic administration of carcinogenic nitroso compounds. There are two classes of these compounds, nitrosamines and nitrosamides, and their discovery and experimental use in brain-tumour research was reviewed. Transplacental or neonatal application of nitroso compounds fulfils the requirements of an ideal experimental model, preferentially inducing a high incidence of neural tumours, following a single dose and through natural pathways. Furthermore, the tumours obtained have structural similarities with human neural tumours.

Experiments on newborn rats, using the acyl-alkyl nitrosamide N-ethyl-N-nitrosourea (ENU) were described, including the incidence, location, structure and histogenesis of tumours that resulted from a single neonatal injection of ENU. Our experiments yielded a high proportion of intrinsic neuroglial tumours including periventricular sub-ependymal-plate gliomas, oligodendrocytomas, astrocytomas and mixed gliomas; schwannomas and neuroblastomas of the cranial- and spinal-nerve ganglia were also obtained.

Hitherto, the mouse nervous system has appeared to be resistant to nitrosamide carcinogens. Neonatal exposure to ENU in four strains of mice resulted in a small number of neural tumours comprising cerebellar medulloblastomas and peripheral schwannomas.

The demonstration in experimental animals of the increased sensitivity of the immature nervous system to minute doses of carcinogen following a single transplacental or neonatal exposure, raises the real possibility that some spontaneous human neural tumours may also be attributable to the action of environmental carcinogens in fetal or early post-natal life.

Dr José Ochoa
(*Institute of Neurology, National Hospital, Queen Square, London WC1N 3BG*)

Schwann Cell and Myelin Changes Caused by Some Toxic Agents and Trauma

Several areas of obscurity and contradiction emerge from reviewing the literature on Schwann cell behaviour following axonal interruption and axonal neuropathies. Questions which await final settlement are, for example: What activates myelinolytic enzymes? What triggers Schwann cell division? Can satellite cells metabolically support diseased axons? To what extent do Schwann cells participate in destruction of axon and myelin? Can these cells transform into wandering phagocytes? Can connective tissue cells really transform into Schwann cells? Do Schwann cells pour organelles into the axon – or the reverse, do they help remove abnormal (axonal) organelles in axonal disorders? Future research in these directions should be profitable.

A simple sequence of Schwann cell and myelin changes which has interested us recently and which, so far as we know, has not been explicitly defined in the past, occurs in association with some axonal disorders of the dying-back type. Such reactions are similar in character to those seen in wallerian degeneration. The sequence is not easy to observe because, by definition, in dying-back neuropathies such changes do not occur simultaneously along the fibre and all fibres are not necessarily affected to an equal extent at a time. Therefore, the study of conventional sections from samples of tissues tends to blur orderly events taking place in individual fibres. Suitably prepared single myelinated fibres (Spencer & Thomas 1970, Dyck & Lais 1970, Ochoa 1972) serve the purpose ideally and, by virtue of the smoothly ascending course of the abnormal process, the whole time-sequence of

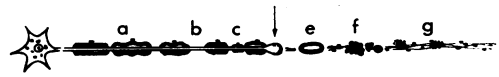

Fig 1 *A single fibre from the sciatic nerve of a rat intoxicated with acrylamide (nerve obtained by courtesy of Dr J A Morgan-Hughes). The fibre has been drawn semi-diagrammatically to illustrate the sequence of changes along its length (true length of teased specimen 16 mm)*