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Nerve Cells and Neuroglia

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Abstract
There are said to be 27,000,000,000 nerve cells in the human brain and there are about ten times as many neuroglial cells. On the whole, nerve cells are large and glial cells are small, so that their weights are about equal. The cytology of nerve cells does not provide any really startling information. There is a nucleus and a nucleolus complete with sex chromatin, and in the cytoplasm there is Nissl substance formed of RNA and endoplasmic reticulum, mitochondria carrying respiratory enzymes, and lipochromes. Fairly certainly the RNA is concerned with the synthesis of proteins which move out along the axon, and the rate of protein synthesis is increased during axon regeneration. The rate of oxygen uptake is very high, and weight for weight is said to be higher than that in any other cell. Its measurement presents great difficulties, as oxygen uptake of nervous tissue in vivo gives values 5 to 100 times those obtained in vitro. The metabolic activity of nerve cells is believed to increase about five times during and after nervous activity. At the same time, the amounts of cytochrome oxidase and RNA present increase, and there is an increased ammonia production suggesting proteolysis. Excessive activity is said to cause a decrease in cytoplasmic protein and a decrease in RNA. There is a vast literature on cytological changes in cells in overaction, exhaustion and after deprivation of sleep, but there cannot be said to be a coherent body of observed facts, let alone a satisfactory biochemical interpretation of the facts.

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NERVE CELLS AND NEUROGLIA

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There are said to be 27,000,000,000 nerve cells in the human brain and there are about ten times as many neuroglial cells. On the whole, nerve cells are large and glial cells are small, so that their weights are about equal. The cytology of nerve cells does not provide any really startling information. There is a nucleus and a nucleolus complete with sex chromatin, and in the cytoplasm there is Nissl substance formed of RNA and endoplasmic reticulum, mitochondria carrying respiratory enzymes, and lipochromes. Fairly certainly the RNA is concerned with the synthesis of proteins which move out along the axon, and the rate of protein synthesis is increased during axon regeneration. The rate of oxygen uptake is very high, and weight for weight is said to be higher than that in any other cell. Its measurement presents great difficulties, as oxygen uptake of nervous tissue *in vivo* gives values 5 to 100 times those obtained in vitro. The metabolic activity of nerve cells is believed to increase about five times during and after nervous activity. At the same time, the amounts of cytochrome oxidase and RNA present increase, and there is an increased ammonia production suggesting proteolysis. Excessive activity is said to cause a decrease in cytoplasmic protein and a decrease in RNA. There is a vast literature on cytological changes in cells in overaction, exhaustion and after deprivation of sleep, but there cannot be said to be a coherent body of observed facts, let alone a satisfactory biochemical interpretation of the facts.

When we turn to the glial cells, we find they are divided into macroglial and microglial. The microglia are made up of astrocytes and oligodendroglia, and these cells may have a common origin. Astrocytes are large star-shaped cells with one or more processes which have end-feet closely applied to a capillary. The processes form fibres which provide mechanical support and perhaps exert tension. The oligodendroglia have fewer dendritic processes and are found especially in white matter where they seem, according to Peters of the Department of Anatomy in this University to be responsible for the myelin sheath, just as Schwann cells provide the myelin sheath of axons in the peripheral nervous system.

The microglia are phagocytic cells. They have been alleged to be mesodermal in origin, though others say they arise from the edge of the neural crest. Certainly they invade the foetal brain at a later stage than the macroglia. They pick up blood cells and lipoid material from disintegrating myelin and remove them from the site of a cerebral haemorrhage.

The glial cells have been studied in tissue culture, in which oligodendroglial cells can be seen contracting and relaxing in a cycle lasting 1-2 minutes. Whether this has any bearing on their function in the brain is not known. Astrocytes forming fibres can also be seen clearly in tissue culture. Pinocytosis, the ingestion of droplets of fluid at the free ends of dendrites, can also be seen in tissue culture.

The most startling fact about glial cells has been produced in the last few years by the electron microscopists, particularly Wyckoff & Young (1956) working on the brain, and recently by others on the retina. This is that in the brain there seem to be no cell spaces, that nerve cells are closely surrounded by glial cells everywhere except at synaptic junctions, where the cell membranes of two nerve cells are thickened or electron-dense, separated by about 200 Angstrom Units, and with an abundance of vesicles in the adjacent cytoplasm of one of the nerve cells. Exactly similar statements are made for the retina, which is, of course, embryologically of the same origin as brain. This is disconcerting to the neurophysiologist who is used to extracellular currents, which in peripheral nerve undoubtedly do flow in extracellular fluid and are responsible for part of the local current flow produced by the nerve impulse. The impedance of the cell wall of glial cells is not known, but it looks as if local circuits set up by impulses in nerve cells have to flow through glial cells.

The other implication of the denial of an extracellular space by electron microscopists is that the nerve cells must have glial cells as intermediaries in the supply of metabolic requirements from the blood stream and in the removal of waste products. This seems inescapable, and though diffusion would presumably slow up the carriage of glucose, etc., the existence of end-feet on the capillary would be satisfactorily accounted for. There are a few odd observations on the metabolism of glial cells, including the statement that their O_2 uptake decreases during cerebral activity.

The absence of an extracellular space in the brain would fit in well with the old observation of Ehrlich that trypan blue in the blood stream passes into the substances of all organs except the brain. This has led to the idea of a 'blood brain barrier' which excludes dyes, sodium thiocyanate and many other substances. The **behaviour** of substances which move slowly into the brain, and these include water labelled with deuterium, suggests that they undergo active transport probably across a cell membrane. It is an attractive suggestion that the cell membranes concerned are those of glial cells.

This view has been criticised on the ground that the tissues prepared for electron microscopy have been fixed and may have shrunk, at the expense of extracellular fluid only. Though this is just possible, it is true that frank shrinkage normally greatly increases extracellular spaces by removing intracellular water as well. If there is an extracellular space, some explanation of the failure of small and diffusible molecules to enter it must be provided, and so far there is no other plausible explanation. Various crude theories have been put forward in the past to suggest, as did Cajal, that swelling of neuroglia might produce sleep by forcing apart nerve cells and interrupting synaptic transmission. There is no evidence for this view, and the fact that glial processes do not intervene in the close proximity of synapses makes it unlikely. There is, however, one condition of cerebral disturbance which is very likely to be due to separation of synaptic surfaces, with or without separation of glial cells from nerve cells and consequent interruption of the metabolic supply lines. This is concussion.

It was shown during the 1939-45 war by Denny-Brown & Russell (1941) that blows delivered to the vertex of the fixed head were much less effective in producing concussion than blows to the occiput with the head free to move. This means that an acceleration is much more effective than compression. The mechanism was worked out later in the war by A. H. S. Holbourn (1943, 1945), who was an Edinburgh physicist attached to Sir Hugh Cairns and working in the Physiology Laboratory at Oxford. He made a model cross section of the brain using gelatin 'ripened' to make it stick adequately to an enclosing rigid layer representing the skull. This model could be made to oscillate about its centre, and polarised light was shone through it. This produced interference phenomena at the points of greatest stress. This is the photoelastic technique by which stresses in bridges, for example, can be predicted by loading models made of perspex. He found that rotatory acceleration produced some shearing stress all round the circumference, just as a tap to the handle of a cup will make the cup move, but the inertia of the coffee will make the bulk of it stay behind, with some shearing between layers of fluid near to the wall of the cup. However, at points where the 'bone' model projected into the gelatin, as the sphenoidal ridge does in a parasagittal section, there was severe stress.

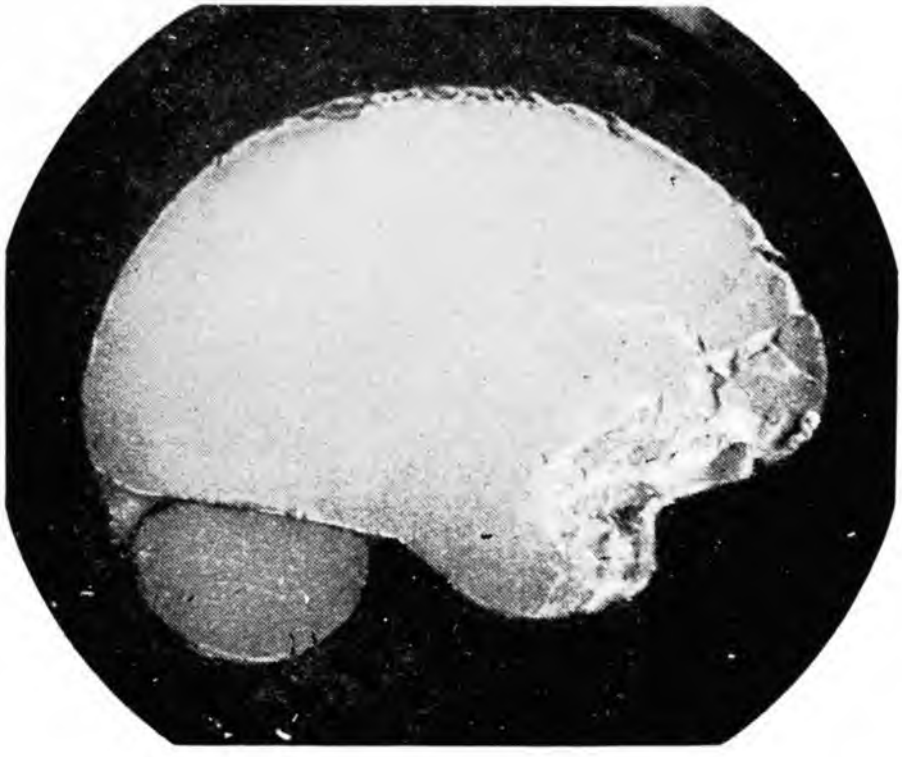

Fig 1.—Effect on a jelly of violent rotational jerking in its own plane.
(Holbourn, A.H.S. (1943). Lancet, 2, 438.)

When Holbourn compared his predictions of the sites of cortical damage with an actual brain of a head injury from a street accident, the fit was complete with the exception that theory predicted symmetrical lesions in both hemispheres, whereas the lesions were more marked in one hemisphere than the other. Subsequently the calvarium in a monkey was replaced by a perspex cap by Pudenz & Sheldon (1948) and the shearing movements of the brain relative to the skull were directly recorded by cine-photography. The gyri were

seen to move several mms relative to the skull during rotation. A blow on the back of the head may accelerate the brain sufficiently to cause severe damage around the temporal pole and the undersurface of the frontal lobe, and this used to be ascribed to contre-coup. Contre-coup injury is, in fact, a figment of the imagination. Naturally, deliberate attempts to produce a rotational acceleration of the skull, as in a blow on the jaw, will readily produce concussion. The ease with which brain damage can be produced in this way does suggest that the only sport in which head injury is deliberately produced, namely boxing, should be suppressed.

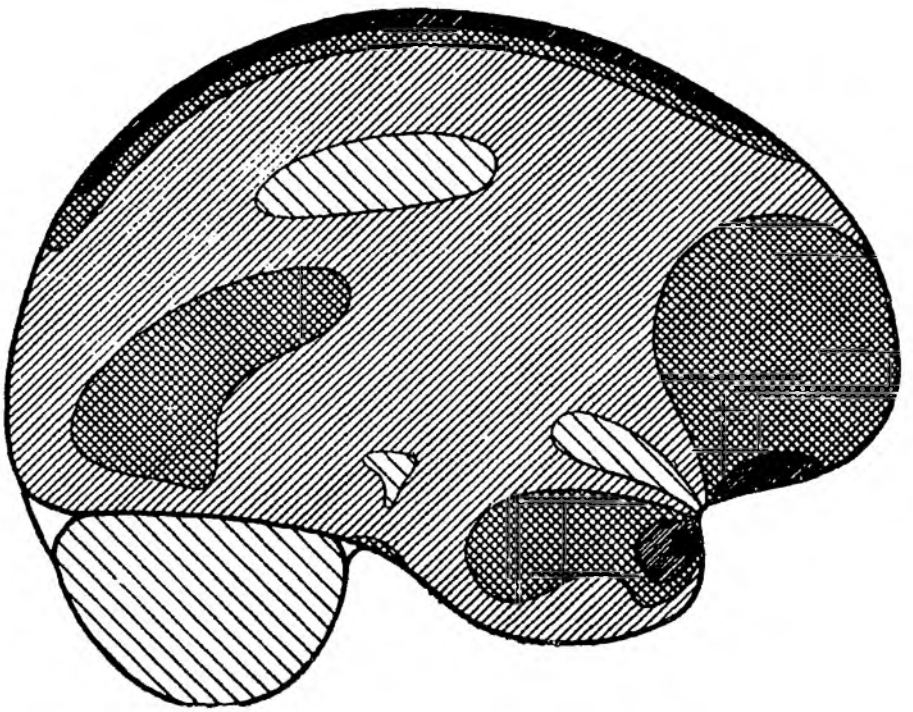

Fig. 2.—The shear-strains (=distortion) which arise when a gelatine model is rotated. The darker the shading, the greater the distortion. Note the comparative absence of distortion in the lateral cerebellar lobe and the high distortion at the tip of the temporal lobe.

(Holbourn, A.H.S. (1945). Brit. med. Bull., 3, 147.)

Recently some careful studies by S. Strich (1956, 1961) of the degeneration found in the white matter in patients who have survived for long periods in coma after severe head injuries have fully confirmed Holbourn's views on the sites of greatest damage in the brain. The whole question of these head injuries has been reviewed by Sir Charles Symonds, who has accepted Holbourn's views on its mechanism and Strich's evidence of its consequences.

The fact that paralysis of nervous activity is immediate, suggests shearing damage to synapses, but the death of nerve cells or their very slow recovery does suggest damage to their metabolic pathways.

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