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SOME RECENT TRENDS IN NEUROPATHOLOGY

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IN his presidential address to the first International Congress of Neuropathology in Rome, Gozzano (1952) raised the question of the future of neuropathology. In his opinion neuropathology was a relatively young branch of pathology and had started with the discoveries of Golgi, Cajal, Weigert and Nissl. Golgi invented "la reazione nera" in 1873; it was applied to the nervous system only a decade later. The first Weigert preparations for myelin were demonstrated in 1884 (Wallenberg, 1925). Nissl, inspired by Weigert's success with aniline dyes in nerve fibres, introduced his method for nerve cells in 1885, using first magenta red, later methylene blue and finally toluidine blue. Cajal made his first scientific appearance in 1889, at a meeting of the German Society of Anatomists.

Neuropathology had its heyday at about 1900 and in the first two decades of this century, which had witnessed first the conquest of the cerebral cortex, and then of the basal ganglia and the grey matter round the third ventricle. Since then the flow has become broader, but also appreciably slower. It is true that more recently much important work has been carried out in the field of vascular pathology, anoxia and oedema, encephalitis, allergy, nutritional deficiencies, tumour, and—especially—comparative neuroanatomy and neuropathology—to mention only a few. It is equally true, however, that there have been relatively few spectacular advances in the last twenty years, a period in which profound advances have been made in the other basic sciences such as biochemistry, biophysics, physiology and endocrinology. More and more, neuropathologists have concerned themselves with the filling of gaps or with disputation over lesser diagnostic detail. As Gozzano puts it, the "disquieting" question thus presents itself, whether the period of neurohistology is coming to a close and is being superseded by neurochemistry and neurophysiology. Perhaps this problem has nowhere arisen with greater urgency than in the pathology of mental disease, since the majority of psychoses, the schizophrenias, manic-depressive insanity, many symptomatic psychoses and the higher grades of mental defect are still left without a generally accepted somatic substrate.

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Development of Morphological Research on the Brain

One might question Gozzano's assessment of the age of neuropathology. Korn (1903), in the only *History of Neuropathology* known to the present writer, dates the effective beginning of neuropathology in the early decades of the 19th century when substantial neurohistological discoveries were made. However, concrete and important *macroscopic* observations had been reported much earlier, for example, by Wepfer (1658) who seems to have been the first to describe haemorrhage in the brain of apoplectics; by Willis (1672) who connected motor paralysis with lesions in the region of the corpus striatum; furthermore, by Bonetus (1679, 1700) and Morgagni (1761), to mention only a few. In the psychiatric monographs of the second half of the 18th century, post-mortem findings in mental patients were frequently mentioned; we owe systematic contributions especially to Greding (1781, 1790), Haslam (1798), Crowther (1811) and Andrew Marshal (1815). A fuller account of these early developments will be found in the present writer's Maudsley lecture (Meyer, 1960).

Microscopes began to be developed early in the 17th century. By the time of the publication of Willis's important books, there had already arrived what Singer (1950) has called the "classical microscopists": two Englishmen (Hooke and Grew), two Dutchmen (van Leeuwenhoek and Swammerdam) and the Italian Malpighi. Much of their work was published in English by the Royal Society. Malpighi demonstrated the capillary system in the frog's lung; Grew investigated the sexual organs in plants. To Leeuwenhoek goes the merit of having discovered the blood corpuscles and their nuclei; Hooke described the constituent microscopic structures of cork, the walls of which he referred to as "cells", and Swammerdam's *biblia naturae* is, according to Singer, "the finest collection of microscopical observations ever produced by a single worker". There is no adequate explanation why these fine early achievements were not followed up in the next century and, in particular, why, during this period, there was little or no successful work on nervous tissue. It may be that there was so much to be discovered about plants and unicellular organisms that there was little inclination to think of anything more specialized. Robert Hooke writes in his *Micrographia* that the microscope makes some men "excell others in their observations and deductions almost as much as they do the beasts"; the complexity of living things thus revealed was as disturbing in its novelty as the astronomical world of Galileo and Kepler. I quote this from Singer, who also points out that the "classical" microscopists were all rather peculiar and withdrawn people of poor general health and—some—also of poor mental health. They had no pupils who could have passed on and spread their discoveries. Moreover there was a widespread belief (first expressed by Malpighi (1669), but still conspicuous in the writings of Boerhaave (1708) and others in the 18th century) that nervous action consists of the propulsion of a subtle fluid which was not accessible to microscopic investigation. Although alcohol had previously been used for the preservation of biological specimens, Reil (1809) seems to have been the first to suggest its application to nervous tissue (Papez, 1953).*

One or all of these reasons may have been responsible for the retardation of

* Chromic acid salts were not introduced before 1844 by Hannover and formalin much later by Blum (1893). Embedding in paraffin was introduced by Klebs in 1869, and was supplemented by collodion (Duval, 1879) and celloidin (Schiefferdecker, 1882). Stilling (1842) devised a primitive microtome for serial sectioning by hand and von Gudden (1875) introduced his famous microtome for sectioning the whole hemisphere. Carmine, advocated by Gerlach in 1858, remained for a long time the standard staining method (Long, 1928; Papez, 1953; and Neubuerger, 1953).

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neurohistology, but once the immense technical difficulties and mental prejudices were overcome, epoch-making discoveries followed. Pre-eminent among those who used the new compound microscope for the study of nervous tissue were Ehrenberg, Valentin, Purkinje, R. Remak, Schwann and Schleiden. They all had in common a remarkable gift for accurate and sober observations which were achieved by (compared with modern standards) primitive dissection techniques and without the use of staining methods.

Their work much overlapped which makes it often difficult to apportion priorities. However, to Ehrenberg (1836) goes the merit of having first described and illustrated nerve cells in the spinal ganglia. This is attested by Remak (1838), Schwann (1839), Waldeyer (1891), von Töply (1903), as well as by Spatz (1929). In 1838 Purkinje was already able to publish a brief account of results, which included what Bartelmez (1953) called the first adequate description of nerve fibres and nerve cells in the brain with their dendrites, among them the flask-like "Purkinje cells". In the same year, Remak showed his familiarity with the "Ganglienkugeln" and their nuclei and nucleoli. Before Schwann, he had already demonstrated (1836, 1837a) myelinated and unmyelinated (primitive) nerve fibres, acknowledging the part played by his teacher Ehrenberg in these discoveries. Schwann soon (1839) confirmed and amplified Remak's findings concerning the myelin sheath and, in addition, clearly described and illustrated the neurilemmal sheath containing the nucleated cells which bear his name.

Among other early and penetrating observations, we find Remak's (1837b) description of fibre plexus ("darmförmige Schlingen") around nerve cells; although he failed to demonstrate the actual endings on the nerve cell, he was fully aware of the significance of this intimate spatial relationship. He also saw (1837c) a bundle, arising from one aspect of the nerve cell, which he thought to be composed of primitive fibres. Later (1844) he observed delicate primitive fibres running through the substance of the "Ganglienkugel" to join this bundle; possibly the first mention of neurofibrils, although accurate observation of these structures was only achieved later by M. Schultze (*vide* Spatz, 1929). In the same paper, Remak gives a diagrammatic illustration of the cerebral cortex distinguishing—like Baillarger four years earlier—six layers of which the outermost is white and the remainder alternately grey and white.

The neuroglia was described—somewhat later—by Virchow. In 1854, this author mentioned, in passing, "a soft mass, belonging to the category of mesodermal tissue which penetrates and sustains the nervous elements, the ependyma being its surface part" (present author's translation). Two years later (1856) Virchow gave a fuller and surprisingly accurate description of this "Kitt" (neuroglia) which consists of nuclei embedded in cells with soft and frail cytoplasm, forming, in pathological conditions, the fat-laden compound granular cells ("Körnchenkugeln") and a dense fibrous band beneath the ventricular (and cortical) surfaces.

Notwithstanding these early triumphs, the relationship between nerve cells and nerve fibres remained obscure and was the object of intense research. The neurone theory received its definitive formulation only about 50 years later by Waldeyer (1891) who coined the term "neurone". It is interesting to note in his historical review that, as early as the 1840's, Remak (as already mentioned), von Köllicker and others came very near the truth. Deiters, in 1865, clearly demonstrated the origin of nerve fibres from anterior nerve cells. The final dénouement was initiated by the introduction of Golgi's method, which played an important part in Cajal's early contributions to the problem between 1889 and

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1891, and by the work of Forel (1887) and His (1887). The theory was not generally accepted in the first decades of the 20th century, Cajal being its most important protagonist, while Nissl (1903), among others (including Golgi himself), remained unconvinced.

The striking developments in neurohistology had their counterpart in the field of pathology. Gross lesions such as haemorrhage, meningitis, abscess, tuberculoma and tumours had been known for a long time. One of the early achievements of the 19th century was the clinico-pathological concept of general paralysis. The clinical picture of this disease had been outlined by Haslam in 1798 (his Case 15), but the merit for establishing the condition on a firmer basis of clinico-pathological experience goes to Bayle (1822, 1826), Calmeil (1826) and other disciples of Esquirol. A macroscopic description of tabetic degeneration was given with surprising accuracy by Romberg in 1851. The atrophy of the brain in demented senile persons also attracted early attention (e.g. that of Calmeil), and McMenemey (1958) quotes the careful post-mortem observations made by Webster in the mid-19th century on cases of dementia developing in middle and old age. In Andrew Marshal's book (1815) (as previously in the writings of Willis (1672), Harper (1789) and Crichton (1798)), we find frequent references—in cases of mania—to patchy ossification of arteries, undoubtedly including arteriosclerotic disease. As McMenemey points out, work on arteriosclerosis was stimulated later by Virchow and his school and in the closing decades of the 19th century also attracted the systematic attention of neuropathologists.

In 1835, Cruveilhier gave his classical macroscopic description of disseminated sclerosis, repeated by Carswell (1838),* but elaborated with the help of the microscope only later by Charcot (1868). The latter and his associates were also responsible for the first clinico-anatomical description of amyotrophic lateral sclerosis (Charcot 1865, Charcot and Joffroy, 1869).

Other important investigations of Charcot and his collaborators included the histopathology of tabes dorsalis and of miliary cerebral aneurysms, and the first description of anterior horn atrophy in infantile paralysis (de Morsier, 1953; Guillain, 1955).

Here should also be mentioned the microscopic investigations on secondary degeneration undertaken by Waller in 1850, a problem to which Türck (1849-1853) also made important contributions; furthermore, the investigations on system degeneration carried out clinically (in the 1850's and 1860's) by Duchenne and, pathologically, by N. Friedreich (1863).

After the eclipse of the phrenological schools, Flourens (1824, 1842) dominated the scene with his view of the equi-potentiality of function within the cerebral cortex. Against this background arose the series of important discoveries of specific localization, beginning with Broca's discovery (1861) of expressive speech disturbed by lesions of the posterior third frontal convolution†, followed by that of "word deafness" (Bastian 1869), of sensory aphasia (Wernicke, 1874), of the motor cortex (Fritsch and Hitzig, 1870, Ferrier, 1874), of focal epilepsy (Jackson, from 1864 onward); temporal lobe epilepsy (Jackson, 1888), visual

* One finds in Carswell's book (his chapter on atrophy) also what is probably the first anatomical description of the lesions of general paralysis in English, but with no indication whether this was his independent observation or taken over from French findings. De Morsier mentions that Carswell had previously been in Paris where he might possibly have seen both Cruveilhier's and Bayle's findings.

† Broca was indirectly influenced by the teaching of Gall whose pre-eminence in the early development of regional localization in the brain has been re-emphasized recently by Grünthal and Strauss (1949), Jefferson (1953) and Ackerknecht (1958).

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cortex (Nothnagel, 1879, Henschen, 1893), the frontal lobe syndrome (Harlow, 1848, Ferrier, 1878, Welt, 1887), the importance of the temporo-parieto-occipital association areas for mental life, based on myelogenetic studies which Flechsig (1876) undertook from 1872 onwards—to mention only some landmarks in a brilliant sequence which still continues with undiminished élan in our own day. Although some of the work was experimental, most discoveries were made in clinico-pathological observations of patients. They were true neuro-pathological contributions, though in the early days achieved without the aid of the microscope.

The Present Phase of Neuropathology

I have dwelt on the earlier phases of development at some length in order to show that the idea of structural integrity of the central nervous system as a pre-requisite of mental and nervous function is an old one. The concept had developed during the 17th and 18th centuries, slowly, with many interruptions and still tainted with ancient "animistic" beliefs. The pace quickened with the beginning of the 19th century, and before and soon after the mid-century many—for that time epoch-making—discoveries were made in normal and morbid anatomy. The era which opened in the closing decades of the century was certainly not a "young" branch of pathology; rather would one liken it to the gathering of the harvest and consider it the autumn of a predominantly morphological approach. There were several reasons why this new phase began at about this time: in the first place enough of the factual foundations had been laid for new men of genius, Golgi, Cajal, Nissl, Weigert and Edinger to build upon. But the more important cause was probably that physical and chemical advances had by that time reached a stage favourable for the development of more adequate techniques and for more refined interpretation of pathological lesions. It is no coincidence that the modern microscope was born in 1878 when the Zeiss firm in Jena began to construct models designed by E. Abbé, who ten years later, became the director of the firm and introduced the new sub-stage condenser which bears his name and which had great influence on the spread of microscopic research (Singer, 1950). With von Gudden began a new era in the development of microtomes and, although Nissl in his earlier years is reputed to have cut his sections by hand with a razor, the appearance on the market of precision instruments greatly facilitated histological accuracy. Even more important was the introduction of metallic impregnation by Golgi and Cajal and of aniline dyes by Nissl and Weigert. Of Weigert Alzheimer used to say that it was this master who created all the tools for neurohistology (Neubuerger, 1953). Although most of these staining methods aimed at making structure visible and, for this reason, were not strictly speaking histochemical, nevertheless they were bound to reveal chemical and physical properties of the components of nervous tissue and were, in a broad sense, the forerunners of modern histochemistry. They probably represent all that chemistry of the brain at that time had to offer for the investigation of nervous tissue. Histochemical thought, as Einarson (1957) reminds us, can be detected in the investigations of Nissl bodies, which were classed by Held as nucleoproteins as early as 1895.

The enormous strides of biophysics and biochemistry during the last fifty years are likely to influence the future development of the histopathology of the nervous system even more profoundly than at the turn of the century.

Neuropathologists, with few exceptions, have been slow to take cognizance of the changing situation; much slower, in fact, than neuroanatomists, who—

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in English-speaking countries, at least—have widely adopted neurophysiological and also, to a lesser degree, biochemical methods of research. The tradition that neuropathology is mainly concerned with rendering structural elements visible by "staining" has been strong and it was often forgotten that pathology is useful to the clinician only when it explains clinical symptoms to him. Chemistry was not entirely ignored, as is exemplified by the somewhat sporadic use of histochemical methods (largely developed by workers outside the neuropathological field) and by theories, such as hysteresis (Ruzicka, 1922, von Braunmühl, 1932), tixotropie (Hallervorden, 1941) and pathoclisis (C. and O. Vogt, 1922), which did not go much beyond general applications. The consequence has been that physiological and chemical investigations have long been conducted without first-hand knowledge of the morphological data, and this has resulted, as admitted by Waelsch (1957b), in widespread and wasteful underrating of the significance of the intricate complexity of nervous tissue.* It has also led to a generation of workers using electron microscopy and other ultra-microscopic and cytochemical methods being recruited almost entirely outside the traditional neuropathological field, and it is only in the very recent past that neuropathologists have tried to make contact with these new groups.

The Changing Scene

The impact of biochemistry and biophysics is likely to transform the very fundament of neuropathology. The present writer has been greatly helped in his analysis of this process by important recent publications, which include textbooks on neurochemistry (McIlwain, 1955/59; Elliott, Page and Quastel, 1956) and Symposia of which the proceedings have been edited by Waelsch (1955, 1957a), Korey and Nurnberger (1956), Richter (1957a, 1957b) and Windle (1958).

Pope and Hess (1957) have discussed the most likely avenues of advance under the following headings:

(1) Classical microscopic histochemistry: this has, as Feigin and Wolf (1955) and Pearse (1958) pointed out, the great advantage of histological localization, but results obtained in this way are prone to artefacts and, at present, they are mainly qualitative. Nevertheless some encouraging results have been achieved in the field of enzyme-histochemistry; for instance, in specific and unspecific phosphatases (Naidoo and Pratt, 1951, 1952), cholinesterases (Koelle, 1954), dehydrogenases (Pearse). They should be appreciated, however, as a beginning only.

Perhaps, the most solid and impressive work of "classical histochemistry" has been carried out on Nissl granules. It is also work in which continuity with earlier research is particularly conspicuous. Einarson (1957) who has contributed steadily to this problem since 1932, has given an excellent survey of developments in this field. As has been already mentioned before, nucleoprotein had been suggested as the principal constituent of the Nissl bodies and nucleus before the end of the 19th century. It had also been realized, from embryological experience, that chromatin material of the nucleus is transferred through the nuclear membrane into the cytoplasm of the cell, and as early as 1899 Holmgreen reported increase of this interchange during activity. In the two decades that followed, many experimental studies were carried out to show that Nissl bodies disappeared in conditions of activity, fatigue and exhaustion

* It is interesting to learn from McIlwain (1958) that as early as 1856 Schlossberger lamented the lack of connection between histological and chemical findings.

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(Dolley, 1909, 1917; Spatz 1923 among others). However, since Nissl bodies do not show the Feulgen reaction, Bielschowsky, as late as 1935 still doubted the presence of nucleo-protein. He could not be aware, at that time, that the Feulgen test (as well as methyl green) react only with desoxyribonucleic acid (D.N.A.), while ribonucleic acid (R.N.A.) is stained by pyronin. Gallocyanin, introduced by Einarson, has proved capable of giving better quantitative information than the above stains, the $(CH_3)2$ N group of its molecule specifically uniting with nucleic acids at strong acid pH. Information, thus obtained, has been confirmed by ultraviolet microspectroscopy as well as X-ray microradiography (Brattgard and Hydén, 1952). Bourghardt, Hydén and Nyquist (1955) have also devised a computing microphotometer for rapid quantitative analysis.

The overall results obtained with gallocyanin and the ultramicroscopic methods of the Swedish school have been formulated by Einarson as follows: Chromo-neutrality of the Nissl bodies indicates rest or indifferent activity; moderate chromophilia may point to initial activity, while extreme chromophilia indicates suppression of activity. Moderate chromophobia is the consequence of prolonged increased activity; in extreme degree, it expresses severe stress and exhaustion. Extreme chromophobia proceeds to liquefaction of the nerve cell, whereas the outcome of extreme chromophilia is sclerosis and atrophy of the cell. R.N.A. itself which plays an important part in the synthesis of proteins is synthesized in the nucleus—under control of D.N.A. In contrast, the nucleolus is almost entirely composed of R.N.A.

(2) *Ultramicroscopes*. Ultraviolet histospectroscopy and X-ray absorption histospectroscopy, as developed by Casperson and Hydén and their associates, has already been discussed in relation to nucleic acids. Their scope is, however, more comprehensive and they may be used for estimation of total solids, lipids and proteins other than nucleotides (Hydén, 1955). Lipochrome pigment has been extensively studied by these techniques and has been found to contain characteristic compounds of the pterin group in addition to neutral fats, chiefly cholesterols. It is also demonstrable with the periodic acid (Schiff) reaction, indicating the presence of polysaccharides. Its increase with advancing age and certain degenerative conditions is related to a corresponding decrease of cytoplasmic R.N.A. (Einarson).

Potentially, the investigations which have been undertaken in the recent past with the *electron microscope* are of profound significance (Palay and Palade, 1955; Palay, 1956; Fernandez-Moran, 1957). Electron microscopists have also devoted much attention to the Nissl bodies which Palay calls "the most impressive single architectural unit in the perikaryon". On the electronic screen it has a reticular appearance; the delicate tubules of this "endoplasmic reticulum" are lined by "Palade" granules containing proteins chiefly compounded of R.N.A. and which are the main source of basophilia. The granules are said to resemble the ergastoplasm of exocrine glandular cells and seem to be a site for continuous protein synthesis.

The nucleus contains a roseate arrangement of granules which are different from the granules lining the endoplasmic reticulum of the cytoplasm; the granules of the nucleolus are exceedingly fine. The nuclear membrane appears on the screen porous, with deep folds filled with cytoplasmic components, thus confirming that close relationship with cytoplasmic components, which had been suggested by early workers.

Among other organelles, *mitochondria* have been extensively studied. They

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show, on the electron-microscopic screen, a diffuse ground substance, surrounded by a double membrane the inner lamella of which forms the characteristic "cristae", beautifully illustrated by Palay and Palade. Other workers (e.g. Belt and Pease, 1956) described "tubuli" (instead of "cristae"), but the difference seems to be one of functional degree, the "cristae" being formations at rest (Wilke, 1959). Mitochondria occur throughout the cytoplasm and extend to dendrites and axons, though, in the latter, they are less numerous. The endoplasmic reticulum also reaches into axons and dendrites.

Mitochondria seem to be particularly frequent in the vicinity of *synapses* of which three main types have been identified by the electron microscope (Fernandez-Moran). Presynaptic and postsynaptic areas are well defined by membranes and are also separated by an intersynaptic space. Thus, the neuron theory has found yet another strong support. Presynaptic terminals contain microvesicles together with numerous mitochondria. It has been suggested by Fernandez-Moran that the transfer of transmitter substances may take place through leakage into the intersynaptic space, the microvesicles constituting, as it were, small packages of one or different transmitters. Though this interesting interpretation is not yet proved, evidence may be forthcoming from electron-microscopic investigations after experimental stimulation.

The electron microscopy of *glial* cells is as yet not as detailed as that of the neuron. However, according to Palay (1958) and Hartmann (1958) all known types of glia cells can be identified and most of the older criteria of Hortega and Penfield confirmed. Apart from the shape and size of the nucleus, there are notable differences in the number of mitochondria which are consistently found in the cytoplasm of microglial cells, and are more numerous in oligodendroglia than in astrocytes (though in none of the glial varieties is the high numerical incidence in nerve cells reached). The processes of oligodendroglial cells are more delicate than those of astrocytes, but even the fibrils of the latter are not extracellular, but cytoplasmic. According to Bairati (1958), they do not contain collagen, as had been suggested by Fernandez-Moran. The processes of both astrocytes and oligodendroglia are capable of flowing movements as revealed by tissue culture. However, as Lumsden (1958) reminds us, no electron-microscopic evidence of *normal* glia is yet available.

So far, electron-microscopic research has continued mainly along morphological lines; it is now rapidly approaching a stage, however, when its results may be usefully correlated with microchemical findings and with microelectrical studies of the nerve cell (for example, those by Eccles, 1957, and his associates).

Some interesting information on the glia has been collected with the help of techniques other than electron-microscopy: tissue culture has proved to be an important instrument of investigation although all workers using this technique are aware that they are dealing with explanted tissue growing in a strange environment (Lumsden, 1958; Pope, 1958). It has, however, been possible to observe different stages of maturation. Canti, Bland and Russell (1937) were the first to observe (in vitro) mitoses in astrocytes. Oligodendroglial cells show rhythmic contraction in cycles of 5 minutes (Pomerat, 1958) which Glees (1958) interprets as indicating participation in synaptic activity (also, perhaps, suggested by the demonstration in thick Golgi preparations of boutons terminaux ending on oligodendroglia (the Scheibels, 1958)). There is fair agreement on the relative frequency of the different varieties of glial cells. In the cerebral cortex, Pope (1958) found the number of oligodendroglia and astrocytes to be almost the same while the incidence of microglia was 6–10 per cent. In the white matter, the percentage of oligodendroglia increases to two-thirds. Elliott (1958) and his

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associates estimating cell density by means of D.N.A., found the respiratory rate to be low in all gliomas except in oligodendrogliomas which are, however, rather cellular tumours. These results are borne out by estimations of cytochrome activity which in astrocytomas is about half that of normal human white matter. It is interesting to be reminded by Pope that, as early as 1919, Marinesco failed to observe indophenol oxidase in glial cells. Cholinesterases and especially pseudocholinesterases have been brought in relation to oligodendroglia (Ord and Thompson, 1952), while carbonic anhydrase is supposed to be active in astrocytes (*vide* Pope, 1958). 5-Nucleotidase is high in white matter (Naidoo and Pratt, 1954) which also contains a larger amount of porphyrins, possibly in a zinc combination (Klüver, 1955).

It is now widely held that glial cells and particularly astrocytes which send processes to the capillaries play an important, though probably not an exclusive part in the transfer of substances from *blood to nervous parenchyma.* Wickoff and Young (1954, 1956) have stressed the intimate adhesion of astrocytic end feet to the vessel in the electron microscope, although this does not, however, prove that there is a continuous glial membrane. While Dempsey and Wislocki (1955) thought that an amorphous substance of moderate electron density filled the interspaces between capillary walls and glial cells, a more recent opinion (Dempsey and Luse, 1958; Lumsden, 1958, Pomerat, 1958 and Glees, 1958) considers the existence of a "ground substance" to be unlikely, for the simple reason that there could not be enough space for it. In favour of this ground substance Hess (1953, 1955) gave as evidence a positive Schiff reaction which seemed to develop parallel with the blood brain barrier. However, hypertrophic astrocytes also give a positive P.A.S. which is absent in young astrocytes (Lumsden, 1958; Pope, 1958).

Myelin Sheath. Striking advances have been made in this field which have led to the "wrap up" or "Swiss roll" theory of the sheath. The new interpretation may be said to have begun with the work of F. O. Schmitt and his associates (Schmitt, Bear and Clark, 1935; Schmitt, 1936; Schmitt and Bear, 1937) in polarized light and with X-ray diffraction, by which they found the myelin sheath to consist of alternate lipid-protein layers, each approximately 180Å thick and wrapped concentrically around the axon. This view was further developed by Geren and Raskind (1953), Geren (1954), Geren and Schmitt (1954) who found that at an early stage of development of chick embryo Schwann cells of the sciatic nerve envelop the axon with a double membrane contributed by the surface of axon and cell. Electron microscopy has confirmed the spiralized laminated appearance of myelin and its relation to the Schwann cell (Sjöstrand, 1953, Robertson, 1955). There is evidence that the myelin of central nerve fibres has a similar spiral appearance, but it is not yet established whether the sheath is derived from the oligodendroglia. Uzman (1958) did not find readily identifiable oligodendro-cells in the neighbourhood of areas of recent deposition of myelin, but saw only a considerable increase of mitochrondria in the axons. Regeneration and myelination of axons may take place in tissue culture without the presence of Schwann cells (Glees, 1958). Costero (1958) never found excessive myelination in oligodendrogliomas, but Pomerat (1958) claims to have obtained myelin formation from oligodendro-cells *in vitro*. This problem, therefore, awaits further clarification.

(3) *Differential centrifugation.* This method, introduced by Bensley and Hoerr (1934) is based on the differing rates of velocities with which subcellular organelles tend to sediment with centrifugation. It suffers, however, from

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serious shortcomings, particularly with brain tissue since the separation is only approximate and certain elements histologically easily identifiable (such as nuclei, nuclear membranes, Nissl bodies, processes) cannot with this method be identified. All these contribute to the microsome fraction which can be separated from the mitochondrial and (recently added) lysosome fraction. Nevertheless, the method has yielded information of great importance and relevance to the neuropathologist. Many important biological oxidations such as those concerned with the Krebs cycle, cytochrome oxidases, phosphorylation, enzymes governing glutamic acid and phosphate metabolism take place more or less exclusively in the mitochondria. According to Quastel (1957) snake venom lecithinase (when all other enzymes have been excluded by heat of 100° C.) has no effect on soluble enzymes of cytoplasm; its action is confined to mitochondrial enzymes, and thus affects respiratory systems. According to Harman (1958), the effect of various other agents such as bacterial toxins, diphtheria toxin, some vitamins and hormones is directed to the mitochondria. In the superior cervical ganglion cells, mitochondria show degeneration, revealed in the electron microscope, after severance of preganglionic fibres (Barton and Causey, 1958).

Earlier workers have maintained that the proteins of the brain are inert. That this view is incorrect, has already been shown by the work of Einarson and the Swedish school, centred on the Nissl bodies which are an important component of the microsome fraction. Microsome particulates have, as Waelsch (1957b) has pointed out, the shortest half-life-time, i.e. the highest rate of incorporation of labelled amino-acids such as methionine (*vide* also Gaitonde and Richter, 1955) and lysine.

There is yet only scanty information available on the lysosome fraction, as far as nervous tissue is concerned. As the name indicates, lysosomes are more related to breakdown processes in contrast to the other two fractions with their concentration on energy release and protein synthesis.

(4) *Quantitative analytical microchemistry*. The prototype of this approach has been the well-known techniques of Linderstrom-Lang and Holter who used alternate microtome sections (preferably of unfixed tissue) for microchemical investigation and histological localization respectively. The most remarkable recent advance has been made by Lowry (1954, 1957a, 1957b) who has been able to dissect by hand frozen-dried dorsal root nerve cells (0·01-0·03γ) or Purkinje cells (0·01-0·05γ). Samples weighing 0·005γ or less require micromanipulator. Lowry found it practical to extend the procedure down to the size of a large mitochondrium. Among his first results he has recorded differences in amount of enzymes between cell bodies on the one side, and neuropil and myelinated fibres on the other. The cell surfaces (capsules) and the fibres contain less hexokinase, malic hydrogenase, transaminase, glutamic dehydrogenase, but are relatively rich in glucose-6-phosphate. In general, there is a striking contrast between the (low) enzyme estimates of cell bodies and the appreciably higher ones of "capsules" and fibres.

These results must, however, for the time being be received with some reserve. Lowry's ingenious procedures share with other quantitative micro-analytical methods the shortcoming that the smaller the size of the dissected cells or organelles, the less certain is the anatomical localization.

Among the structures which Lowry has investigated, is the hippocampus. He chose this centre because of its relatively simple alternate lamination of predominantly cellular and fibrous layers: i.e. for a reason similar to that which induced Spielmeyer, more than 30 years ago (1927) to use the simple cortical

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architecture of Ammon's horn for his pathogenic analysis of selective vulnerability in vascular and anoxic conditions. This extensive neuropathological work, which did not remain confined to one school, was apparently not known to Lowry when he began his important studies. Nothing could better illumine the gap between traditional neuropathology and these new approaches, and the necessity for bridging it.

Conclusions

The present writer's prognosis for neuropathology is as far removed from the warnings of Cassandra as it is from complacency. It appears to him that the neuropathologist, even with his traditional techniques, will continue to be an indispensable collaborator of the clinician, whether he be neurologist, neurosurgeon or psychiatrist. His participation in the diagnosis and teaching of these disciplines will remain essential. The results of this collaboration will not be spectacular, but it will be steady work on a broad front, patiently resolving controversies, filling gaps and widening the basis of experience from anecdotal case reports to sound statistical significance. All this, however, would not be enough: neuropathology will continue to make *fundamental* contributions only in a measure as it falls into line with the basic sciences, particularly biochemistry and biophysics. This may be achieved by the neuropathologist either by acquiring additional training in the one or other basic science, according to his personal propensities, or by participation in a team. He would not enter such a team with empty hands because he has the key to a wealth of morphological data, normal and abnormal, without which the chemical or physiological approach to the nervous system would remain in a vacuum. He could become, in fact, the custodian of continuity and of a sound balance between the old and new. One cannot but agree with Waelsch that lack of this continuity (due to ignorance of each other's province) has considerably delayed progress and has been the source of misinterpretation of biochemical and physiological data. As this review of development clearly shows, this gap has been closing during the last few years, and the transformation of neuropathological thought and techniques is now in full progress.

Perhaps, to the contemporary onlooker, the present transformation appears to be more unprecedented than it actually is. The historian is able to point to earlier changes of considerable magnitude: the application of the microscope to nervous tissue in the 1830s, the substitution, from 1861 onwards, of the principle of localization for that of equipotentiality of the cerebral cortex and in the closing decades of the 19th century the introduction of precision instruments for cutting, of analytical staining methods and of greatly improved microscopes, all of which produced changes in neuropathology which, in essence and direction, are certainly comparable to those of to-day. Only the pace has immeasurably quickened and organization and communication of research has been perfected beyond expectation. It took more than 200 years from the invention of the microscope to the first major histological discoveries in the nervous system from 1830 onwards. In contrast, barely 20 years after the invention of the electron microscope in 1932, interesting and seemingly fundamental facts of nerve and glia cells, and of fibres are already extant. Electron micrographs of inorganic substances and unicellular organisms (e.g. viruses) were available at an even earlier date. The "classical" microscopists worked in isolation and for reasons which are not quite established seemed unable to disseminate the results of their work. Nowadays, particularly in the U.S.A., hardly

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a month passes in which prominent scientists from all over the world do not gather to discuss problems of ultrastructure, electron microscopy, neurochemistry, neuroglia or the neurological basis of behaviour. The results of these symposia are published in monographs which, increasingly, replace the textbooks and systems of earlier and more leisurely times. They contain both new facts and new, often speculative, generalizations, and only subsequent generations may eventually be able to disentangle the facts from all their erroneous admixtures.

Today one often hears pronouncements of the end of the morphological approach in pathology. Such predictions overlook that structure and function are inextricably interlinked, and that, as a consequence, there will always be a morphological aspect of pathology. Now that the electron microscope enables us to visualize structure of molecular or near molecular size, sweeping predictions of this kind may well be confounded by new and unexpected developments.

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