Current trends in Australian neurology

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Introduction

In a preface to Volume 4 of the *Proceedings of the Australian Association of Neurologists* (1966), Dr John A. Game, the President of this Association, remarks: 'Some responsible and otherwise not unsympathetic critics have levelled the taunt of mediocrity at Australia. A young nation, seeking to contribute to the cultural history of mankind, can not ignore these strictures'.

A. W. Campbell, who prepared the first cyto-architectonic map of the cerebral cortex (1905), and Sir Grafton Elliott Smith, who contributed so much to the knowledge of the anatomy of the nervous system, were Australians who pursued their studies in England at a time when adequate facilities were lacking in their home country. In more recent years the work of Professor Sydney Sunderland of Melbourne has covered many aspects of neuro-anatomy and achieved world recognition.

In the field of neurophysiology the genius of Sir John Eccles needs no emphasis and was rewarded by the Nobel Prize. His students are continuing his fundamental investigation into the function of the nervous system at several Australian universities.

The development of clinical neurology, however, lagged behind that of many other countries. This may be attributed to the small population scattered over a vast continent, and to the slow evolution of specialization in medicine in general. It is only during the last 25 years that physicians were able to confine themselves to neurology, and during the past 10 years that rapid progress was made.

This progress was fostered by the Australian Association of Neurologists, founded in 1951 by a small group of physicians who had brought the art of British neurology to Australia. The Association's first President, Dr Leonard Cox of Melbourne, established neuropathology in relation to clinical neurology in this country. Dr E. Graeme Robertson, the second President set the standards of clinical neurology in Australia, standards of which we are now justly proud. His work on the methods and

interpretation of pneumo-encephalography is well known throughout the world. Robertson initiated the publication of the *Proceedings of the Australian Association of Neurologists*, which have appeared annually since 1963.

There are now more than forty clinical neurologists in Australia. Almost all of them received their post-graduate education at the National Hospital for Nervous Diseases, Queen Square, London. Many of them, apart from their clinical responsibilities, are concerned also with clinical or electrophysiological research. Neurological units have been established at all major teaching hospitals throughout Australia and their various fields of interest now cover much of the broad spectrum of nervous disorders.

At the Annual Meetings of the Australian Association of Neurologists both the basic scientists and clinicians have an opportunity to present their work. It is not easy to select from a wealth of good papers those which are most representative of current trends in neurology in our country. The space available, the need for illustrations and—inevitably—personal inclinations have determined the selection of five topics which were presented at our meetings during the last 3 years. Although some of the subjects may appear to be highly specialized and somewhat esoteric, they have wider implications and point to avenues of future research, which may unravel some of the many secrets of the nervous system.

Central synaptic transmitters

Professor David R. Curtis of the Australian National University, Canberra, has for some years concerned himself with the investigation of a number of substances, which are suspected to operate as synaptic transmitters, either excitatory or inhibitory, in the central nervous system. His technique of 'micro-electrophoresis' involves the use of specially designed multi-barrelled micro-pipettes, through which minute amounts of drugs are administered just outside a selected neurone in the brain or spinal cord.

This is combined with intra- or extracellular recording of the responses of single cells (Fig. 1).

FIG. 1. Some of the types of micro-pipette used in the microelectrophoretic technique. Extracellular action potentials are recorded with the central NaCl-containing barrel of five and seven barrel micro-pipettes, the other barrels of which contain aqueous solutions of drugs to be tested. The over-all tip diameter of these pipettes ranges between 4 and 8 μm . Intracellular records are obtained from impaled neurones, using either the central barrel of a 'co-axial' electrode or the projecting electrode of a parallel pair of micro-pipettes.

Curtis has recently reviewed the results of research throughout the world as well as his own contributions to this interesting and important subject (Curtis, 1968, 1970; Curtis & Crawford, 1969).

The identification of substances present in the nervous system as transmitters at particular synapses rests on strict criteria:

- (i) they must have a post-synaptic effect identical to that of the synaptically released compound,
- (ii) they should be antagonized by substances which block synaptic transmission by a specific action at post-synaptic receptors,
- (iii) similarities may be established between the processes which remove the artificially administered transmitter suspect from the extra-neuronal space and the enzymic or other mechanisms of transmitter inactivation,
- (iv) the transmitter substance, released by impulses in the appropriate nerve fibres, may be detected in an artificial tissue space, from the surface of nervous tissue, or in the venous effluent.

Acetylcholine is one synaptic transmitter which has been shown to satisfy most of these criteria. It is generally accepted as the excitatory transmitter released from motor axon collateral terminals upon spinal Renshaw cells. These cells are readily excited by cholinomimetic substances having nicotinic properties. Both this chemical excitation and the synaptic excitation evoked by axon collateral volleys are blocked by dihydro- β -erythroidine, and are

enhanced by cholinesterase inhibitors, such as neostigmine and edrophonium. The synaptic response is diminished by hemicholinium, which limits the synthesis of acetylcholine within cholinergic pre-synaptic terminals (Fig. 2).

Although a large number of neurones in the brain, brain-stem, cerebellum and spinal cord can be either excited or depressed by electrophoretically administered acetylcholine, there is increasing evidence that the major afferent and efferent pathways in the central nervous system are not cholinergic. It is thought, however, that some of the pathways connecting reticular, thalamic, striatal and cortical neurones may depend on cholinergic transmission, although much of the required evidence is incomplete. The muscarinic nature of the receptors involved in most of these supraspinal cholinergic pathways probably accounts for the central effects of atropine and related drugs.

Catecholamines and tryptamine derivatives

Regional differences in the intra-cerebral distribution of noradrenaline (NA), dopamine (DA) and 5-hydroxytryptamine (5-HT), and their associated enzymes, suggested that these catecholamines may have significant transmitter functions. There is direct neuropharmacological proof that each of them can excite and depress many neurones, and some can be isolated from nerve terminals in brain tissue. Fluorescent histochemical techniques have demonstrated their presence within fine nerve fibres. However, apart from the reported antagonism of the 5-HT excitation of cortical neurones by LSD-25, no specific antagonists of the central effects of these substances have been discovered.

There is growing experimental and clinical evidence for the significance of dopamine in the pathogenesis of Parkinsonian akinesia. A dopaminergic pathway from the substantia nigra to the caudate nucleus was proposed (Andén *et al.*, 1964), and it was postulated that dopamine has an inhibitory synaptic transmitter function. As yet, however, no specific antagonist for dopamine has been demonstrated, and the criteria for its identification as a central synaptic transmitter have still to be satisfied.

Profound alterations in spinal reflexes, which result from systemic administration of dihydroxyphenylalanine, 5-hydroxytryptophan, and of substances which are antagonists of peripheral 5-HT and noradrenaline receptors, indicate the effect of these amines on spinal neurones, effects possibly related to their function in pathways descending from supraspinal centres. Noradrenaline depresses spinal motoneurones, interneurones and Renshaw cells, while 5-HT has both depressant and excitant actions. Confirmation of the relationship of such actions to a transmitter function for NA or 5-HT is handicapped

FIG. 2. Summary of the pharmacology of Renshaw cells. These neurones are fired monosynaptically by impulses in motoneurone axon collaterals; characteristically the firing is repetitive and prolonged. The cells can also be excited by electrophoretically administered acetylcholine and L-glutamic acid, the period of administration being indicated by the black horizontal lines beneath the records. The synaptic and acetylcholine-induced firing are both reduced by dihydro-β-erythroidine (DH-β-E) and potentiated by edrophonium, an inhibitor of choline esterase. Hemicholinium suppresses synaptic firing in the absence of an alteration of acetylcholine sensitivity. None of these substances active at acetylcholine sites affect the sensitivity of Renshaw cells to glutamic acid.

by the difficulties of stimulating the cells of origin of the descending pathways, and by the lack of specific antagonists for these agents.

Amino acids

The acidic amino acids, glutamic and aspartic acid, when administered electrophoretically, excite neurones throughout the mammalian central nervous system. As minute extracellular concentrations of these substances are effective, it is clear that changes in their distribution between intra- and extracellular phases in a localized region may suffice to produce profound alterations in nerve cell activity. No specific substances have yet been found which either antagonize or prolong the excitatory effects of these amino acids, but it is thought that they may be removed from the extra-neuronal space by rapid carrier-mediated uptake. It is probable, but not proven, that either

glutamic or aspartic acid, or both, are the excitatory transmitters of the central terminals of the major mammalian afferent and efferent pathways.

In contrast to the acidic amino acids, the neutral amino acids glycine and γ-aminobutyric acid (GABA) are central depressants. Their mechanism of action is identical to that of synaptically released inhibitory transmitters, and they appear to be involved in different inhibitory systems. Glycine depresses predominantly spinal motoneurons and interneurons, while the action of GABA is mainly in the cerebral cortex, brain-stem and cerebellum. This regional differentiation of inhibitory amino acid function is supported by the observation that strychnine and related substances, which diminish spinal inhibition, will suppress the hyperpolarization and depression of spinal neurones by glycine without affecting that produced by GABA (Fig. 3).

FIG. 3. Intracellular records obtained from a motoneurone in response to the extraneuronal electrophoretic administration of glycine. The upper trace of each pair shows the alteration in the resting membrane level, a hyperpolarization of approximately 4 mV. The administration of glycine is signalled by the deflection of the lower trace and the arrows. A: control. B: during the simultaneous administration of strychnine from another barrel of the extraneuronal micro-pipette. C: 4 min after termination of strychnine administration. Calibration: 4 mV for intracellular records. Time: 5 sec.

No antagonist of either GABA or of supraspinal synaptic inhibition has been found, nor do we have any convincing evidence for enzymic inactivation after electrophoretic administration of glycine or GABA. It is therefore probable that cellular uptake may be the mechanism of terminating the transmitter action of neutral amino acids.

This work is obviously of great importance; it is fundamental in the continuing search for therapeutically effective substances which will specifically modify the synthesis, storage, release and removal of central synaptic transmitters.

Serotonin metabolism in migraine

During the last 5 years Professor J. W. Lance and his co-workers at the Prince Henry Hospital, and the School of Medicine, the University of New South Wales, Sydney, have studied the significance of serotonin (5-hydroxytryptamine, 5-HT) in the pathogenesis of migraine (Lance, 1966).

Serotonin is synthesized in the gut, transported in blood platelets and metabolized in the liver, mainly to 5-hydroxyindole-acetic acid (5 HIAA), which is excreted in the urine. Sicuteri, Testi & Anselmi (1961) reported an increased urinary excretion of 5 HIAA during a migraine attack. This could result from an increased metabolic breakdown of serotonin, and Curran, Hinterberger & Lance (1965) demonstrated that the total plasma serotonin usually, but not invariably, drops at the onset of a migrainous headache. This fall in plasma serotonin seems to be specific for migraine, and not just a chance accompaniment, because:

- (a) intramuscular injection of 2.5 mg of reserpine produces a fall in plasma 5-HT levels and precipitates a migraine attack in susceptible subjects,
- (b) intravenous administration of 5-HT relieves both spontaneous and reserpine-induced migraine,
- (c) stressful medical procedures, such as pneumoencephalography which cause headache and vomiting of a degree comparable to migraine,

produce no change in plasma 5-HT levels (Anthony, Hinterberger & Lance, 1968).

An elegant series of experiments designed by Anthony *et al.* (1968) attempts to elucidate the mechanisms involved in the abnormal metabolism of serotonin. They confirmed a significant decrease in plasma serotonin (5-HT) content in thirty-one of thirty-three migraine attacks experienced by twenty-nine patients. As almost all of the plasma 5-HT is present in platelets, the individual (ATP, ADP and AMP) and total adenine nucleotide content of platelets was determined in nine normal subjects and compared with nine patients before, during and after a migraine headache. As no significant differences were found, adenine nucleotides do not appear to be involved in the marked fall of plasma 5-HT during migraine. Neither during an attack, nor during periods of freedom from headache, was there any impairment in the ability of platelets to take up 5-HT when incubated with an excess of this amine. Cross-incubation experiments, using platelets isolated from blood collected during headache-free intervals, suggested that during the migraine attack one or several substances are present in the plasma, which deplete platelets of their 5-HT content. When these platelets were incubated with platelet-poor plasma, prepared from blood specimens collected during a migraine attack, they lost a considerable amount of their 5-HT content. This loss did not occur when they were incubated with platelet-poor plasma obtained during a headache-free period. The identity of the substances which denude platelets of their serotonin content during a migraine headache is unknown; their action is similar to that of reserpine.

If abnormalities in the metabolism of serotonin, and perhaps of other vaso-neuro-active substances including noradrenaline and bradykinin, contribute to the production of a migraine headache, where and how do they act? Lance & Anthony (1968) postulate that the extracranial arteries of migrainous subjects may be abnormally susceptible to humoral agents. Serotonin, in general, constricts large arteries and dilates small vessels. The next step was to determine its specific action on extracranial blood vessels in man and to decide if this was a direct action on the vessel wall, or if it involved a neural reflex. As the carotid body is known to be sensitive to serotonin, nineteen patients with intractable migrainous hemi-crania were subjected to the operation of carotid glomectomy on the affected side after the experimental nature of the procedure had been clearly explained to them. No complications ensued, but the therapeutic results were disappointing. The operation, however, provided an opportunity for the study of the effect of serotonin injected into the common carotid artery. In six out of seven subjects this injection produced constriction of the extra-

cranial arteries without altering the calibre of the intracranial vessels. As this constrictor effect persisted after removal of the carotid body, it is not a neural reflex, but probably a direct action on the arterial wall. This action, however, is not specific for migraine, because similar results were observed in two non-migrainous subjects where the amine was introduced into the carotid artery during diagnostic angiography.

Lance & Anthony (1968) have formulated the hypothesis, based on these observations, that serotonin normally exerts some degree of tonic vasoconstriction on extracranial arteries. Its effect on scalp capillaries has not been documented, but is assumed to be dilation, similar to its effect on capillaries in other areas of the body. Therefore, the sudden reduction in circulating serotonin at the onset of a migraine attack will cause a relaxation of the scalp arteries, while the smaller vessels constrict and thereby increase intra-arterial pressure, thus adding to the distension of the arterial wall.

This hypothesis faces an apparent paradox in the frequently beneficial effect of methysergide, a serotonin 'antagonist' in the prophylaxis of migraine. It is postulated that this antagonism may be competitive, or that methysergide may simulate the action of serotonin on certain vessels.

While these experiments clearly demonstrate the importance of serotonin in the pathogenesis of extracranial vascular distension, they have thrown light on only one facet of the enigma of migraine, and many interesting questions await an answer. A comprehensive concept of aetiology will have to account for the participation of diverse aetiological factors (heredity, stress, diet and hormonal changes), for the many varieties of clinical presentation broadly divided into a 'classical' and a 'common' form of migraine, for the peculiarities of cluster headaches and various types of 'complicated' migraine, and particularly for the hemicranial situation of pain which may alternate in different attacks. It is not unreasonable to assume that biochemical events will provide many, though not all, the answers.

Diphenylhydantoin metabolism

During 1968 neurologists all over Australia were confronted with an unprecedented number of cases of anticonvulsant drug intoxication. Several letters appeared in the *Medical Journal of Australia*, and it soon became clear that ataxia, nystagmus, diplopia, slurred speech and drowsiness were the characteristic clinical manifestations, and that phenytoin sodium ('Dilantin', 'Epanutin') was the offending drug.

Tyrer, Eadie & Sutherland (1970) of the Medical Professorial Unit of Queensland University, Royal Brisbane Hospital, Brisbane, studied forty-seven of these patients between April and November 1968; only six of these had increased their anticonvulsant

dose within 4 weeks of the onset of symptoms. As all had taken the same brand of phenytoin sodium capsule, 100 mg, it was suspected that some batches of these capsules containing an excessive amount of the active drug might have been marketed in error. An assay of several capsules taken by different patients during the time when they developed symptoms of intoxication showed, however, that their phenytoin content ranged between 93 and 98 mg per capsule.

The therapeutic range of blood phenytoin concentration is from 10 to 20 $\mu\text{g/ml}$. Toxic manifestations usually begin to appear at blood concentrations above 20 $\mu\text{g/ml}$. Tyrer, Eadie & Sutherland (1970) measured blood phenytoin levels in thirty-five of their forty-seven patients and found them in the toxic range (above 20 $\mu\text{g/ml}$) in thirty (86%); in four cases the blood level exceeded 40 $\mu\text{g/ml}$. What then accounted for the rise in blood concentration to toxic levels while patients were taking standard doses of an anticonvulsant drug which had been widely used for over three decades? Enquiry from the manufacturers of 'Dilantin' capsules revealed that calcium sulphate had been used as an excipient until November 1967. After that date they were made up with lactose instead of calcium sulphate. Could these toxic blood levels be attributed to the change in the 'inert' excipient? The next step was a comparison of blood phenytoin concentration and faecal phenytoin excretion in a patient taking the same dose of 'Dilantin' capsules made up with the lactose excipient, or with the calcium sulphate excipient. Within a few days of changing to the capsules containing calcium sulphate, a marked drop in the blood phenytoin level to about 25% of its previous value occurred, and this was not accompanied by any increased faecal excretion. The different excipient, therefore, did not appear to alter absorption (Fig. 4).

In thirty-five out of thirty-nine patients the dose of 'Dilantin' capsules with the lactose excipient had to be reduced by from 25 to over 50% of the dose of the calcium-sulphate-containing capsules to avoid toxic changes, while maintaining seizure control. This provides further indirect evidence for the highly significant effect of the excipient on phenytoin metabolism. Unfortunately we have no data on blood phenytoin concentrations in patients who took the lactose-containing 'Dilantin' capsules without developing signs of toxicity. The simultaneous occurrence of many cases throughout Australia makes it unlikely that some personal idiosyncrasy or enzymic defect in the metabolism of phenytoin with the lactose excipient had caused this toxicity.

These observations have clearly shown that the excipient in phenytoin preparations is by no means 'inert', a discovery which could well have wide implications in clinical pharmacology.

FIG. 4. The fall of blood phenytoin concentration when 'Dilantin' with calcium sulphate excipient was substituted for 'Dilantin' with lactose excipient, followed by a rise of blood phenytoin concentration when 'Dilantin' with lactose excipient was resumed. Faecal excretion of phenytoin in mg/day (cross-hatched columns), measured during the period of drug change-over, showed that the fall in blood level was not due to increased faecal excretion.

Eadie, Tyrer & Hooper (1970) went on to study some other aspects of diphenylhydantoin metabolism. They confirm previously published investigations, which showed that with repeated oral dosage, phenytoin levels in the blood rise for 4-12 days and then stabilize. Twice daily oral administration will then maintain a constant blood level within $\pm 10\%$ (Svensmark, Schiller & Buchthal, 1960); hence a more frequent dosage is not required. They also draw attention to several studies which have shown that certain drugs, including sultiame ('Ospolot'), chlor-diazepoxide ('Librium'), chlorpromazine ('Largactil'), prochlorperazine ('Stemetil'), INAH and PAS, oestrogens, disulfiram ('Antabuse'), phenylramidol, phenylbutazole and dicumarol, when given concurrently with phenytoin, will cause increased blood concentrations of the latter, possibly because both use a common metabolic pathway. Conversely, phenobarbitone and probably methylphenobarbitone ('Prominal') and primidone ('Mysoline'), which are converted in the body to phenobarbitone, may decrease the blood phenytoin concentration, presumably by inducing an increased formation of enzymes in the microsomes of liver cells. Larger doses of hydantoins may therefore be needed to maintain an effective blood level in patients who are taking these drugs in combination with barbiturates.

Measurements of blood phenytoin concentration in epileptic patients have shown that:

- (a) there is a wide scatter of blood levels attained in different persons taking the same oral dose of phenytoin,
- (b) in less than one half of cases was a satisfactory blood level of 10–20 $\mu\text{g/ml}$ achieved with standard doses of 300–400 mg of phenytoin per day,
- (c) adequate blood concentrations of phenytoin were reached in less than a quarter of the patients who took this drug in combination with another anticonvulsant.

A comparison of plasma and CSF levels of phenytoin in nine patients revealed that an average of 83% of plasma phenytoin is bound to protein. In a tenth patient, who developed signs of phenytoin toxicity with a low plasma level of 8.9 $\mu\text{g/ml}$, only 19% of the plasma phenytoin was protein-bound. The free concentration of drug in his plasma was therefore comparable to that of other patients with signs of toxicity. As he was taking several anticonvulsant drugs, it was thought that the aberrant findings could be attributed to competition by these drugs for plasma protein binding sites. Such competitive binding to plasma proteins may be an important factor in the behaviour of anticonvulsant combinations.

From these observations, Eadie *et al.* (1970) draw the conclusion that therapeutic blood levels of phenytoin should be attained before other anticonvulsant drugs are introduced. A simple method of measuring the blood concentration of phenytoin would be a great asset for the determination of correct dosage requirements in individual patients. This would be a step towards a solution of the vexed problem of inadequate seizure control in patients who can be relied on to take their anticonvulsant drugs regularly.

The mechanism of action of anticonvulsant drugs is not understood. Recent work (Reynolds, 1968) drew attention to an interference with folic acid metabolism and postulated that a reduction in serum folate levels contributed in some way to the inhibition of seizures. Apart from further studies of the various factors which influence the metabolism of phenytoin, a comparison of blood phenytoin concentrations with serum folate levels in epileptic patients may be rewarding.

Alcoholic neuropathy

Peripheral neuropathies have been under close scrutiny in recent years, and are currently a field of interest of Dr J. G. McLeod and his collaborators at the Department of Medicine, University of Sydney, and the Royal Prince Alfred Hospital, Sydney.

Walsh & McLeod (1969, 1970) report findings of nerve conduction studies and sural nerve biopsies in eleven patients with alcoholic peripheral neuropathy. Two distinct groups of cases emerged from the clinical history. The evolution of symptoms was slow

and extended over many months or years in four patients, who ate a normal diet and did not admit to acute episodes of increased alcohol consumption (Group I). The remaining seven patients presented with an acute peripheral neuropathy, which progressed rapidly over a period of a few weeks, and in all but one of these the diet was poor (Group II).

Motor conduction velocity in the median, ulnar and lateral popliteal nerves was significantly slowed, and the amplitude of the sensory action potentials of the median and ulnar nerves, and the mixed nerve action potentials of the ulnar and lateral popliteal nerves was reduced in all cases. The mean fibre density in the sural nerve was much below that of control subjects in the same age group. There was a loss of fibres of all diameters, which was most severe in patients with a prolonged history of heavy alcohol intake in repeated bouts.

In the patients of Group I pathological examination of single fibres teased from the sural nerves showed some normal fibres, as well as fibres with uniformly short internodes, indicating that regeneration after axonal degeneration had occurred. Active axonal degeneration was inconspicuous, and the number of fibres which had undergone segmental demyelination did not exceed normal limits for this age group.

In subjects of Group II, in contrast, many fibres were in the process of active axonal degeneration, but again without evidence of active segmental demyelination (Fig. 5).

FIG. 5. Alcoholic neuropathy. Single fibres teased from sural nerve of patient with acute alcoholic neuropathy are undergoing active axonal degeneration.

These pathological findings are consistent with the moderate degree of impairment of motor and sensory conduction in patients with alcoholic neuropathy. There is a chronic degeneration and regeneration of peripheral nerve fibres in those taking a good diet, whereas a poor diet and bouts of increased alcohol intake are responsible for a more active axonal degeneration, which becomes clinically manifest as an acute and rapidly progressive neuropathy.

The natural history of some muscular dystrophies

At the University of Western Australia and the

Neuropathology Laboratory, Royal Perth Hospital, Dr B. A. Kakulas and his collaborators have for some years pursued research into various aspects of muscular dystrophies.

Serial muscle biopsies from three patients with pseudo-hypertrophic muscular dystrophy (Duchenne), examined by light microscopy, reflected the clinical progression of the disease and suggested that muscle fibre necrosis is the basic morphological lesion and that some evidence of regeneration can be found even at an advanced stage of the disease (Mastaglia & Kakulas, 1968).

An ultrastructural study of the natural history of Duchenne muscular dystrophy (Papadimitriou, Mastaglia & Kakulas, 1969) revealed an association of both regenerative and degenerative phenomena in the same muscle fibre. Degenerative changes were seen both in the contractile apparatus and in the mitochondria and sarcoplasmic reticulum. In younger children, up to the age of 9 years, regeneration was of the 'discontinuous' type and involved a change of satellite cells into myoblasts. In patients older than 10 years, satellite cells were only rarely found, but there was evidence of 'continuous' regeneration, i.e. without the intervention of these satellite cells, from histological changes reflecting active protein synthesis, which could contribute towards the production of new myofilaments. Obviously, these attempts at regeneration are insufficient for the demands of the affected muscle fibre and they may also be qualitatively abnormal. They have no influence on the inexorable loss of muscle fibres or on the clinical progression of the disease.

It is thought that the ultrastructural and functional abnormalities in Duchenne dystrophy result from a genetically determined abnormality of sarcomere components, which shorten its life-span and reduce its efficiency.

A further study of regeneration in Duchenne dystrophic muscle, using histochemical as well as electron-microscopic methods (Mastaglia, Papadimitriou & Kakulas, 1969a) revealed active ribonucleo-protein synthesis even in fibres showing advanced degenerative changes. This 'continuous' type of regeneration was observed mainly in the less damaged muscle fibres and in parts of the muscle close to necrotic segments. In early stages of the disease virtually mature muscle fibres are achieved, but at a later stage most fibres are small, short and show degenerative features, including abnormalities of sarcomere size and structure in the myofibrils (Fig. 6). Such fibres were found to have low succinic dehydrogenase and phosphorylase activities, and their failure to mature may result from a deficiency of metabolic pathways concerned with energy production (Fig. 7). The biochemical and structural abnormalities in these regenerating fibres may therefore be related to

FIG. 6. Electronmicrograph of a biopsy from a patient with Duchenne dystrophy, showing a strap-like myocyte with a vesicular nucleus and prominent nucleolus. There are abortive attempts at sarcomere formation in the cytoplasm. The muscle fibre in the lower part of the field shows loss of myofibrils. Magnification $\times 5500$.

FIG. 7. A group of regenerating fibres in Duchenne dystrophy, showing low succinic dehydrogenase activity. Magnification $\times 400$.

the same metabolic defect which is primarily responsible for necrosis of the muscle fibre in the first instance.

From clinical, histopathological and electron-microscopic observations in eleven patients, Mastaglia, Papadimitriou & Kakulas (1969b) have attempted to formulate a theory of the pathogenesis of 'restricted forms' of muscular dystrophy. Their report is concerned with seven sporadic cases of limb girdle myopathy, three cases of facio-scapulo-humeral dystrophy, and one case of distal myopathy. They postulate that a primary genetic defect causes a segmental coagulation necrosis of muscle fibres, which is much less severe and involves a smaller

proportion of fibres than in the Duchenne type of dystrophy. There is again histological and ultra-structural evidence for limited regeneration, which is not as pronounced as in the Duchenne form. In view of the slowly progressive nature of the disease, this regeneration must be either inadequate or ineffective. As the disease advances there is progressive loss of muscle fibres with replacement by fibrous and adipose tissue. In spite of a compensatory hypertrophy of some of the surviving muscle fibres, there is clinically obvious muscle atrophy and weakness. Serum creatine kinase levels were elevated in nine of the ten patients tested. Electron-microscopic findings consisted of dilatation of the sarcoplasmic reticulum and of varying degrees of myofibrillary degeneration leading to coagulative necrosis.

It is suggested that the initial segmental coagulative necrosis may again be related to a deficiency of high energy phosphate compounds, and that the limited regenerative capacity can be attributed to the same metabolic defect.

Conclusion

The five topics reviewed above may at first sight appear to be a motley collection with little in common; yet they all exemplify the importance of metabolic or biochemical factors as a cause of functional derangements in the central and peripheral nervous system, in the control of the extracranial and cerebral circulation, and in muscle dystrophies. It is getting increasingly obvious that future progress in the prevention and treatment of many of the devastating, chronic neurological disorders will demand a better understanding of the chemistry of the nerve cell and fibre, of the pharmacology of synaptic transmission, and of the metabolic requirements of muscle cells.

Australia, 200 years after its discovery, is a progressive and prosperous country, which now has the men and the means to continue the tradition of British Neurology and to make its contribution to the advancement of the neurological sciences.

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References

ANDÉN, N.E., CARLSSON, A., DAHLSTRÖM, A., FUXE, K. HILLARP, N.Å. & LARSSON, K. (1964) Demonstration and

- mapping out of nigrostriatal dopamine neurons. *Life Sciences*, **3**, 523.
- ANTHONY, M., HINTERBERGER, H. & LANCE, J.W. (1968) Studies of serotonin metabolism in migraine. *Proceedings of the Australian Association of Neurologists*, **5**, 109.
- CAMPBELL, A.W. (1905) *Histological Studies on the Localisation of Cerebral Function*. Cambridge University Press.
- CURRAN, D.A., HINTERBERGER, H. & LANCE, J.W. (1965) Total plasma serotonin, 5-hydroxyindoleacetic acid and p-hydroxy-m-methoxy-mandelic acid excretion in normal and migrainous subjects. *Brain*, **88**, 997.
- CURTIS, D.R. (1968) Recent advances in neuropharmacology of neurological interest. *Proceedings of the Australian Association of Neurologists*, **5**, 101.
- CURTIS, D.R. (1970) Central synaptic transmitters. *Proceedings of the Australian Association of Neurologists*, **7** (In press).
- CURTIS, D.R. & CRAWFORD, J.M. (1969) Central synaptic transmission—Microelectrophoretic studies. *Annual Review of Pharmacology*, **9**, 209.
- EADIE, M.J., TYRER, J.H. & HOOPER, W.D. (1970) Aspects of diphenylhydantoin metabolism. *Proceedings of the Australian Association of Neurologists*, **7** (In press).
- LANCE, J.W. (1966) Studies in migraine. *Proceedings of the Australian Association of Neurologists*, **4**, 81.
- LANCE, J.W. & ANTHONY, M. (1968) The effect of serotonin on cranial vessels and its significance in migraine. *Proceedings of the Australian Association of Neurologists*, **5**, 639.
- MASTAGLIA, F.L. & KAKULAS, B.A. (1968) The natural history of human muscle diseases studied by means of serial biopsy. *Proceedings of the Australian Association of Neurologists*, **5**, 537.
- MASTAGLIA, F.L., PAPADIMITRIOU, J.M. & KAKULAS, B.A. (1969a) Regeneration in Duchenne muscular dystrophy. A histological, electron-microscopic and histochemical study. *Proceedings of the Australian Association of Neurologists*, **6**, 93.
- MASTAGLIA, F.L., PAPADIMITRIOU, J.M. & KAKULAS, B.A. (1969b) Restricted forms of muscular dystrophy: a study of 11 cases. *Proceedings of the Australian Association of Neurologists*, **6**, 107.
- PAPADIMITRIOU, J.M., MASTAGLIA, F.L. & KAKULAS, B.A. (1969) The natural history of Duchenne muscular dystrophy—an ultrastructural study. *Proceedings of the Australian Association of Neurologists*, **6**, 87.
- REYNOLDS, E.H. (1968) Mental effects of anticonvulsants, and folic acid metabolism. *Brain*, **91**, 197.
- SICUTERI, F., TESTI, A. & ANSELMINI, B. (1961) Biochemical investigations in headache: Increase in hydroxyindoleacetic acid excretion during migraine attacks. *International Archives of Allergy*, **19**, 55.
- SVENSMARK, O., SCHILLER, P.J. & BUCHTHAL, F. (1960) 5,5-Diphenylhydantoin (Dilantin[®]) blood levels after oral or intravenous dosage in man. *Acta pharmacologica et toxicologica*, **16**, 331.
- TYRER, J.H., EADIE, M.J. & SUTHERLAND, J.M. (1970). Investigation of an outbreak of anticonvulsant intoxication. *Proceedings of the Australian Association of Neurologists*, **7** (In press).
- WALSH, J. & MCLEOD, J.G. (1969) Alcoholic neuropathy. An electrophysiological and histological study. *Journal of the Neurological Sciences* (in press).
- WALSH, J. & MCLEOD, J.G. (1970) Alcoholic neuropathy. *Proceedings of the Australian Association of Neurologists*, **7** (in press).