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The Graeme Robertson Memorial Lecture, 1981

Sir Sydney Sunderland, D.Sc., M.D., F.R.A.C.P., Professor Emeritus of Experimental Neurology, University of Melbourne, was invited to give the Graeme Robertson Memorial Lecture for 1981, at the Annual Scientific Meeting of the Australian Association of Neurologists held in May 1981 in Adelaide, Australia. Sir Sydney chose 'Stretch-compression Neuropathy' as his topic and his text appears as the first paper of this volume.

Stretch-compression Neuropathy

*Sir Sydney Sunderland**

I would first thank the Council of the Australian Association of Neurologists for inviting me to deliver the 1981 Graeme Robertson Lecture. It is indeed an honour and a privilege to have been asked to accept this assignment as well as a pleasure to have the opportunity of paying tribute to an old friend with whom I enjoyed a close association for almost 40 years.

Since this is a commemorative lecture, tradition requires that I should say something about the man and his achievements. However, I do not propose to retrace in detail Graeme Robertson's many-sided life, for Dr Hooper, in the first Graeme Robertson lecture, has given biographical details, anecdotes and impressions so vividly and so fully that he has left to his successors in these lectures little fresh to add in these respects.

Casting one's mind quickly over Graeme Robertson's crowded career, one would select for special mention his dedication to the cause of neurology in this country. He sacrificed a promising career in London to return to Australia to become one of a very small band of pioneers who were instrumental in securing for neurology its firm recognition as a respectable specialty.

His potential as an experimentalist, revealed in earlier work with Denny-Brown on the physiology of micturition, found expression in a different direction on his return to Australia when he embarked on his investigations into pneumoencephalography which attracted world-wide attention. Pneumoencephalography is now passé but in those days it was a powerful addition to the limited diagnostic armament of the neurologist.

However it was as a clinical neurologist that Graeme Robertson excelled and in those early days all were impressed by his clinical style. The searching and painstaking history taking, the methodical and thorough neurological examination, the meaningful correlation of clinical and pathological data on which clinical interpretation must be based, and the detail and clarity of his reporting of clinical events were

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all outstanding. These attributes were, of course, the hallmarks of the Queen Square trained neurologist. He was, in every sense of the term, a true chip off the Queen Square block and he was, understandably, intensely proud of his association with that great institution. Though originally appointed to the honorary staff of the Royal Melbourne Hospital as a general physician in 1934, he did not become Honorary Neurologist until 10 years later when, through sheer clinical ability and persistence, he finally succeeded in securing a place for neurology as a separate specialty in the hospital structure. Meanwhile the Alfred Hospital had established a neurological clinic for Leonard Cox in 1934, the first, I believe, in this country. This was a development which I had watched with close personal interest for I joined Len Cox as his clinical assistant in 1936. With two neurological clinics in Melbourne the way was opened for similar developments elsewhere. What followed is now history and another story.

Turning now to the subject matter of the present Graeme Robertson lecture, it should be said, in explanation of the title, that stretch-compression neuropathy covers a wide variety of peripheral nerve lesions not all of which can be usefully discussed on this occasion. This immediately raises the question of what is to be included and what should be omitted.

I propose to exclude those neuropathies in which there is partial or total loss of continuity of the nerve trunk because these introduce a host of additional problems and complications that are of more direct interest and concern to the surgeon. This leaves for consideration those nerve lesions caused by physical forces in which the pathophysiological changes are confined to nerve fibres.

Having qualified stretch-compression neuropathy in this way we can now proceed to consider 3 questions:

1) Are there predisposing local factors that may render a nerve more susceptible to stretch-compression injury in some individuals than in others? Thousands of sedentary workers sit with elbows on tables for hours every day without harm. Why should one and not others develop an ulnar nerve palsy?
2) What mechanisms are involved in the production of stretch-compression neuropathy?
3) What is the nature of the nerve lesion produced in this way?

The answers to these questions are concealed in the internal and regional anatomy of peripheral nerve trunks and nerve roots (Sunderland, 1978). In identifying and discussing these anatomical features there is an advantage in examining nerve trunks and nerve roots separately because of the significant differences which exist between them.

Structural and Functional Features of Peripheral Nerve Trunks

General

The nerve fibres of a nerve trunk are collected into bundles, or funiculi, which are embedded in openly arranged areolar connective tissue, the epineurium. This con-

nective tissue provides the funiculi with a protective cushion against compression.

Within the funiculi the nerve fibres are closely packed together with a supporting framework of fine connective tissue, the endoneurium, which is specialised around each nerve fibre to form an outer limiting sheath, the endoneurial sheath. This sheath outlines an endoneurial tube containing the axon, Schwann cell layer, and the myelin (when present). The endoneurial sheath has some elasticity. It also resists and maintains a pressure within the endoneurial tube.

Each funiculus is encircled by a thin, but distinctive, perineurial sheath composed of interlocking specialised perineurial cells. This sheath has a number of important properties:

1) It has elasticity and considerable tensile strength, and is the chief component resisting elongation of the nerve.
2) It maintains and resists an intrafunicular pressure.
3) It functions as a diffusion barrier.

Funicular Structure of Nerves and Its Significance

The funicular structure seen in any transverse section of a nerve does not remain constant along the length of the nerve. On the contrary, the size, number and arrangement of the funiculi are all subject to repeated and rapid change because the funiculi are repeatedly dividing and fusing to form complicated funicular plexuses. At some levels the nerve fibres may be collected for a short distance into a single large funiculus whereas at others they are contained in a large number of small funiculi. Between these two extremes all combinations of size and number are to be found though these two features are always inversely related at any particular level.

The epineurial connective tissue separating the funiculi also varies in amount from level to level, being greatest when the funiculi are small and numerous. Finally these plexus formations also result in the gradual mixing and funicular redistribution of the different branch fibre systems as these are traced centrally in the nerve above the site of branching. In this respect the feature to be emphasised is that for a variable distance above the site of branching, the fibres of that branch will be sharply localised at the surface of the nerve.

Blood Supply of Peripheral Nerves

Features of the blood supply to the nerve that are worthy of special mention are:

1) The major nutrient vessels are found in the epineurium. They are superficially placed where the funiculi are few in number (1 to 3) but are also found more deeply where the nerve is composed of many small funiculi.
2) The nutrient veins outnumber nutrient arteries.
3) The largest vessels inside the funiculi are capillaries. Sometimes precapillary arterioles are found in intrafunicular septa which mark either the impending division of a funiculus or the recent fusion of two funiculi.
4) The profuse intrafunicular capillary network which is present.

Effect of Intrafunicular Fibrosis on the Nutrition of Nerve Fibres

This is a convenient point at which to discuss the effect of intrafunicular fibrosis on the nutrition of nerve fibres.

The blood flow through the capillary bed of a funiculus is decisive in maintaining the nutrition of nerve fibres and so ensuring their survival and functional efficiency. In order to reach and enter a nerve fibre, nutrient materials must cross the capillary endothelium the endoneurial sheath and the interval between these two barriers. Transcapillary transport and exchange depend, inter alia, on blood flow velocity and the condition of the capillary endothelium. Transfer is more complicated in the case of the endoneurial sheath of the nerve fibre, involving as it does both diffusion and the active transport of materials by their attachment to and release from a mobile or fixed carrier in the membrane. Regarding the movement of nutrients between the capillary endothelium and the endoneurial sheath, this is influenced by the distance between them and the composition of the intervening tissue.

Any thickening of the capillary wall and/or endoneurial sheath and the deposition of collagenous tissue between them would impede the transport of nutrients to the components of the nerve fibre and in this way would impair its functional efficiency and subsequently threaten its structural integrity.

Special Features of Nerve Trunks that Protect them from Stretch and Compression

Nerve trunks are stretched and displaced during normal limb movements but there are structural devices to ensure that nerve fibres do not suffer as a result.

Course of the nerve in relation to joints. With two notable exceptions, nerves cross the flexor aspect of joints. This means that they are subjected to less tension during limb movements. The two exceptions are the ulnar nerve which crosses the extensor aspect of the elbow joint, and the sciatic nerve where it crosses the extensor aspect of the hip joint. As a result these two nerves are under tension during full flexion at the elbow and hip respectively.

It is also of interest that where nerves cross joints they are composed of many small funiculi separated by large amounts of epineurial tissue. This is particularly so in the case of the sciatic nerve where it crosses the extensor aspect of the hip joint, the amount of epineurial tissue representing as much as 88% of the cross-sectional area of the nerve.

Undulating arrangement of nerve trunks and nerve fibres. The nerve trunk runs an undulating course in its bed, the funiculi run an undulating course in the epineurium and the nerve fibres run an undulating course inside the funiculi. This means that the length of nerve fibres between any two fixed points on the limb is considerably greater than a straight line between those points. The initial effect of stretching a nerve is to take out the undulations in the nerve trunk. With continued stretching this is followed by the elimination of the undulations in the funiculi and finally

the undulations in the nerve fibres. It is only at this last point that the nerve fibres are subjected to tension. These structural features of nerve trunks mean that during normal limb movements the axons are adequately protected against traction deformation.

Elasticity of nerve trunks. Over a certain range of elongation nerves behave as an elastic structure with tensile properties that protect the contained nerve fibres from being overstretched. The prinicipal component imparting elasticity to the nerve trunk and giving it tensile strength is the perineurium.

Cushioning effect of the epineurium. Nerve fibres are more susceptible to compression injury where the nerve trunk is composed of large and closely packed funiculi with little supporting epineurial tissue. Forces then fall maximally on the main content of the nerve trunk which is funicular tissue and, therefore, nerve fibres. On the other hand, the effects of compression are minimised when the nerve is composed of a large amount of epineurium. The deforming forces are then dispersed through, and cushioned by, the epineurium.

Intraneural Localisation of Specific Branch Fibre Systems and Its Significance

The localisation of a particular branch fibre system in a superficial position in the nerve may render it unduly susceptible to compression injury. Thus the concentration of the pupilloconstrictor fibres in the superior arc of the oculomotor nerve between the midbrain and cavernous sinus means that they are the first to suffer when the nerve is compressed from above by vessels or tentorial herniations (Sunderland and Hughes, 1946; Sunderland, 1952, 1958; Sunderland and Bradley, 1953). This accounts for the premonitory pupillary signs in these cases.

At one time it was mistakenly believed that a similar explanation accounted for the displacement of the affected vocal cord after compression of the recurrent laryngeal nerve. This explanation was based on the belief that the nerve fibres innervating the abductor muscles of the cord are superficially placed in the nerve and so are anatomically more exposed to compression injury. However, no such localisation exists (Sunderland and Swaney, 1952) and the explanation for the movement of the vocal cord to the midline is to be found in the fact that the adductor muscles outweigh the abductor by about 4 to 1.

Structural and Functional Features of Nerve Roots

The structure of nerve roots differs from that of peripheral nerves in certain important respects:

1) The perineurium is absent. Nerve roots accordingly lack the tensile strength of peripheral nerves and so are more vulnerable to traction injury.
2) The epineurium is absent so that nerve roots are more susceptible to compression.

3) The protective undulations in nerve trunks, funiculi and nerve fibres, which are such a characteristic feature of peripheral nerves, are not a prominent feature of nerve roots.
4) The root entry zone at the cord and brain stem is a transition zone where axons are more exposed to chronic irritation.
5) Large vessels are more directly related to nerve fibres than in peripheral nerves (Sunderland, 1948).

Regional Factors Predisposing to Stretch-compression Neuropathy

Sites of potential nerve involvement are legion but, to generalise, a nerve is at risk where:

1) It is directly in contact with an unyielding surface against which it can be compressed, e.g. The ulnar nerve behind the medial humeral epicondyle and the lateral popliteal nerve at the neck of the fibula.
2) It occupies:
   i) A bony or osseo-fibrous canal, e.g. The facial nerve in the facial canal and the median nerve in the carpal tunnel or supracondylar foramen.
   ii) A bony foramen, e.g. the nerve roots and spinal nerve in an intervertebral foramen.
   iii) A compartment with unyielding walls such as the lumbar plexus in the psoas compartment.
3) It passes through fascia or fibro-tendinous tissue, e.g. the suboccipital nerve and the lateral cutaneous nerve of the thigh.
4) It passes beneath a fibrotendinous arcade, e.g. the posterior interosseous nerve beneath the supinator arcade, the anterior interosseous nerve beneath the pronator teres arcade, and the ulnar nerve beneath the arcade formed by the flexor carpi ulnaris at the elbow joint.
5) It crosses a fibro-tendinous ridge against which it rides during movement or may be compressed, e.g. the ulnar nerve where it crosses the medial intermuscular septum of the upper arm.
6) It is so intimately related to another structure that enlargement of the latter would stretch or compress the nerve, e.g. the facial nerve in the cerebellopontine angle and in the parotid gland, and the paratracheal lymph nodes about the recurrent laryngeal nerve.

Nerves are also in jeopardy where they:

1) Cross the extensor aspect of a joint, e.g. the ulnar nerve at the elbow and the sciatic nerve at the hip joint
2) Are composed of a single or few large funiculi with little epineurial connective tissue packing, e.g. the ulnar nerve at the elbow
3) Become constricted by encircling scar tissue or compressed by a constricting band applied to the limb.

Pathogenesis of Stretch-compression Neuropathy

The pathogenesis of stretch-compression neuropathy will be discussed firstly in relation to the production, nature and severity of the nerve lesion and secondly the relationship between the rate at which the nerve is deformed and the onset of disturbances of function in the field of the affected nerve. Before considering these two topics some general points call for comment:

1) Though the physical force deforming the nerve often introduces elements of both stretch and compression, for convenience, the effects of each on the nerve will be considered separately.
2) Normal nerve fibres possess a remarkable tolerance to mechanical deformation but, once damaged, they are particularly sensitive to mechanical deformation and ischaemia.
3) Subclinical neuropathies of toxic or metabolic origin may remain latent until precipitated by some traumatic incident.
4) Some febrile condition of viral or other origin may lower the threshold at which local stretch and/or compression damage the nerve.
5) In compression ischaemia:
   i) large fibres are more sensitive than thin fibres
   ii) motor fibres are more sensitive than sensory fibres
   iii) when sensory nerve fibres fail they appear to do so in the following order: proprioception, touch, temperature and lastly pain.
6) The development of compression lesions follows a pattern which varies according to the circumstances under which the nerve is compressed.
7) Nerve fibres subjected to abnormal stretch or compression suffer in 3 ways:
   i) by sustaining structural damage which is directly attributable to the deforming force
   ii) by the impairment of their blood supply
   iii) by constriction from fibrosis developing inside and around the funiculi, and about the entire nerve trunk.
8) The severity of the lesion in stretch-compression neuropathy can be expressed in 5 degrees of damage of increasing severity.

First degree damage. Structural continuity of the axon is preserved but conduction is either impaired or lost. The conduction loss is usually transient but it will persist if the cause or pathology responsible for arresting conduction persists. Local pathology often requires surgical correction to relieve the block.

Second degree damage. The axon degenerates distal to the lesion but the endoneurial sheath of the nerve fibre is preserved. Axonal continuity with the periphery is restored by the regeneration of the axon and the restored pattern of innervation is precisely the same as the original so that function is fully restored.

Third degree damage. This is the lesion in which endoneurial sheath and endoneurial tube damage is severe and the outlines of the nerve fibre are lost. However, the perineurium survives so that the lesion is, in every respect, an intrafunicular lesion.

Fourth and fifth degree damage. Represent loss of funicular and nerve trunk continuity, respectively. As mentioned earlier lesions of this severity are excluded from the present discussion.

Partial and mixed lesions. Some nerve fibres and funiculi may escape damage to give partial lesions. Again, lesions in continuity often present a spectrum of damage, every degree of nerve fibre damage being represented to give a mixed lesion.

Pathogenesis of Stretch Lesions

Traction on a peripheral nerve removes first the undulations in the nerve trunk, then those in the funiculi and finally the undulations in the nerve fibres. With increasing traction the nerve fibres begin to suffer in two ways. In the first place they are now directly exposed to the deforming force and are stretched along with the nerve. Secondly, as the funiculi are stretched their cross-sectional area is reduced and the intrafunicular pressure raised. This in turn threatens the intrafunicular capillary circulation and the nutrition of nerve fibres. Initially nerve fibres suffer first degree damage. Continuing traction leads to second degree damage and, finally, the rupture of nerve fibres inside the funiculi. The funiculi rupture only when the elastic limit of the perineurium is finally exceeded and the nerve is then pulled apart.

Most traction injuries are the result of acute and violent trauma to the limb and so, as indicated earlier, do not qualify for further consideration in this text. However, traction may contribute to the production of a chronic lesion. Thus adhesions, which fix a nerve trunk in its bed or reduce its mobility, and changes in the connective tissue of a nerve, which reduce its elasticity, prejudice nerve fibres by lowering the threshold at which stretching produces pathological effects. Furthermore, constant friction over or against a roughened surface, or between two closely applied surfaces, or under a tendinous arcade, may involve repeated trauma to the nerve during movement. This ultimately results in the development of a friction fibrosis which may fix the nerve at that site and also adversely affect nerve fibres by constricting them and impairing their blood supply. Traumatising nerve fibres in this way results in the outgrowth of fine axon terminals from damaged axons.

This is the basis of the tender painful lesion in which the formation of ephaptic synapses could also contribute to abnormal activity in sensory nerve fibres. Good examples of this type of lesion are provided by the ulnar nerve behind the medial humeral epicondyle and the lower cervical spinal nerves in the intervertebral foramina in cervical spondylosis; there are, of course, many others.

The ulnar nerve is at risk when it rides over bone roughened by periarticular arthritic changes and because:

a) it passes through a narrow cubital tunnel
b) it crosses the extensor aspect of the elbow joint
c) it is composed of a single large or a few large funiculi with little protective epineurium.

The arrangement of a lower spinal nerve and its sheath in the cervical intervertebral foramen is such that the nerve-sheath complex is drawn in and out of the foramen with every movement of the cervical column and upper limb. In addition, the

nerve fibres in the spinal nerve are concentrated in a single funiculus. Trauma to the nerve caused by its repeated movement against the rough and irregular bony margin of the foramen in cervical spondylosis damages nerve fibres and results in a fibrous tissue reaction which contributes to nerve fibre involvement (Sunderland, 1978).

Pathogenesis of Compression Neuropathy

Compression produces its harmful effects on nerve fibres in two ways:

1) By the direct action of the deforming force on the nerve fibres.
2) By modifying the intrafunicular circulation in such a manner as to impair the blood supply and nutrition of nerve fibres.

Mechanical Factor in Acute Compression Neuropathy

Characteristic structural changes have been observed experimentally in nerve fibres subjected to severe acute compression beneath a compression cuff or tourniquet (Ochoa et al., 1972). They take the form of paranodal bulbous swellings and nodal intussusceptions at the margins of the cuff, with a direction of displacement that leaves no doubt that they are the result of mechanical pressure. These changes are followed by segmental demyelination and thinning of the axons, and ultimately by more advanced pathology culminating in axonal degeneration.

The compression forces required to produce these effects were of considerable magnitude (1000mm Hg for 1 to 3 hours) and it is unlikely that such forces would leave the blood supply to the compressed segment of the nerve unaffected. There is experimental evidence to confirm this, total ischaemia of the compressed segment being reported at pressures of 250mm Hg (Nobel et al., 1973) and, clinically, ischaemic necrosis of the compressed segment has also been reported (Allen, 1938; Speigel and Lewin, 1945). In such a situation the acute compression lesion is almost certainly the result of the combined destructive effects of both mechanical and vascular factors.

Vascular Factor in Chronic Compression Neuropathy

Special conditions apply where a nerve occupies an entrapment location in a bony canal or compartment with unyielding walls (Sunderland, 1976, 1977). Illustrative examples are provided by the facial nerve in the facial canal and the median nerve in the carpal tunnel. Within such a confined space there are at least 5 interrelated pressure systems. These are the pressure in the nutrient arteries in the epineurium (P^A), the pressure in the intrafunicular capillaries (P^C), the pressure inside the funiculi (P^F), the pressure in the veins in the epineurium (P^V) and the pressure in the canal or compartment (P^T).

In order to maintain an adequate blood supply to nerve fibres, the pressure gradient across this system must be:

$$P^A > P^C > P^F > P^V > P^T$$

These various pressure systems are delicately balanced and easily disturbed. If, for any reason, the pressure in the compartment should increase, the nutrient veins in the epineurium would be the first to suffer, the nerve fibres being protected initially by the cushioning effect of the epineurium. Increasing venous obstruction originating in this way slows the circulation through the funiculi and results in intrafunicular capillary congestion. The nerve fibres are particularly sensitive to the related hypoxia and anoxia, the larger fibres being affected earlier and suffering to a greater degree than the finer ones. Persisting and increasing capillary congestion is soon followed by changes in the capillary endothelium which allow the leakage of a high protein exudate into the endoneurial tissues. These changes are not confined to the funiculi but also affect the epineurium though the most damaging effects are occurring inside the funiculi.

Consequent on these pathological changes, the intrafunicular pressure rises owing to:

i) the diffusion barrier properties of the perineurium which traps the high protein exudate inside the funiculus
ii) the movement of tissue fluid across the perineurial barrier into the funiculus under osmotic influences so that the endoneurial tissues become oedematous and
iii) the resistance of the perineurium to swelling of the funiculus.

The increasing intrafunicular pressure represents a further threat to the integrity of nerve fibres by contributing to the failure of the intrafunicular circulation and by introducing a direct pressure effect on nerve fibres.

Nerve fibres are most vulnerable and suffer sooner and to a greater degree where they are collected into a single funiculus, as in the facial nerve in the lower facial canal. In a multifunicular nerve with a large amount of epineurial tissue, as in the median nerve in the carpal tunnel, not all funiculi will be affected simultaneously or to the same degree. As a result the developing lesion is invariably of a mixed variety. More resistant fibres may still be conducting normally, in others conduction velocity will be reduced, a third group will have sustained first degree or conduction block damage, for a fourth group fibres will be undergoing segmental demyelination at the compression site and the most severely affected will have undergone Wallerian degeneration denoting second degree damage. If the pressure is unrelieved all fibres will ultimately suffer second degree damage. At this stage of the development of the lesion, any change or procedure which relieves the pressure on the nerve will result in the rapid correction of the pathological changes that have occurred. As the circulation through the compressed funiculi improves, the oedema inside the funiculi is gradually resolved, the intrafunicular pressure falls, and regeneration follows in degenerated fibres.

Continuing and increasing pressure on the nerve results in further capillary damage, the introduction of an ischaemic factor and complications in the form of a proliferation of fibroblasts and the appearance of a constrictive endoneurial and epineurial fibrosis. The lesion now takes on a more permanent state. Fibroblasts proliferating in the intrafunicular protein exudate promote the development of an irreversible intrafunicular fibrosis which results in the constriction of increasing num-

bers of nerve fibres. The final stage is reached when nutrient vessels are obliterated and the affected segment of the nerve becomes converted into a fibrous cord in which only a few fine nerve fibres survive inside fibrosed funiculi which are encased in a now dense, relatively avascular, epineurium. This represents third degree damage from which any recovery is unlikely because regenerating axons are now faced by an impenetrable barrier.

Time Factor in Stretch-compression Neuropathy

In stretch-compression neuropathy the rate of deformation of the nerve is a significant factor in the production of symptoms.

Thus it is possible to stretch and/or compress a nerve so slowly that it can be deformed to a remarkable degree without the appearance of any disturbances of function at the periphery. For example, if nerves are stretched at a rate of 7.5cm/min, the elastic limit is reached and mechanical failure occurs after elongations of 6 to 22% depending on the nerve and its funicular structure (Sunderland and Bradley, 1961). On the other hand, nerves may be stretched so slowly that their length can be doubled without any disturbance of function. This occurs, for example, when the facial nerve is gradually stretched over a slowly enlarging acoustic neuroma or parotid tumour.

The point is perhaps best illustrated by reference to those expanding supratentorial lesions which result in the herniation of the uncal region of the temporal lobe through the hiatus of the tentorium. As such herniations enlarge they impinge on and compress the oculomotor nerve from above where it is slung between the midbrain and the cavernous sinus. In the case of extradural haemorrhage the associated tentorial herniation develops rapidly and in doing so abruptly deforms the nerve. The first nerve fibres affected are those located superiorly in the nerve which are the pupillo-constrictor fibres. These are first irritated and then blocked. Involvement of the somatic motor fibres follows. This sequence of nerve fibre involvement and conduction failure is responsible for a distinctive order of succession in the appearance of oculomotor signs which provides an important diagnostic guide to the nature and rate of development of this complication (Sunderland and Bradley, 1953; Sunderland, 1958). On the other hand, a slowly growing pituitary tumour may escape from the pituitary fossa and continue to enlarge in the interpeduncular region in such a way as to gradually stretch the oculomotor nerve. Considerable deformation of the nerve can occur in this way without the appearance of any signs or symptoms pointing to involvement of the nerve (Sunderland, 1978).

Summary

1) Whether a nerve subjected to stretch-compression escapes damage or succumbs depends on factors such as:

i) the internal structure of the nerve
ii) regional features which increase its vulnerability; and
iii) the rate of application as well as the magnitude of the deforming force.

2) Those who seek a common pathogenesis for all stretch-compression neuropathies will seek in vain unless, of course, their efforts are directed at the molecular level. The pathogenesis of these lesions follows a pattern which varies according to the circumstances under which the nerve is deformed.
3) Nerve fibres stretched and/or compressed beyond their protective limits suffer in several ways:

i) they sustain structural changes directly attributable to the deforming force. These changes are characteristic of acute compression and traction
ii) their nutrition is impaired due to circulatory changes in the capillary bed involving progressively hypoxia, anoxia, ischaemia and finally ischaemic necrosis and fibrous tissue replacement. Once the circulation through the capillary network of a funiculus is impaired a train of self-generating pathological changes follows which results in the progressive destruction of the conducting elements of the nerve
iii) by fibrosis developing inside and around the funiculi and around the entire nerve trunk. This fibrosis is caused by friction, trauma or by impairment of the blood supply to the affected segment of the nerve. Fibrosis threatens the integrity of nerve fibres by constricting them and by still further impairing their blood supply.

4) The nature of stretch-compression neuropathy can be expressed in terms of first, second and third degree damage using a recognised classification of nerve injury.
5) The symptomatology of stretch-compression neuropathy fluctuates according to the pathology of the lesion.

There is abundant clinical evidence that simple compression lesions are not painful. Pain becomes part of the compression syndrome when:

i) the blood supply to nerve fibres is seriously impaired
ii) intraneural fibrosis, regardless of its cause, is impairing the nutrition of nerve fibres
iii) recurrent friction has damaged axons to the point where sensitive collateral axon terminals, which develop in response to injury, grow into the fibrous tissue which is accumulating at the site of trauma.

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Myasthenia Gravis: Immune Mechanisms and Implications

*John Newsom-Davis**

Based on the Roche-ICI lecture given to the Australian Association of Neurologists, Adelaide, May 25, 1981.

Knowledge of the immune mechanisms concerned in myasthenia gravis has increased remarkably in the last few years. For the neurologist, this has implications both with respect to the diagnosis of the disorder and its treatment. But interest is further increased by the possibility that these advances could have a broader relevance. Myasthenia gravis appears to provide an exceptionally good model of a group of disorders whose pathology was predicted by Lennon and Carnegie (1971), and that is now increasingly being recognised, in which an autoantibody reacts with cell-surface receptors for neurotransmitters or for peptide hormones. Thus understanding the nature of the immunological disorder in myasthenia that leads to the breakdown of self-tolerance to the auto-antigen (acetylcholine receptor) may throw light on the aetiology of other autoimmune diseases.

In retrospect, one can view some of the early case reports as providing the first clues to the nature of the disorder. Weigert (1901), for example, reported the association of myasthenia with a thymic tumour. The immunological importance of the thymus as the site of development of T lymphocytes is now, of course, well established, and thymoma has since been shown to associate not only with myasthenia but also with a number of other immunological disorders including systemic lupus erythematosus, rheumatoid arthritis, polymyositis and thyroiditis (Souadjian et al., 1974). In 1911, Professor Sauerbruch removed an enlarged thymus from a young woman who also had thyrotoxicosis (Schumacher and Roth, 1919), another disorder in which an autoimmune aetiology is now recognised. Thymectomy did not become an accepted treatment for myasthenia until after Blalock's report in 1939 of its benefit in a patient with a thymic tumour. Follow-up studies on several

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large series of cases since then have all tended to suggest the benefits of the procedure which, paradoxically, has proved to be least evident in those with thymoma.

Pathophysiology

The idea that myasthenia was a disorder of neuromuscular transmission originated in the nineteenth century, and the demonstration by Mary Walker (1934) of the effectiveness of physostigmine, the antidote to curare poisoning, lent further support to this view. Elmqvist and his colleagues (1964) gave the first detailed account of the pathophysiology of the disorder, based on microelectrode recording from biopsied intercostal muscle. They demonstrated that the amplitudes of the miniature endplate potentials and endplate potentials were both decreased. The endplate potential was often insufficient to reach the critical firing threshold for the cell and conduction block therefore resulted (fig. 1). The use of a snake toxin, alpha-bungarotoxin (α – BuTx), which binds specifically and essentially irreversibly to the acetylcholine recognition site on the acetylcholine reception (AChR; fig. 1) has established that the principal defect in myasthenia gravis is a reduction in the number of functional AChRs in the post-synaptic membrane (Fambrough et al., 1973). This reduction is sufficient to account for the physiological abnormalities (Ito et al., 1978).

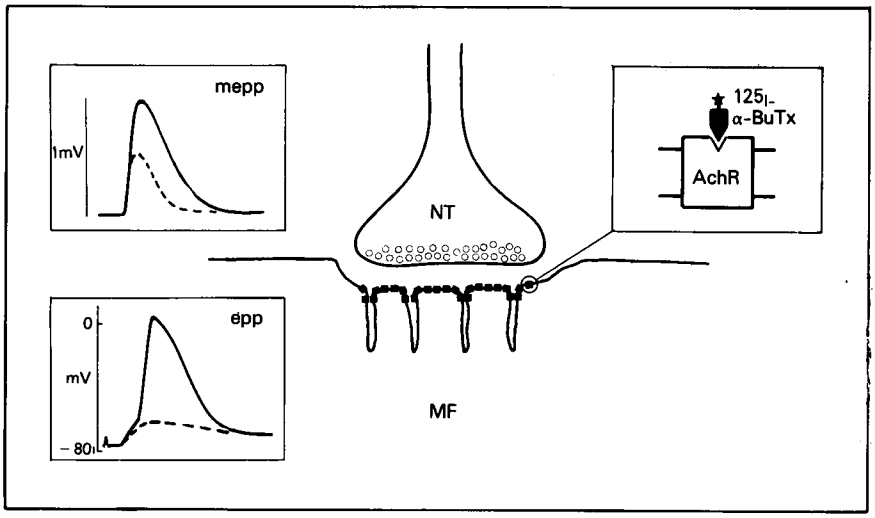

Fig. 1. Diagram of the neuromuscular junction. Spontaneous release of an individual quantum of acetylcholine from the nerve terminal (NT) evokes a miniature end-plate potential (mepp.). A nerve impulse causes release of 50 to 100 quanta and generates an end-plate potential (epp.) which is normally adequate to trigger an action potential. Mepp and epp amplitudes are reduced in myasthenia gravis (dashed lines), and the epp may be insufficient to reach the critical firing threshold for the muscle fibre (MF), causing conduction block. Acetylcholine receptors (AChR) are located on the peaks of the post-synaptic folds, and can be labelled with ^{125}I-α-bungarotoxin (α-BuTx) which binds at the acetylcholine reaction site.

Anti-acetylcholine Receptor Antibody and Receptor Loss

At about the time when a reduction in the number of AChRs at the endplate was recognised in myasthenia, Patrick and Lindstrom (1973) discovered that rabbits immunised with purified AChR, obtained from the eel electric organ, developed a myasthenia-like illness (experimental autoimmune myasthenia gravis, EAMG) that responded to neostigmine; when induced in primates (Tarrab-Hazdai et al., 1975) it strikingly resembled the human disease. Serum from animals with EAMG contained anti-acetylcholine receptor antibody, and many groups have since reported the presence of this antibody in myasthenic patients (Almon et al., 1974; Mittag et al., 1976).

Anti-AChR antibody is an IgG antibody (fig. 2) that is specific for myasthenia. The antibody is not detected at elevated titre in healthy controls, in other neurological patients or in those with other immunological disorders. It is usually assayed by an immunoprecipitation method using AChR extracted from amputated human calf muscle and labelled with ^{125}I-α-BuTx. The antibody may be represented in any of the IgG subclasses and it is heterogeneous (Vincent and Newsom-Davis, 1979), i.e. antibody can be directed against several different antigenic determinants on the AChR as indicated schematically in figure 2. It should be noted that the standard assay does not detect antibody binding to the acetylcholine recognition site, which is occupied by the toxin. In order to detect this antibody it is necessary to look for inhibition of ^{125}I-α-BuTx binding to receptor.

Anti-AChR antibody is present in 85 to 90% of those with generalised disease (Lindstrom et al., 1976; Compston et al., 1980) and in about 75% of those in whom the disease is restricted to ocular muscles (Vincent and Newsom-Davis, 1980). It is undetectable in congenital myasthenia, a disorder that does not appear to have immunological origins. Figure 2 illustrates a further feature of the antibody, namely the lack of correlation between antibody titre and disease severity between individuals, a finding that could theoretically be accounted for by antibody heterogeneity.

From the clinical standpoint, the specificity of the antibody gives it considerable diagnostic value. It is also now clear that the antibody is implicated in the pathophysiology of the disorder and plays a critical part in causing AChR loss from the postsynaptic membrane. Indirect evidence that the antibody might be concerned in the disease process comes from the clinical observation that 1 in 8 babies born to myasthenic mothers have a transient illness (neonatal myasthenia) [Namba et al., 1970] which is associated with the placental transfer of the IgG antibody (Keesey et al., 1977). Breakdown of the IgG in the child usually leads to the resolution of symptoms within 4 weeks of birth.

It has been shown experimentally that myasthenic serum and its IgG fraction can transfer myasthenia to mice, as shown by weakness (in some animals) together with the typical physiological changes of myasthenia and loss of AChR (Toyka et al., 1977). The complement system appeared to be involved in that C3 depleted animals were relatively less affected by the myasthenic IgG.

The response to plasma exchange provides further evidence favouring a humoral factor (Pinching et al., 1976). Improvement typically occurs 1 to 5 days after the initiation of a course of plasma exchange and longitudinal studies of muscle strength

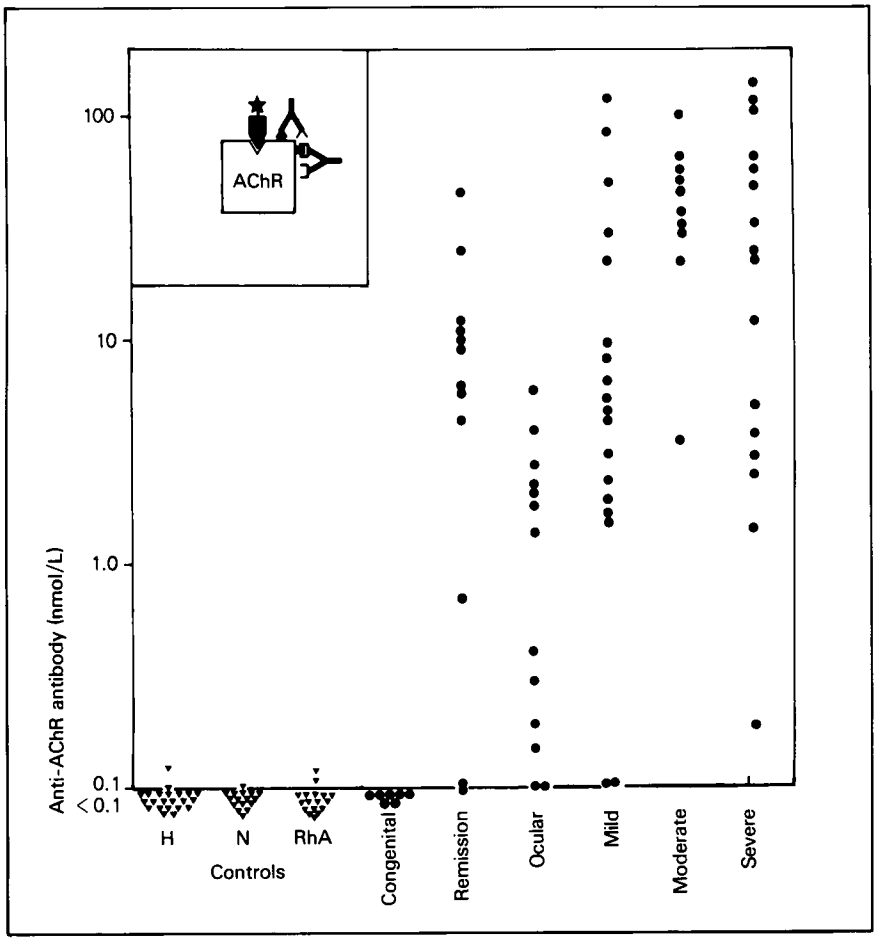

Fig. 2. Anti-acetylcholine receptor antibodies. The antibody is measured by an immunoprecipitation method in which serum is incubated with ^{125}I-α-BuTx-labelled AChR, and precipitated with an anti-human IgG antisera. Note that the antibody can be of more than one specificity. Healthy subjects (H); patients with other neurological disorders (N); rheumatoid arthritis (RhA). Inset: anti-acetylcholine receptor antibody.

and serum anti-AChR titres reveal a clear inverse relationship (Dau et al., 1977; Newsom-Davis et al., 1978; Carter et al., 1980), in contrast to the lack of correlation between individuals. This is consistent with the implication of anti-AChR in the process of AChR loss.

Anti-AChR antibody appears to lead to loss of receptor by more than one mechanism. Immunohistochemical methods have revealed IgG and C3 on the postsynaptic membrane and also coating degradative products in the synaptic cleft (Engel et al., 1977). More recently the lytic component (C9) has also been identified with a

similar distribution (Sahashi et al., 1980). These observations, taken together with the simplified morphology of the postsynaptic folds in myasthenia (Santa et al., 1972), suggest that complement-mediated lysis of the membrane may be an important mechanism of AChR loss.

A further mechanism of AChR loss that could also be important relates to the ability of the divalent antibody to cross-link acetylcholine receptors in the membrane, and thereby to increase the rate at which receptors are internalised into the muscle cell and degraded there by lysosomal enzymes (Drachman et al., 1978). In the absence of any concomitant increase in AChR synthesis, this would lead to a net loss of receptor.

Theoretically, anti-AChR antibody could also block access of transmitter to the ACh recognition site of the acetylcholine receptor. In practice, there is no convincing evidence yet that this occurs in the human disease.

Disease Heterogeneity

There are grounds for suggesting that myasthenia gravis may be a heterogeneous disorder. If this is established, it could have implications both for the aetiology of the disease and for its management. Two clinical features pointing to such heterogeneity are the differing pathology of the thymus and the age distribution of the onset of the disease (Compston et al., 1980). Thymoma is present in about 10% of cases (Namba et al., 1978), and these have a peak age of onset in the fifth decade. Non-thymoma cases then fall into 2 broad groups with a bimodal age distribution (Compston et al., 1980). Those in whom the disease presents under the age of 40 show hyperplasia of the thymus. Females exceed males in this group. Those presenting at a later age are more commonly males, and when the thymus is examined it typically shows an atrophic appearance.

We found that these 3 clinical groups showed significant differences in their immune characteristics (Compston et al., 1980). For example, anti-AChR antibody levels were highest in thymoma cases, intermediate in those with hyperplasia and lowest in the older age group. Anti-striated muscle antibody is almost always detectable in thymoma cases but is much less frequent in the other forms of the disease. Other autoimmune disorders and the incidence of other autoantibodies showed different representations in the 3 groups. There were also significant differences in the frequency of particular HLA antigens as first recognised by Pirskanen et al. (1972). In those with thymic hyperplasia HLA A1, B8 and DRw3 were increased and in the older age group HLA A3, B7 and DRw2 were increased. No clear HLA association exists for thymoma cases, but in Japanese patients a Gm allotype association has been recognised (Nakao et al., 1980).

What interpretation should be placed on these observations? Given that the association with particular HLA antigens appears to increase the susceptibility to a particular type of myasthenia gravis, one could argue that heterogeneity is determined by the immune response characteristics of an individual to a single triggering factor, such as a virus. But an alternative interpretation is at least as attractive, namely that more than one potential defect exists in the mechanism that normally maintains

tolerance to the AChR, that the triggering factor itself may be diverse, and that susceptibility to these is linked to particular HLA antigens or Gm allotypes.

From the practical standpoint it is interesting to note that differences in the form of the disease are also reflected in their response to treatment. Thus the group with thymoma generally shows a less good response to thymectomy than in those with thymic hyperplasia (Simpson, 1958); in contrast, their response to immunosuppressive drug treatment tends to be better (Newsom-Davis et al., 1979).

Role of the Thymus

Clinicians have for a long time regarded the thymus as contributing to the autoimmune process in myasthenia, and the recent evidence that developing T cells may acquire tolerance in the thymus to self-antigens lends support for such a view (Zinkernagel et al., 1980). In this context, it may be noted that the auto-antigen in myasthenia, acetylcholine receptor, has been demonstrated in the thymus by several groups. Lindstrom et al. (1976) were able to precipitate ^{125}I-α-BuTx binding material from the rat thymus using EAMG antisera, and Kao and Drachman (1977) showed that the muscle-like (myoid) cells present in the thymus would express AChR in culture. Engel et al. (1977) reported ^{125}I-α-BuTx binding to epithelial cells using a peroxidase method, and Fuchs et al. (1980) recently reported that immune sera raised against the electric organ AChR bound 80% of mouse thymocytes.

The presence of lymphoid follicles with germinal centres in the thymic medulla of younger myasthenic patients suggests the possibility of specific antibody production in the thymus. These germinal centres might also be expected to contain antigen. Lisak and his colleagues (1978) found that the proportion of thymic B cells in thymic hyperplasia was increased and the proportion of T cells decreased compared to controls and to those with thymoma.

We have tested the possibility of anti-AChR production in the thymus by culturing thymic cells obtained from patients who have undergone thymectomy (Vincent et al., 1978; Scadding et al., 1981). Anti-AChR antibody was measured in the culture supernatants at 4 and 8 days. Cultures in the presence of cycloheximide, which inhibits protein synthesis, served as controls. Thymic cells from those showing thymitis regularly produced anti-AChR antibody, whereas cells from involuted thymuses or thymus associated with thymoma produced little or no antibody. Interestingly, anti-AChR antibody synthesis occurred early in culture and was not enhanced by pokeweed mitogen, suggesting that the antibody producing cells were already maximally stimulated *in vivo*.

Although anti-AChR antibody production by cultured thymocytes was a regular feature of those with thymitis, the rate of production did not correlate with the degree of the histological changes, assessed without knowledge of the culture results. The rate of production did, however, significantly correlate with the duration of the disease. But, even in those with the longest history, the rate of antibody production calculated for the thymus as a whole would account for only a small proportion ($< 5\%$) of anti-AChR synthesis.

These culture studies of thymic cells provide further support for disease heterogeneity in myasthenia gravis in that thymic cells from thymitis glands clearly differ from those with thymoma with respect to *in vitro* antibody production. The observations also suggest that the role of the thymus in these different forms of the disease may not be the same.

In contrast to thymic cells, blood lymphocytes from myasthenic patients make little or no anti-AChR antibody when cultured alone, and the responses to pokeweed are very variable (Newsom-Davis et al., in press). But when thymic cells are co-cultured with the patient's own blood cells, a striking enhancement of anti-AChR antibody production often results. The thymic cells are first irradiated in order to prevent their making any antibody themselves and to abolish any thymic suppressor cell activity. The enhancing effects of thymic cells on anti-AChR antibody production by autologous blood lymphocytes appears selective for this antibody. Thus total IgG is not increased. Enhancement also appears to depend on the viability of the thymic cells, for the effect was lost if the cells were heated to 46°C. Thus it seems likely that if enhancement is due to antigen driving of the response, it must depend on cell-bound rather than free AChR-like material.

An alternative cell type that could be mediating the effect is an AChR-specific T helper cell. Some evidence in support of this comes from enumerating the number of T helper and T suppressor cells by indirect immunofluorescence, using monoclonal antibodies specific for these subsets. The ratio of helper to suppressor cells in the thymus significantly correlated with the ability of these cells to enhance anti-AChR antibody production by autologous blood lymphocytes (Newsom-Davis et al., 1981).

We interpret our results at present as indicating that either antigen-presenting cells with AChR-like material on their surface or AChR-specific T helper cells (or both) could be mediating the enhancement of antibody production by the peripheral blood B cells. These cell types are likely to be long lived, and their migration from the thymus would lead to the dissemination of anti-AChR antibody production elsewhere, such as lymph nodes and spleen. The continued expansion and emigration of a thymic population of specific T helper cells provides a theoretical argument in favour of early thymectomy, and indeed some clinical studies have suggested that the response to the operation is best in this group (Simpson, 1958).

Implications for Management

Broadly, one can regard treatment in myasthenia as either pharmacological or immunological. The former depends principally on anticholinesterase drugs such as pyridostigmine and neostigmine, and there is no doubt that drugs of this type have saved many lives since their introduction nearly 50 years ago (Walker, 1934). Nevertheless, as the immunological nature of myasthenia has become increasingly understood, the case for relying solely on these drugs in the treatment of this condition has steadily weakened. Moreover, there is now evidence from animal studies that anticholinesterase drugs can themselves reduce the content of acetylcholine receptor at the neuromuscular junction, thus paradoxically inducing a myasthenia-like abnormality (Chang et al., 1973; Engel et al., 1973). In the management of acquired

myasthenia gravis, therefore, these drugs should either be used as an adjuvant to immunological treatment or, if used alone, confined to those with mild disease in whom it appears inappropriate to use immunosuppressive therapy. In any event, overdosage should be avoided; few patients benefit in the long term from pyridostigmine at a dose in excess of 600mg daily.

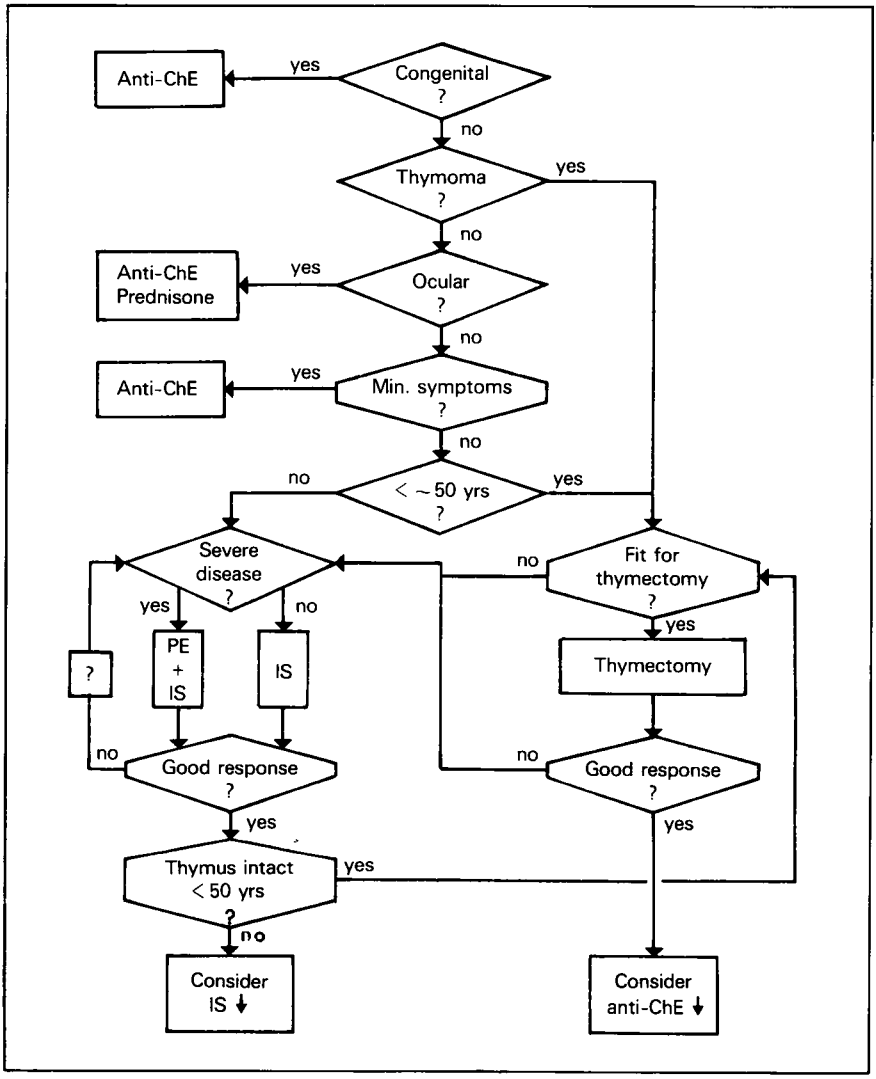

Fig. 3. Flow diagram of treatment strategy for myasthenia (see text). Anti-AChE, anticholinesterase drugs; IS, immunosuppressive drugs; PE, plasma exchange.

One can formulate a treatment strategy for myasthenia gravis in the form of a 'flow diagram' (fig. 3). It should first be enquired whether the patient has congenital myasthenia because, should this be the case, immunological treatment is not appropriate and anticholinesterase drugs should be used. Next, it needs to be established whether the patient has a thymoma; if so, thymectomy is indicated because of the risks of local infiltration by tumour. Diagnosis of thymoma can be assisted by computerised tomography of the mediastinum, and by measurement of anti-striated muscle antibody in serum. This antibody virtually always accompanies thymoma, and its absence therefore makes the diagnosis very unlikely.

In non-thymoma cases in whom the disease is restricted to the eye muscles, anticholinesterase drugs can be used but response is often unsatisfactory. In that event, there is a good case for using prednisolone, assuming there are no individual contraindications to its use (Fischer and Schwartzman, 1976). Treatment should always be on an alternate day regimen, starting with a low dose (e.g. 10mg on alternate days). The dose can then be incremented by 5 to 10mg per week until symptoms resolve or a dose of 60 to 80mg is reached. After 2 to 3 months in remission, a slow reduction in dosage (5mg per month) is begun with the aim of defining the effective minimal dose. Response to steroids is usually excellent and is associated with a decline in anti-AChR antibody (Newsom-Davis and Vincent, 1981). The treatment is generally well tolerated even by the elderly, and the relief from symptoms is usually greatly appreciated.

For patients with generalised myasthenia and appreciable symptoms, the next decision to be taken concerns thymectomy (fig. 3). The question of whether thymectomy is valuable in the treatment of myasthenia has been controversial since the operation first became regularly used 40 years ago. As Simpson (1958) has pointed out, evaluation of thymectomy requires separating thymoma cases (who respond poorly with respect to myasthenic weakness) from the remainder. When this is done, the non-thymoma younger age group in particular appears to benefit as many reports of large series of patients have shown (Simpson, 1958; Papatestas et al., 1971; Emeryk and Strugalska, 1976). Controls have been inadequate in most of these but a retrospective computer-matched study at the Mayo Clinic (Buckingham et al., 1976) in which thymectomy was compared to medical (non-immunological) treatment showed clear benefits in the operated group. Taking the results of several large series together, it seems that about 25% of thymectomised patients will enter remission after thymectomy and about 50% will show improvement.

We have measured the change in clinical grade and in serum anti-acetylcholine receptor antibody titre in 25 non-thymomatous patients 1 to 3 1/2 years after thymectomy. Clinical assessment was made without knowledge of the antibody results. Seven patients were in remission and in each of them anti-AChR antibody had fallen by more than 25%. Eleven patients showed improvement in clinical grade and most showed a fall in anti-AChR. Seven patients were judged to be unchanged clinically but in the majority of these, too, the anti-AChR was less than the pre-thymectomy value. Interestingly, no patients appeared to be clinically worse than at the time of thymectomy, and in none had the anti-AChR titre risen appreciably.

The decision of whether to recommend thymectomy is at present probably best made on the basis of the patient's age at the clinical onset of disease. Thymectomy is

best recommended for non-tumour cases under the age of 45 to 50, since the evidence for the benefits of the procedure is more convincing in this group than in older patients. If the patient is not fit enough for the operation, it may be necessary to undertake immunosuppressive therapy or perhaps plasma exchange with a view to improving the clinical state sufficiently for thymectomy to be possible.

In patients who fail to show a good response to thymectomy and who are significantly disabled by symptoms, immunosuppressive therapy is indicated, as in those for whom thymectomy is not indicated on grounds of age.

Choice of immunosuppressive drug therapy should be in part determined by the severity of symptoms (fig. 3). If symptoms are less than severe the treatment of choice would either be alternate day prednisolone (Mann et al., 1976) or azathioprine (Mertens et al., 1969; Hertel et al., 1979). In the case of prednisolone, a similar dose schedule to that set out above should be used, but perhaps accepting a higher peak dose (e.g. 100mg on alternate days) to achieve remission. Starting therapy at high daily dosage should be avoided because of the risks of initial deterioration in symptoms (Seybold and Drachman, 1974), but there may be exceptional circumstances in hospitalised patients where this is justified. If prednisolone is contraindicated, azathioprine should be considered. There is now good evidence for its having long term beneficial effects in myasthenia gravis (Hertel et al., 1979). The recommended dose is 2.5mg/kg, and patients require weekly full blood counts and liver function tests for 8 weeks and monthly tests thereafter. Higher doses can be used if the response is incomplete and the white blood cell count satisfactory. Occasional cases develop severe and immediate abnormalities of liver function with systemic disturbance and the drug then has to be discontinued. In others who appear to tolerate the drug well, minor but stable abnormalities of liver function may develop which do not necessarily constitute a reason for withdrawing the drug. Response to azathioprine is slow, the decline in anti-AChR antibody having a half time of at least 8 months (Newsom-Davis et al., 1979), and improvement can continue well beyond one year after starting treatment.

In severe cases, the optimal treatment at present appears to be prednisolone combined with azathioprine. Plasma exchange can be useful in this type of case because of the rapid, although temporary, improvement of symptoms that can result, but there is no evidence that it interacts positively with immunosuppressive drug treatment. Patients receiving immunosuppressive drugs together with regular intense courses of plasma exchange did no better when assessed 8 months after the start of treatment than those treated with immunosuppressive therapy alone, the mean fall in antibody over the period being similar in the 2 groups (Newsom-Davis et al., 1979). Moreover, the rise time of antibody after plasma exchange is not significantly retarded in those receiving immunosuppressive drug treatment compared to those who are not (Hawkey et al., 1981).

The place of plasma exchange in the treatment of myasthenia should at present depend on the extent to which a short term improvement is required (Newsom-Davis, 1979). This improvement typically lasts for 2 to 4 weeks after a 5-day course of exchange at a daily rate of exchange of 55ml/kg. In cases of unusual severity, we have given similar courses of exchange for 3 years or more until immunosuppressive drug therapy became effective. This enabled patients to live independently at home during

this period of slow improvement which would probably not otherwise have been possible.

Future Prospects

Present therapy for myasthenia gravis still has many shortcomings despite the advances evident recently from the increasing use of immunosuppressive drugs and the availability of plasma exchange. First, the outcome of thymectomy is unpredictable and some patients undergoing this procedure gain no apparent benefit. Secondly, immunosuppressive drugs are not specific in their action and unavoidably expose patients to risks of opportunistic infection and other side effects. Finally, rare cases are unresponsive to, or intolerant of, immunosuppressive drugs, and in these no satisfactory alternative exists in severe cases to repeated courses of plasma exchange, as indicated by the 'endless loop' in figure 3. Research in autoimmune disease is now beginning to focus on the development of specific immunological therapy in which the goal will be to control the disordered immune process without interfering with other immunological functions. Theoretical possibilities here would include raising anti-idiotype antibody, i.e. antibody to the unique combining site determinant of a particular antibody, or inducing specific T suppressor cells. Many of the features of myasthenia gravis make it a particularly good model in which to try to work out new treatments of this kind.

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Disordered Muscle Tone and Movement

Special Lecture by Invitation

*James W. Lance**

For some 30 years I have meandered through the motor system and it may be of interest to members of the association if they travel with me as I retrace the voyage down this tortuous stream of thought. The raft was first launched with the help of Peter Bishop, now Professor of Physiology at the John Curtin School of Medical Research. He had just formed the Brain Research Unit at Sydney University, having worked with Professor J.Z. Young in London for 4 years, and encouraged me to study the motor system as I had been intrigued by movement disorders as a student. The pyramids in the medulla were stimulated electrically to set up an orthodromic discharge in the lateral corticospinal tract and an antidromic discharge to the cerebral cortex. By this means (Lance and Manning, 1954) the origin of the pyramidal tract from various cortical areas was plotted (fig. 1b) and the distribution of the tract to different levels of the spinal cord was determined (Lance, 1954a). The pyramidal tract was found to comprise 2 groups of fibres with different properties (Bishop et al., 1953), the conduction velocities of which were 22 to 70m/sec and 8 to 22m/sec respectively (Lance, 1954a). At the time, it was thought likely that the faster of these groups controlled rapid phasic movements and the slow group postural changes. Later work has provided confirmation of this (Evarts, 1965) although the 2 groups may interact so that their relationship to the type of movement produced may be complex (Phillips and Porter, 1977). An attempt to produce regeneration of the pyramidal tract after section by inhibiting glial scarring with pyrogenic agents proved unsuccessful but served instead to study the process of retrograde degeneration (Lance, 1954b).

I then had to leave experimental work to complete training in general medicine and neurology in England, returning to Sydney as Superintendent of the Northcott

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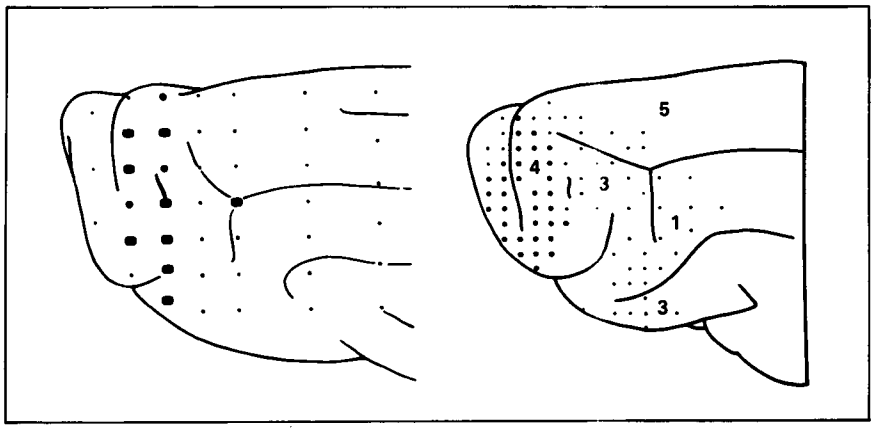

Fig. 1. Left hemisphere of the cat from above showing points from which inhibition of the tonic vibration reflex (TVR) was obtained (on left) compared with origin of the pyramidal tract (on right). On left, the large squares indicate total inhibition of TVR, large round dots partial inhibition and small dots no inhibition (reprinted from Ashby et al., 1972). On right, cortical spike potentials elicited by antidromic stimulation of the medullary pyramid are indicated by large dots (consistent responses) and small dots (variable responses). (Reprinted from Lance and Manning, 1954). The left figure is reproduced by courtesy of the editor of Brain, and the right by courtesy of the editor of the Journal of Physiology.

Neurological Centre since no academic appointment was available. It was not until it was announced that a new medical school was to be started at the University of New South Wales that I saw the opportunity to establish a research laboratory for clinical neurology in Sydney. To gain further experience I went to Boston as a Lilly Overseas Fellow in 1960 to work with Professor Raymond Adams. In the course of an exciting year at the Massachusetts General Hospital, I investigated the basis of myoclonic jerking and akinetic periods in post-hypoxic myoclonus (Lance and Adams, 1963) and the mechanisms of tremor and cogwheel rigidity in Parkinson's disease (Lance et al., 1963). In September 1961 I returned to Sydney as neurologist to The Prince Henry and Prince of Wales Hospitals, the foundation teaching hospitals of the new medical school of the University of New South Wales. The former had shrunk over the years to a hospital of 200 beds, of which half were devoted to infectious disease, and the latter was a collection of wooden huts dating back to the first world war, arranged behind a gracious stone quadrangle built in 1856 as a home for foundlings, 'The Asylum for Destitute Children'. The task of developing a new medical school and modern teaching hospitals from such an inauspicious beginning was challenging rather than daunting.

Reflex Irradiation

The first research programme undertaken at The Prince Henry Hospital was the 'irradiation of reflexes', the reflex contraction of muscles remote from the point of

percussion, such as the crossed adductor jerk. Sherrington (1898) had shown that the crossed adductor jerk persisted after longitudinal section of the spinal cord but disappeared when dorsal roots were severed on the side of contraction, opposite to the point of percussion. He considered that the jar excited afferent fibres in the region of the dorsal root ganglion. Wartenberg (1944a,b) reiterated that 'multiple reflexes may arise from the purely mechanical transmission of the concussion'. In spite of these observations, the view still persisted that reflex irradiation arose from afferent impulses being disseminated through some hyperexcitable network in the spinal cord. Experiments in our laboratory using procaine infiltration of muscle bellies, ischaemic blockade of peripheral nerves and measurement of the velocity of the vibration wave set up by percussion, showed that the vibration wave radiating from the point of percussion stimulated receptors in the muscles traversed by the vibration wave, thereby initiating a reflex contraction in those muscles the reflex arcs of which were intact (Lance, 1965; Lance and de Gail, 1965). The propagation of vibration along a taut tendon and muscle fibre is probably the mechanism of production of a normal tendon jerk as well as signs of hyperreflexia such as reflex irradiation, the Hoffman sign and the 'inverted radial jerk' (Lance and McLeod, 1981).

Tonic Vibration Reflex (TVR) and the Supraspinal Control of Muscle Tone

The next step was to try to elicit a tendon jerk by applying a vibrator to a muscle belly instead of percussing the tendon. To my surprise, the application of a physiotherapy vibrator to muscle evoked a slowly augmenting tonic contraction of that muscle (Lance, 1965). If tendon jerks were being elicited at the time the vibrator

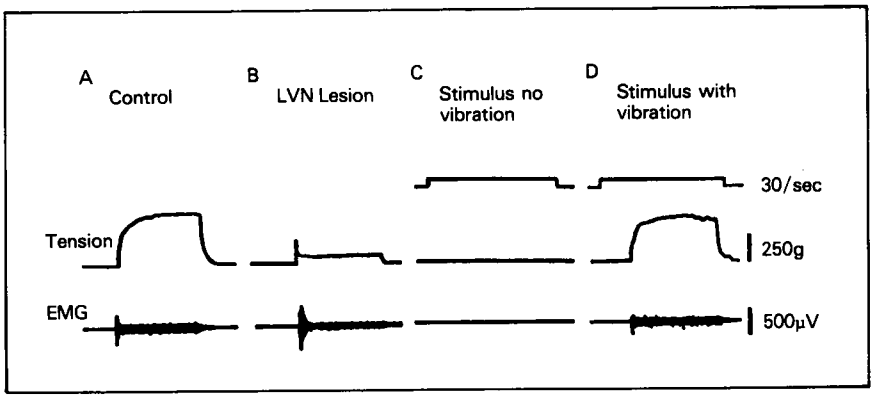

Fig. 2. Restoration of TVR by stimulation of lateral vestibulospinal tract after ablation of the lateral vestibular nucleus. After the ablation, stimulation of vestibulospinal fibres (C) does not evoke muscle contraction but when tendo Achillis is stimulated during vibration (D) the TVR is recorded at the control amplitude. Reprinted from Gillies et al. (1971a) by courtesy of the editor of the Journal of Neurophysiology.

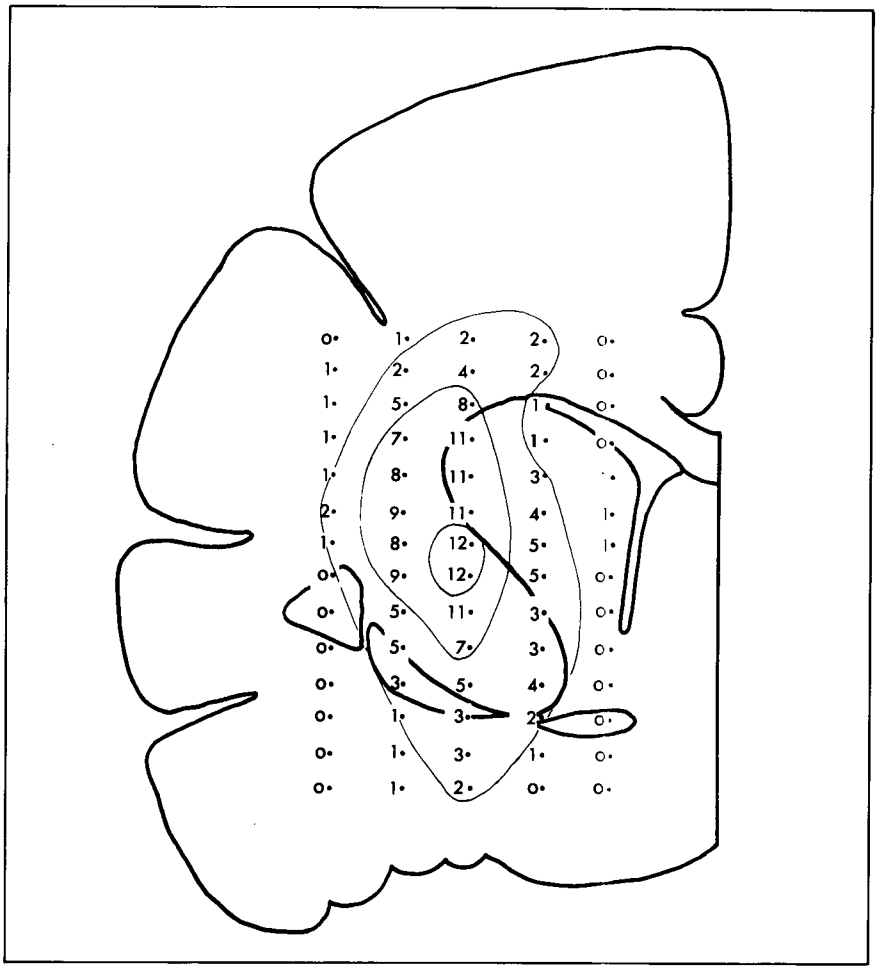

Fig. 3. Cross-section of the internal capsule of the cat, showing the path of corticoreticular fibres potentiating brain stem inhibition of the TVR. The diagram is based on experiments in 15 cats; the numerals indicate the number of animals in which inhibition of the TVR was obtained from each point. Reprinted from Ashby et al. (1972) by courtesy of the editor of Brain.

was applied, these diminished in amplitude or were abolished by the vibration (Lance, 1965; de Gail et al., 1966). It thus appeared that vibration produced a tonic reflex while suppressing phasic reflexes (Lance et al., 1966). The production of a tonic muscle contraction by vibration was reported at about the same time independently by Hagbarth and Eklund (1965). This led to correspondence between our group and the workers in Uppsala, then subsequently to reciprocal visits with a resulting happy collaboration in elucidating the mechanism and applications of the TVR. The TVR is brought about by vibration stimulating the muscle spindle, predominantly the prim-

ary endings, so that volleys of impulses are set up in the 1a afferent fibres which traverse the stretch reflex arc to cause a sustained muscle contraction (Lance et al., 1973). For the first time, a means was available to test tonic mechanisms in normal human subjects, as well as in the intact animal, whereas previously an experimental animal had to be decerebrated to produce a tonic stretch reflex. The suppression of tendon jerks by vibration was later shown in our laboratory to be caused by presynaptic inhibition (Gillies et al., 1969). Muscle vibration suppresses the tendon jerks and H reflexes of spastic patients less than that of normal subjects (Lance et al., 1966; Burke and Ashby, 1972; Ashby et al., 1980), presumably because of diminished presynaptic inhibition in spasticity.

Our group has used the TVR extensively to study the control of tonic mechanisms in the cat. The TVR was shown to depend upon the integrity of the lateral vestibular nucleus and vestibulospinal tract (Gillies et al., 1971a). If the lateral vestibular nucleus was destroyed, the TVR of gastrocnemius-soleus virtually disappeared (fig. 2a,b). If the lateral vestibulospinal tract was then stimulated at the same time as the tendon of gastrocnemius-soleus was vibrated, the TVR reappeared (fig. 2c,d). It was found that stimulation of the lateral medullary reticular formation facilitated the TVR in the same manner as the vestibulospinal tract (Gillies et al., 1971b; Andrews et al., 1973) and that this facilitation could not be influenced in either direction by stimulation of the motor cortex. On the other hand, the ventromedial reticular formation of the medulla inhibited the TVR of gastrocnemius-soleus and this inhibition was consistently potentiated by simultaneous stimulation of the motor cortex in the areas illustrated in figure 1a (Andrews et al., 1973). The corticoreticular pathway responsible for 'driving' the medial medullary reticular formation and the inhibitory reticulospinal tract which arose from it was carefully mapped through the internal capsule and midbrain. It was found to lie in the medial part of the internal capsule (fig. 3) and to form a bundle in the midbrain just dorsal to the medial part of the cerebral peduncle (Ashby et al., 1972). Although the general principles of the control of muscle reflexes from the brain stem and motor cortex had been laid down by Magoun and Rhines (1974), our experiments confirmed the application of these principles to tonic reflexes and established for the first time the precise path of the corticoreticulospinal pathway responsible for the regulation of muscle tone by inhibiting segmental mechanisms. As a corollary, it follows that the increase in muscle tone which characterises a lesion of the 'upper motor neurone' is caused by the interruption of this corticoreticulospinal inhibitory pathway rather than a lesion of the pyramidal tract itself.

Studies of Spasticity in Cat and Man

In human patients with disease of the upper motor neurone, the resistance reflexly exerted by muscle increases approximately linearly in response to the velocity of stretch (Burke et al., 1970, 1971). This is in contrast to the rigidity of Parkinson's disease which has little dynamic component. In spasticity, once the stretching movement stops, there is little or no response to maintained stretch whereas a continuing reflex discharge (static response) may be seen in Parkinson's disease (Andrews et al.,

1972). During stretch of the quadriceps muscle in spastic patients (but not in those with Parkinson's disease), resistance suddenly melts away once a certain muscle length is attained, giving rise to the 'clasp-knife phenomenon'. Past the clasp-knife point, the muscle is relatively or completely hypotonic so that the knee-jerk may actually be pendular in a spastic patient if the legs are dangling over the edge of an examination couch. In the hamstrings, the contrary effect is seen. As this flexor muscle is stretched, its stretch reflex increases with muscle length (Burke et al., 1971). It thus appears that there is a receptor within muscle responsive to muscle length, the reflex effects of which are released in spasticity, facilitating the stretch reflex in flexors and diminishing it in extensors. These reflex effects continue as long as muscle stretch is continued, so that they cannot be attributed to Golgi tendon organs and their group 1b afferent pathways since tendon organs are in series with muscle fibres and discharge selectively while the relevant muscles are actively contracting (Houk and Henneman, 1967). The opposing reflex effects on flexors and extensors are consistent with the responses to group II afferents which discharge in response to increasing muscle length, maintain their discharge as long as the muscle is stretched, and facilitate flexors while inhibiting extensors through the flexor reflex afferent (FRA) pathways (Burke and Lance, 1973). Burke et al. (1972) demonstrated that a decerebrate cat, in which the stretch reflex of quadriceps is *increased* as the muscle lengthens, can be transformed into a spastic cat in which the quadriceps stretch reflex is *diminished* as the muscle lengthens (clasp-knife phenomenon) by a lesion in the dorsolateral quadrant of the spinal cord. Such a lesion sections the dorsal reticulospinal system (Lundberg, 1975) which normally inhibits the central effects of flexor afferents, thereby releasing flexor reflexes and permitting the clasp-knife effect to take place. Impairment of this pathway is almost certainly responsible for flexor spasms in the paraplegic patient and other fractional manifestations of flexor reflexes such as the Babinski response since extension of the great toe is a part of a total flexion movement of the lower limb. These physical signs are not observed in Parkinson's disease because flexor reflexes remain under the control of the brain stem. There is evidence that the central effects of flexor reflex afferents may be reversed in decerebrate rigidity so that the stretch reflex of extensor muscles is increased as muscle length increases, emphasizing the difference between this condition and spasticity (Matthews, 1969).

The release of flexor reflexes in spasticity can also be demonstrated by studying H reflexes in man. In spasticity, the H reflex can be elicited in tibialis anterior (a flexor muscle) as well as in gastrocnemius-soleus (an extensor muscle). Stretching of tibialis *increases* the amplitude of the H reflex in that muscle and stretching the gastrocnemius-soleus *diminishes* the H reflex in that muscle (Burke et al., 1971) [fig. 4], thus confirming the release of group II afferent effects in spasticity.

Conclusions about the Signs of an 'Upper Neurone Lesion'

The stretch reflex in man is potentiated by the lateral vestibular nucleus via the lateral vestibulospinal tract and by the lateral medullary reticular formation via the facilitatory reticulospinal tract, neither of which is under direct cortical control. Modulation of muscle tone by the motor cortex is achieved through the cor-

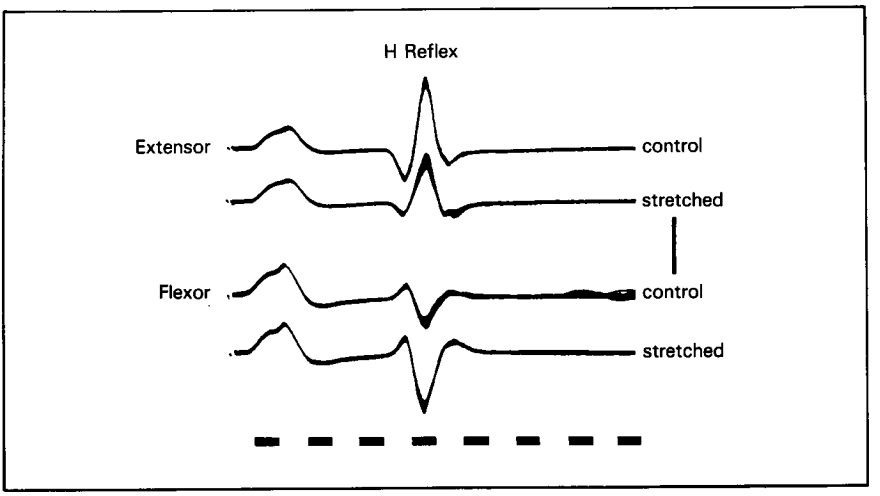

Fig. 4. The contrasting effect of muscle length on the H reflex of flexor and extensor muscles in spasticity. The upper 2 traces show *diminution* of the H reflex of gastrocnemius-soleus as that muscle is stretched. The lower 2 traces show *increase* of the H reflex of tibialis anterior as it is stretched. Time marker 100/sec. Reprinted from Burke et al. (1971) by courtesy of the editors of Archives of Neurology.

ticoreticulospinal tract which accompanies the pyramidal tract through its course, occupying the medial part of the internal capsule and of the midbrain just dorsal to the cerebral peduncle. The corticoreticular connection acts by enhancing the dampening effect exerted by the medial medullary reticular formation on the stretch reflex via the inhibitory reticulospinal tract. Damage to the corticoreticulospinal tract in any part of its course releases the stretch reflex, accounting for a dynamic increase in resistance to muscle stretch ('spasticity'), increased tendon jerks, the irradiation of reflexes and clonus. If, in addition, the control of flexor reflex afferent pathways from the brain stem via the dorsal reticulospinal system is impaired, the clasp-knife phenomenon, flexor spasms and the Babinski response may appear.

The young child, when first standing erect, is demonstrating the control of segmental mechanisms by the brain stem inhibiting flexor reflexes and facilitating extensor stretch reflexes in the lower limbs, while the upper limbs are flexed to oppose the force of gravity. For useful movement, including walking, the pyramidal tract has to break up this standing posture, by extending and abducting the upper limbs and flexing the lower limbs. For this reason the pattern of weakness in a pyramidal lesion comprises weakness of extensors and abductors in the upper limbs and of flexors in the lower limbs. Loss of phasic pyramidal function is manifested by impaired dexterity in skilled movements, particularly those involving rapid contraction of distal muscles. The upper motor neurone lesion seen clinically can thus be understood in terms of loss of tonic and phasic functions of the pyramidal tract and loss of the inhibitory effect of the corticoreticulospinal tract which accompanies the pyramidal fibres through brain stem to spinal cord.

Summary

The author's interest in the motor system is traced over a period of 30 years. Early studies on the cat pyramidal tract proved to be of relevance to later work on the control of muscle tone by brain stem and cortical mechanisms. Application of physiological methods disclosed fundamental differences between the increased tone of Parkinson's disease, spasticity and decerebrate rigidity. These differences depend upon the extent to which dynamic and static stretch reflexes are released, and whether the control effects of flexor reflex afferents remain under the control of the brain stem (as in Parkinson's disease), are released (as in spasticity) or even reversed (as in decerebrate rigidity).

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Hypotensive Central Spinal Cord Infarction: A Clinicopathological Study of 3 Cases of Aortic Disease

P.C. Blumbergs, D. Chin† and J.P. Rice†*

Interference with aortic blood flow has long been recognised as a cause of paraplegia. Thus, surgical occlusion (Adams and van Geertruyden, 1956; Beattie et al., 1953; Ekstrom, 1952; Hogan and Romanul, 1966), resection of abdominal aortic aneurysm (Mehrez et al., 1962), thrombosis of the aorta (Cook, 1959; Rudar et al., 1962), aortic trauma (Hughes, 1964) and dissecting aneurysm of the aorta (Herrick and Mills, 1971; Hill and Vasquez, 1962; Kalischer, 1914; Kepes, 1965; Moersch and Sayre, 1950; Reitter, 1916; Schwarz et al., 1950; Scott and Sancetta, 1949; Thompson, 1956; Tuohy et al., 1941; Weisman and Adams, 1944) have all resulted in pathologically confirmed spinal cord infarction.

The present 3 cases of aortic disease demonstrate that, in addition, systemic hypotension plays a major contributing role to the pattern and extent of spinal cord infarction.

Case Reports

Case 1

(Reproduced with the permission of the publisher of Journal of Neurology, Neurosurgery and Psychiatry. Blumbergs and Byrne, 1980).

A 68-year-old caucasian male underwent quadruple coronary artery saphenous vein by-pass grafts for relief of persistent angina pectoris after an acute inferior myocardial infarction. The postoperative course was uneventful, except for an episode of exertional angina 3 weeks after the operation, followed 1 week later by the sudden development of severe dyspnoea and circulatory collapse. For 10 hours the patient remained severely hypotensive with systolic blood pressures ranging from 70 to 90mm Hg. At this

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stage a dense flaccid paraparesis was noted with a spinothalamic sensory level on the right at T12 and on the left at T7. Vibration sense was absent up to the iliac crest. Joint position sense was absent in the toes. Gross movements could be appreciated at the ankles but frequent mistakes were made. Over the next 16 days the blood pressure stabilised to about 110mm Hg systolic. The neurological signs remained unchanged. Terminally the patient developed severe central chest pain and died a few hours later.

At autopsy a localised dissection of the ascending aorta was found, which had extended into the right atrial wall to produce a large intramural haematoma compressing the proximal superior vena cava. An intimal tear was present in the posterior wall of the aorta beginning at the posterior margin of the uppermost vein graft and descending to the level of the aortic valve cusps. Histological examination at the margins of the haematoma showed organising granulation tissue consistent with rupture 16 days earlier.

All the grafts were patent. The coronary arteries showed severe atheroma and the right coronary artery was thrombosed proximal to the skip graft. A 10mm diameter, recently healed infarct was present in the posterior wall of the left ventricle. The aorta was severely involved with ulcerative atheroma. The intercostal arteries were normal. The ostia of the lumbar and ilio-lumbar segmental arteries were severely stenosed by atheroma, but none was completely occluded.

Neuropathology

The brain was normal. The medullary arteries including the great anterior medullary artery of Adamkiewicz (left eleventh thoracic anterior nerve roots) and the anterior median and posterior spinal arteries were patent. Spinal cord examination showed central grey matter necrosis extending from T8 to S5 with maximal involvement at L4-S5 levels (fig. 1), where there was symmetrical total loss of neurones and neuroglia and replacement by foamy macrophages. In segments T11 to L3 there was partial sparing of grey commisures and in T8-T10 the necrosis was limited to the posterior horns. The white matter was normal. The intrinsic spinal cord vessels were all patent.

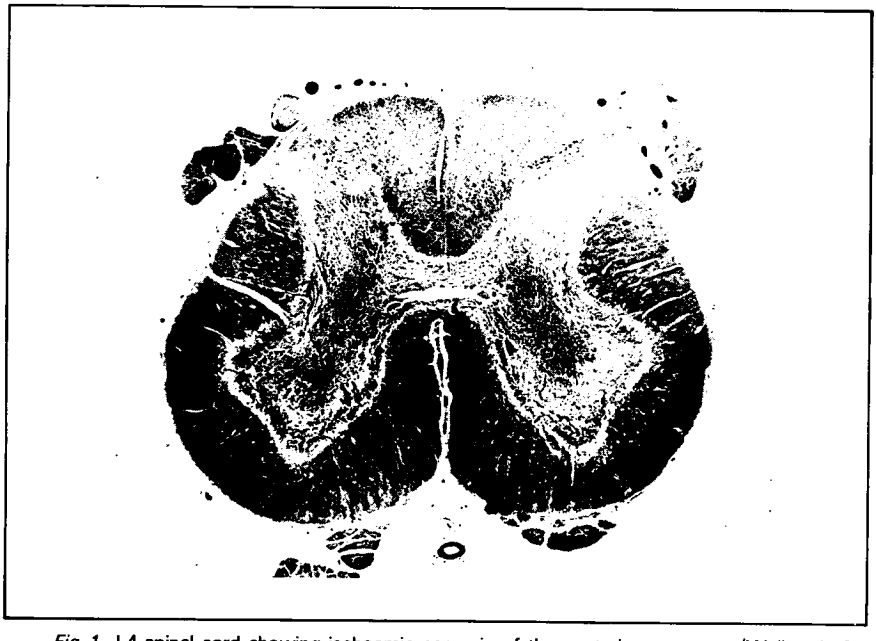

Fig. 1. L4 spinal cord showing ischaemic necrosis of the central grey matter (Weil stain for myelin).

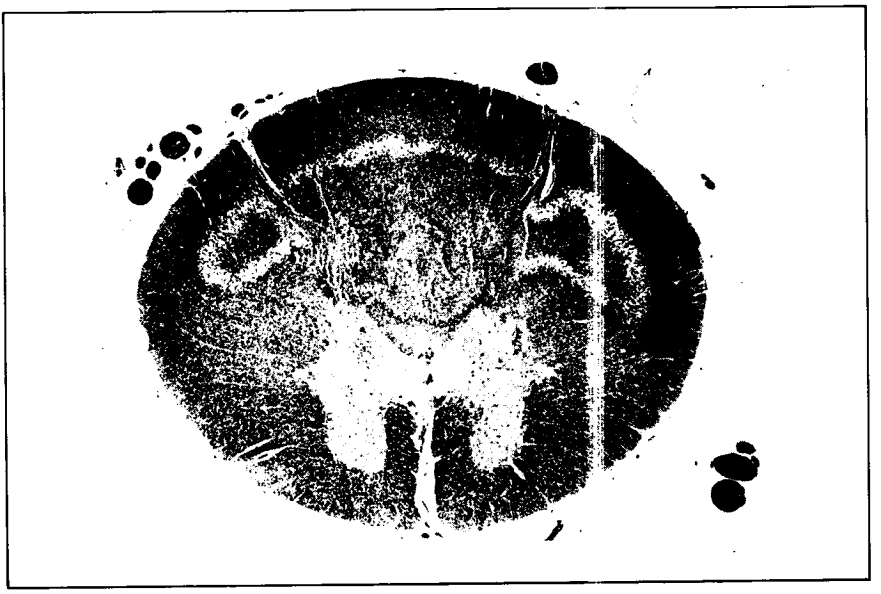

Fig. 2. T3 spinal cord showing watershed infarction at the junction of anterior and posterior spinal arterial blood supply (Weil stain for myelin).

Case 2

A 71-year-old previously healthy caucasian male suddenly developed severe low chest pain radiating into the back and down both legs. 10 minutes later he noticed numbness and weakness of the legs which progressed to complete paralysis over the next 30 minutes. On arrival at the Royal Adelaide Hospital, his blood pressure was 85/50mm Hg, his pulse was 80/min regular and there were no cardiac or carotid bruits. The carotid pulses were equal. Both femoral arteries were weakly palpable. Neurological examination showed complete flaccid paraplegia with absent lower limb tendon reflexes and plantar responses. There was dense sensory loss to all modalities below T4 level. The upper limbs were normal. Resuscitation, including isoprenaline infusion, resulted about 10 hours later in stabilisation of the BP at 110mm Hg systolic. An arch aortogram showed an extensive aortic dissection with preservation of the renal arteries. He died suddenly on the third day of his illness.

At autopsy, a dissecting aortic aneurysm extended distally without re-entry to the level of the common iliac arteries, from an intimal circumferential tear just proximal to the left subclavian artery. Proximally the dissection extended along the aortic root to rupture into the pericardial sac with resultant cardiac tamponade. The intercostal, lumbar, ilio-lumbar and renal arteries were structurally intact. The aorta was severely involved with ulcerative atheroma.

Neuropathology

The brain was normal. There was softening and swelling of the T4-T11 segments of the spinal cord. The medullary arteries including the great anterior medullary artery of Adamkiewicz and the anterior median and posterior spinal arteries were patent. Microscopic examination of transverse sections of the spinal cord showed a butterfly area of recent ischaemic necrosis of the posterior grey matter and adjacent gracile and cuneate fasciculi (fig. 2) of the T3 segment. The marginal white matter was preserved. The T4 and T5 segments showed central ischaemic necrosis of both grey and white matter with preservation of the marginal white matter and at T6 level there was almost complete necrosis of all white and grey matter. All the segments below T6 showed severe but subtotal 'acute ischaemic cell change' of the anterior and posterior horn neurones. There was severe oedema of the white matter of T7-T12 segments particularly

involving the posterior columns. The intramedullary and extramedullary arteries and arterioles were histologically patent.

Case 3

A 76-year-old caucasian male suddenly developed severe abdominal pain closely followed by circulatory collapse and inability to move the lower limbs. On arrival at the Royal Adelaide Hospital 4 1/2 hours later he was in shock with blood pressure of 40mm Hg and tachycardia of 120/min. A large pulsatile abdominal aortic aneurysm was palpable. For the next 7 1/2 hours he remained severely hypotensive with his blood pressure ranging from 0 to 90mm Hg despite vigorous resuscitation. Neurological examination showed complete flaccid paraplegia with absent lower limb tendon reflexes and plantar responses. A clear spinothalamic level was present at T9-T10 level and there was loss of proprioception in the feet and toes. 13 1/2 hours after onset a ruptured fusiform atherosclerotic abdominal aortic aneurysm, just above the aortic bifurcation, was resected and replaced with a Dacron graft. The inferior mesenteric artery was anastomosed to the graft. The aneurysm had ruptured predominantly into the retroperitoneum. The renal arteries were patent.

The patient was moribund preoperatively with an unrecordable blood pressure. Postoperatively there was no improvement in the paraplegia despite initial treatment with hyperbaric oxygen. He died 16 days later from respiratory failure.

At autopsy the Dacron aortic graft and inferior mesenteric artery anastomosis were patent. The remaining aorta showed severe ulcerative atheroma. The intercostal and renal arteries were patent. The lumbar arteries were sacrificed during the operation.

Neuropathology

Examination of the brain showed small recent cerebellar 'watershed' infarcts and several small old lacunes of the central white matter of the cerebral hemispheres. Macroscopic examination of the spinal cord showed recent haemorrhagic infarction of the central grey matter extending from T10 to the conus

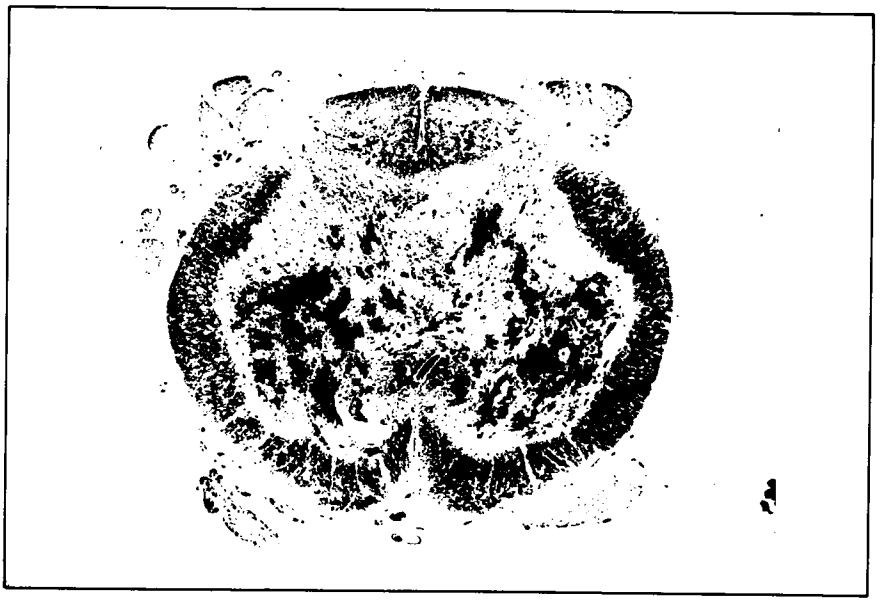

Fig. 3. Spinal cord below T10, showing haemorrhagic infarction of central grey matter and ischaemic infarction of adjacent white matter (Weil stain for myelin).

medullaris. The medullary arteries including the great anterior medullary artery of Adamkiewicz and the anterior median and posterior spinal arteries were patent. Microscopic examination of the spinal cord showed haemorrhagic infarction of the central grey matter below T10 level (fig. 3) and ischaemic infarction of much of the adjacent white matter maximal in the L2-S1 segments where there was almost complete infarction of all the spinal cord. The intrinsic spinal cord vessels were all patent.

Discussion

Spinal cord blood flow is a function of mean arterial blood pressure and peripheral vascular resistance. Autoregulation similar to that of cerebral blood flow is believed to exist (Osterholm, 1974) such that no alteration in blood flow occurs with slow reduction of the systemic blood pressure to half normal values. This may be the explanation for the apparent rarity of spinal cord damage in states of hypotension. Zülch (1954) suggested that zones of particular vulnerability exist within the spinal cord during states of circulatory arrest and prolonged hypotension. These border-zone areas (Grenzzonen) exist at the junction of different vascular territories and in the transverse plane are located between the area of supply of the central branches of the anterior and posterior spinal arteries. In the longitudinal plane the boundary zones are at T12-L1 and especially T4 level at the junction of the radicular vessels of the vertebral arteries and aorta. In contrast, Gruner and Lapresle (1962) claimed that the most vulnerable areas are those most richly vascularised and experimental studies have shown that the central grey matter of the lumbar cord has a very dense capillary network (Fairholm and Turnbull, 1971) and has the highest blood flow of all within the spinal cord (Flohr et al., 1971). In support of this latter concept, Gilles and Nag (1971) described a pattern of subtotal symmetrical necrosis of the anterior grey matter of the caudal spinal cord in 6 young children after cardiac arrest. Schneider et al. (1973) described similar subtotal necrosis of the grey matter in 4 adults after circulatory arrest. This apparent vulnerability of the central grey matter of the lumbosacral spinal cord was also observed by Azzarelli and Roessmann (1977) who studied the spinal cords of 16 patients who had suffered from 'anoxic' episodes. A thoracic central cord infarction (T3-T5 segments) was described by Zülch and Behrend (1963) in a 63-year-old woman who died after multiple Stokes-Adams' attacks. Another case in which hypotension may have been important in producing spinal infarction is that reported by Madow and Alpers (1949) in which T5-T9 infarction occurred during prolonged hypotension after myocardial infarction. The authors discussed this possibility but concluded that embolism was a more likely cause in their case.

All 3 of our cases were characterised by severe prolonged hypotension but all were complicated by aortic vessel disease. Hypotension is most clearly implicated in the first case where an unusual localised dissection of the ascending aorta, not interfering structurally with any of the spinal cord vasculature, resulted in selective grey matter infarction of the caudal spinal cord. Selective central grey matter necrosis of the lower thoracic and lumbosacral cord has been previously documented in dissecting aortic aneurysms (Moersch and Sayre, 1950; Kepes, 1965; Herrick and Mills, 1971), related to severance or occlusion of intercostal and lumbar arteries. Selective

central grey matter infarction has also been noted in a case where the thoracic aorta was surgically clamped (Beattie et al., 1953) and secondary to cholesterol emboli from an atheromatous aorta (Herrick and Mills, 1971). Review of the literature of spinal cord injury in dissecting aortic aneurysms suggests that a whole spectrum of spinal cord damage exists from no lesions at all (despite severance of intercostal and lumbar arteries) to massive necrosis of the cord, which in one case was even associated with infarction of vertebral bodies (Hill and Vasquez, 1962).

In the second case an extensive aortic dissection compressed but did not physically rupture any of the intercostal or lumbar segmental feeders. The caudal lumbosacral cord showed subtotal central grey matter ischaemic damage and a striking 'watershed' infarction at the boundary zone of the anterior and posterior intramedullary circulation of the T3 segment. Central infarction of T4-T6 segments was probably related to compromise of the local segmental extramedullary circulation in addition to the severe prolonged hypotension. Thus this case demonstrates a combination of both patterns of hypotensive cord damage, namely the 'watershed' infarct described by Zülch (1954) and the vulnerability of the caudal central grey matter.

The third case is unusual in that the extensive caudal spinal cord infarction showed haemorrhages limited to the central grey matter and was the result of a ruptured infrarenal abdominal atherosclerotic aneurysm. Adams and van Geertruyden (1956) in their comprehensive analysis of the neurological complications of aortic surgery concluded that temporary blockage of the abdominal aorta distal to the renal arteries did not result in ischaemic injury to the spinal cord. Subsequently Hara and Lipin (1960) reported a clinical study in which resection of an infrarenal aortic aneurysm resulted in urinary retention and faecal incontinence. This was followed by the report of 2 cases with pathologically confirmed spinal cord infarction (Mehrez et al., 1962) and a report by Hogan and Romanul (1966) in which central lumbosacral cord infarction followed resection of an infrarenal aneurysm during which the aorta and the artery of Adamkiewicz were clamped for a prolonged period of time. Systemic hypotension was also present in all these cases. In our case the collateral blood flow was inadequate to prevent infarction of the caudal spinal cord despite the high take-off and anatomical preservation of the artery of Adamkiewicz. We believe that the major factor leading to this perfusion failure was the state of prolonged hypotension. The haemorrhagic component was produced when the circulation stabilised and blood flow once more occurred through the anatomically intact collateral circulation.

In conclusion, these cases indicate that systemic blood pressure is of vital importance in the spinal cord circulation particularly when combined with abnormalities of the collateral spinal cord circulation. Perfusion failure results in 2 basic patterns of spinal cord damage. In total sudden circulatory arrest the central grey matter of the caudal spinal cord is most vulnerable and in states of hypotension where some perfusion of the spinal cord is still present there may be additional ischaemic damage in the boundary zone areas, as described by Zülch (1954). In an individual case, the pattern may be modified by a number of other factors, the most important of which are the individual anatomical variations in the extramedullary collateral blood supply and the number, site and nature of the lesions affecting the blood vessels of the spinal cord.

Summary

Neuropathological studies of 3 cases of aortic disease, complicated by severe prolonged hypotension, revealed a spectrum of central spinal cord infarction not corresponding to a specific arterial territory. The findings support the concept that the central grey matter of the caudal spinal cord is most vulnerable to oligaemic hypoxia. Variation in the longitudinal distribution of ischaemic damage in the individual case depends primarily on the anatomical pattern of the spinal arterial net and on the nature and distribution of the vascular pathology.

Acknowledgements

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A Comparison of Australian Caucasian and Aboriginal Brain Weights

*C. Harper and L. Mina**

Normal ranges of brain weights for various races and populations are available in the literature. Such figures are not available for the Australian population although it is reasonable to expect that they would be similar to analyses from European studies. More importantly, no figures exist concerning brain weights of the Australian Aboriginal population. In 1868 it was suggested by Davis, from studies of Aboriginal skulls, that, 'they stand apart from the people of all the other great divisions of the globe by possessing the smallest brain'.

The Department of Neuropathology in Royal Perth Hospital functions as the regional centre for neuropathology in Western Australia and has access to neuropathological material from the major hospitals in Perth and more importantly to forensic material supplied by the Perth City Coroner's Department from all over the state. This latter material provides many normal brains, which has made possible a compilation of normal brain weight statistics for both the Caucasian and Aboriginal subpopulations and a comparison of these groups.

Materials and Methods

Cases for the study were selected from about 6000 autopsy records of the Department of Neuropathology, Royal Perth Hospital, between 1971 and 1979. Cases were only included if the brain was considered normal at autopsy, after sectioning the fixed organ and after examination of histological sections.

The 791 brains that comprised the series were derived from autopsies performed by the Perth City Coroner's Department (58%) and the Royal Perth Hospital (42%). All brains were weighed at autopsy immediately after removal. The dura mater was

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Table I. Sex, age and mean brain weight at autopsy for Caucasians

Sex	Age group	Number of cases	Mean weight (g)	SD[1]
M	21 to 30	41	1435	127
M	31 to 40	47	1433	128
M	41 to 50	51	1422	145
M	51 to 60	80	1441	150
M	61 to 70	120	1407	142
M	71 to 80	78	1379	115
M	81 to 90	25	1329	127
F	21 to 30	21	1283	118
F	31 to 40	20	1279	112
F	41 to 50	31	1258	115
F	51 to 60	44	1263	100
F	61 to 70	79	1258	122
F	71 to 80	70	1216	107
F	81 to 90	21	1208	140

1 SD = Standard deviation.

removed before weighing on balances which are checked at regular intervals and have an accuracy of ± 5g. The brains were then fixed in 10% formol-saline for about 2 weeks. After external examination, the cerebellum and brain stem were removed and sectioned in the horizontal plane and the cerebral hemispheres were sectioned in 10mm slices in the coronal plane. The majority of the brains were examined histologically even in the absence of macroscopic abnormalities. With this type of screening, it was considered that any significant neurological diseases which could have altered brain weight would have been excluded.

From the autopsy report on each case, the following data were extracted: age, sex, body height and weight, race and the brain weights at autopsy (fresh) and after

Table II. Sex, age and mean brain weights at autopsy for Aboriginals

Sex	Age group	Number of cases	Mean weight (g)	SD[1]
M	21 to 30	8	1256	127
M	31 to 40	7	1274	62
M	41 to 50	5	1161	140
M	51 to 60	12	1247	120
M	61 to 70	4	1181	96
F	21 to 30	11	1096	71
F	31 to 40	5	1171	119
F	41 to 50	7	1115	49
F	51 to 60	4	1118	18

1 SD = Standard deviation.

Table III. Sex, age, race and mean brain weight at autopsy

Sex	Age group	Race	Number of cases	Mean weight (g)	SD[1]
M	21 to 70	Caucasian	339	1424	141
M	21 to 70	Aboriginal	36	1235	114
F	21 to 60	Caucasian	116	1268	109
F	21 to 60	Aboriginal	27	1118	74

1 SD = Standard deviation.

fixation. Cases were subdivided according to age, sex and race as shown in tables I and II. All results were analysed separately for fresh and fixed brain weights. As fixation added another variable, the results in this paper refer only to fresh brain weights.

There were 728 Caucasians and 63 Aboriginals in the series. Statistical comparisons were made between the brain weights of the Caucasians and the Aboriginals (tables III and IV). It is known that brain weight relates to body height (Ho et al., 1980). To minimise the effect of this variable in the comparison of Caucasian and Aboriginal brain weights, 63 age and height matched Caucasians (age — within the same decade, height — equal ± 2cm) were selected from the 728 Caucasian cases for a paired statistical analysis with the 63 Aboriginal brains (table V).

All statistics were analysed using a Hewlett-Packard calculator and significance of results were determined using Student's 't' test for the unpaired (table IV) and paired (table V) groups.

Results

The analysis of normal brain weights of 728 Caucasians and 63 Aboriginals are summarised in tables I and II and are represented diagrammatically in figures 1 and 2.

Results (table III) indicate that Caucasian and Aboriginal men had higher mean brain weights than women of the corresponding racial groups. The mean difference between the male and female brain weights was 156g for Caucasians and 117g for Aboriginals. Caucasian women had a higher mean brain weight than Aboriginal men, but the difference of 33g was not statistically significant.

There was a tendency for the mean brain weights of both men and women to decrease in later life, particularly in the eighth and ninth decades (figs. 1 and 2). Standard deviations (tables I and II) were high, indicating a very wide range of normal brain weights with some overlapping between all 4 groups. In male Caucasians, the normal brain weight varied from 990g (60 to 70 years) to 1850g (41 to 50 years). Female Caucasian brain weights varied from 970g (71 to 80 years) to 1652g (61 to

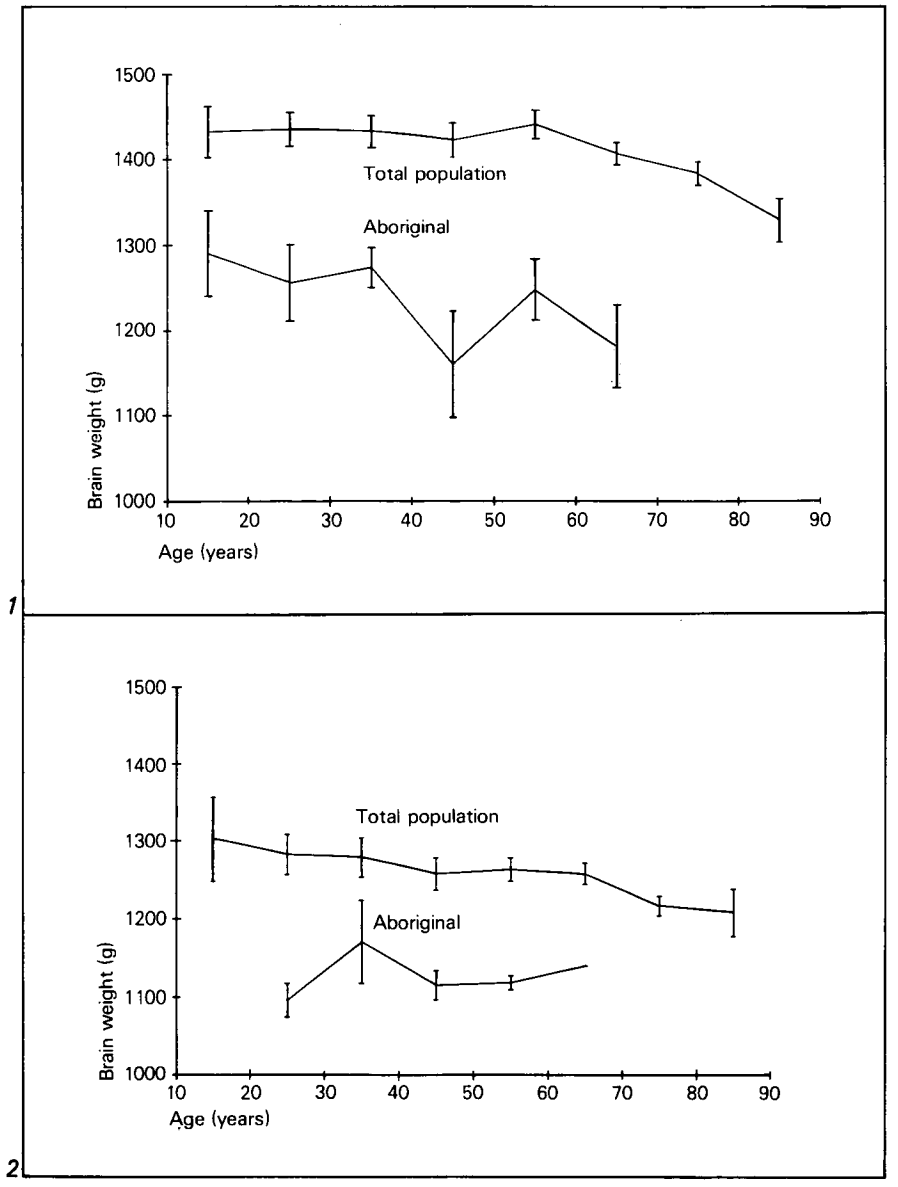

Fig. 1. Comparisons of the normal mean brain weights of Caucasian males (total population) and Aboriginal males as derived from tables I and II. The bars represent the standard errors of the means for each 10-year group.

Fig. 2. Comparisons of the normal mean brain weights of Caucasian females (total population) and Aboriginal females as derived from tables I and II. The bars represent the standard errors of the means for each 10-year group.

Table IV. Statistical comparison of Caucasian and Aboriginal brain weights (unpaired groups)

Sex	Age group (years)	df[1]	t^2	Significance
M	21 to 70	373	7.78	$p < 0.001$
F	21 to 60	141	6.79	$p < 0.001$

1 df = degrees of freedom.
2 Student's *t* test.

Table V. Statistical comparison of Caucasian and Aboriginal brain weights (paired samples, matched for age and height)

Sex	Age group (years)	df[1]	t^2	Significance
M	21-70	35	8.94	$p < 0.001$
F	21-60	26	5.06	$p < 0.001$

1 df = degrees of freedom.
2 Student's *t* test.

70 years). Male Aboriginal brain weights varied from 970g (41 to 50 years) to 1488g (31 to 40 years) and female Aboriginal brain weights varied from 946g (21 to 30 years) to 1327g (31 to 40 years).

Brain weights were generally, although not invariably, higher after fixation in 10% formol-saline for about 2 weeks. The mean fixed brain weight for all 728 cases was 7g heavier than the mean fresh brain weight. This is in keeping with the study by Frontera (1953) who showed that, using 10% formol-saline as the fixative, the brain increases in weight initially and then slowly its weight decreases.

As shown in tables IV and V, statistical comparisons were made between Aboriginal brain weights and Caucasian brain weights for both sexes using the total Caucasian population in an unpaired analysis (table IV) and using 63 age and height matched Caucasians in a paired statistical analysis (table V). The mean male Aboriginal brain weight was 189g less than for Caucasians and the mean female Aboriginal brain weight was 150g less than for Caucasians. In both the paired and unpaired analyses, there was a highly significant difference ($p < 0.001$) between the brain weights of Caucasians and Australian Aboriginals of each sex.

Discussion

Data concerning normal brain weights have been accumulating for over 130 years. However, many of the studies are difficult to compare because of variations in

Table VI. Normal mean brain weights (in g) from published studies

Reference	White males	Black males	White females	Black females
Harper and Mina (present study)	1424	1235[1]	1268	1118[1]
Ho et al. (1980)	1392	1286[2]	1252	1158[2]
Miller and Corsellis (1977)	1424	—	1265	—
Tomlinson et al. (1968)	1460	—	1268	—
Pakkenberg and Voigt (1964)	1440	—	1282	—
Vint (1934)	—	1276[2]	—	—
Matiegka (1902)	1450	—	1306	—
Davis (1868)	1367	1214[1]	1229	1111[1]

1 Australian Aboriginals.
2 Negroes.

the collection and presentation of data. Table VI summarises the mean brain weights of 8 comparable studies, 3 of which include studies on Negroid or Aboriginal brains.

The mean brain weight of Caucasian males in the present analysis was 1424g. The mean weight in other studies has varied from 1367 to 1470g. The lowest figure of 1367g (Davis, 1868) could be explained on the basis of a secular increase in brain weight during the last century. Miller and Corsellis (1977) showed that the fresh brain weight of men increased by an average of 0.66g per year from a mean of 1372g in 1860 to 1424g in 1940. Female brain weights showed a similar but lesser rise with time. The mean brain weight of Caucasian females in our analysis was 1268g. Mean female brain weights are consistently lower than those of males, which presumably reflects the smaller body dimensions of females. Pakkenberg (1964) and Ho et al. (1980) both showed a positive relationship between brain weight and body height.

As in other studies, there was a progressive reduction in the mean brain weight of both males and females which is most evident after the seventh decade.

Studies concerning normal brain weights in various racial groups have included Negroes (Ho et al., 1980; Vint, 1934; Davis, 1868), and Asiatic races (Takahashi and Suzuki, 1961; Shibata, 1936; Davis, 1868). Tobias (1970) reviewed the literature on comparative studies of brain weights in various human populations and concluded that most of the studies were invalid. There is only scant reference to Australian Aboriginal brain weights (Davis, 1868). The mean brain weights of both male and female Negroes appears to be lower than for Caucasians (Ho et al., 1980). It should, however, be remembered that the standard deviations in all groups studied are large and there is a good deal of overlap between males and females of all racial groups. The Asiatic races have mean brain weights similar to Caucasians (Takahashi and Suzuki, 1961).

The Australian Aboriginal population is a minority group within the country, the most recent census (1976) indicating an Aboriginal population of only 161,000 in a total population of 13.5 million. As a result, it is difficult to accumulate large amounts of data. Nevertheless, careful screening of the cases should have ensured a true normal group. The mean brain weights calculated (males — 1235g, females —

1118g) correspond closely with the figures of Davis (1868) (males — 1214g, females — 1111g), but are slightly lower than the mean brain weights of Negroes (Ho et al., 1980) shown in table VI.

Comparative analyses between Caucasian and Aboriginal brain weights showed a highly significant difference ($p < 0.001$). The mean male Aboriginal brain weight was 189g less than the Caucasian and the mean female Aboriginal brain weight was 150g less. Even when compared with Caucasian cases matched for age and height, the Aboriginal brain were significantly lighter ($p < 0.001$). It should be emphasised that the standard deviations for these 4 groups were large with overlapping of the ranges of brain weights in the various subgroups studied.

The significance of the variations of mean brain weights in various racial groups is uncertain, but an awareness of the existence of the difference is important and ranges of normal values should be available for each race. In 1849 Morton published observations on the cranial capacities of skulls and showed that Negro skulls were smaller than Caucasian skulls. Unfortunately, some authors (Putnam, 1963) used this information to draw the erroneus conclusion that '. . . the Negro brain is lighter than the White and that this in turn indicates a lower average level of intelligence'.

Enormous variations in brain size may occur within the limits of normal function. Bismark, the creator of the German Reich, had a brain in the order of 2000g whereas Anatole France, the great French writer, had a brain weight of little more than 1000g. On the other hand, most neuropathologists will have seen brains weighing 2000g or more in patients with mental retardation.

The brain to body weight ratio has been cited as an indication of levels of intelligence in different species. Thus, the brain to body weight ratio in the rhinoceros is 1 : 3000 whereas in man it is 1 : 45 (Cobb, 1965). It is sobering to note that the ratio in the lowly house mouse is 1 : 40! There seems to be little, if any, relationship between brain weight and intelligence in any species.

Summary

The weights of normal brains obtained at autopsy from Royal Perth Hospital and the Perth City Coroner's Department during the last decade were reviewed. The analysis involved 728 Caucasian and 63 Aboriginal brains. The ages ranged from 21 to 90 years, but the Aboriginal group were generally younger than the Caucasian. All brains were examined in detail by the Neuropathology Department, Royal Perth Hospital. Brains with any significant macroscopic or microscopic abnormality were excluded from the analysis.

Statistical comparisons between the brain weights of the Caucasians and Aboriginal subpopulations show that Aboriginals had smaller brains than Caucasians. Even after correcting for body height, Caucasian brain weights were significantly heavier than Aboriginal brain weights. Results also showed that men had significantly higher mean brain weights than women of the same age. There was a tendency for the mean brain weight of both men and women to decrease in later life, particularly in the eighth and ninth decades. Ho et al. (1980) showed in their analysis of 1261 brains in the USA, that brain weight decreases from white males to black males

to white females to black females. The tendency in both this and the present investigation for the non-Caucasians to have smaller brains than the Caucasians warrants further study.

Acknowledgements

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Bilateral Optic Nerve Hypoplasia

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Hypoplasia of the optic nerve is a developmental anomaly involving the retina and the optic nerve. The classic clinical sign of the nerve hypoplasia is a subnormal diameter of the optic nerve head. The hypoplastic disc is commonly surrounded by a yellowish ring of approximately normal disc diameter, the peripapillary disc zone. Frequently there is increased pigmentation between the rim of the true nerve head and the outer margin of the peripapillary disc zone. At times the peripapillary region is confused with the nerve head and the hypoplasia goes unrecognised. Optic nerve hypoplasia may be diagnosed with confidence when the disc is one-third to half the normal size but there are some cases in which hypoplasia may occur in the presence of apparently normal-sized discs. First well-described in 1915, the condition was considered to be rare until early in the last decade when reports appeared in the ophthalmological literature describing series of 20 and 25 cases (Walton and Robb, 1970; Edwards and Layden, 1970).

Although De Morsier (1956) had first clearly suggested the important association between bilateral hypoplastic discs and cerebral malformation, in particular absence of the septum pellucidum (the septo-optic syndrome), it was not until 1970 that Hoyt and his colleagues described the association between bilateral optic nerve hypoplasia and hypopituitarism. In 3 of the cases reported by Hoyt et al. (1970), who were investigated by pneumoencephalography, the septum pellucidum was absent. However, subsequent reports have detailed cases of hypopituitarism in which the septum pellucidum was present (Billson, 1975; Patel et al., 1975) and in whom optic nerve hypoplasia was unilateral rather than bilateral (Patel et al., 1975).

Because case reports in the ophthalmological literature have tended to concern themselves only with the ophthalmic aspects of the condition, whereas reports in the general and neurological literature have concentrated on the septo-optic syndrome, a

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clear picture of the spectrum of clinical and neuroradiological abnormalities associated with bilateral hypoplasia of the optic nerves has not emerged. In the present report, 15 cases of bilateral optic nerve hypoplasia are described in order to demonstrate the varied associations of this abnormality.

Patients and Methods

At the Royal Alexandra Hospital for Children between 1971 and 1980, 15 patients were diagnosed as having bilateral optic nerve hypoplasia. The age at diagnosis varied from 4 days to 25 months (mean 5 months). Nine patients were first-born. Five presented with suspected blindness and 7 with abnormal eye movements — nystagmus or less commonly, squint. The other 3 came to attention because of fits or developmental delay.

Twelve of the patients were investigated by computerised axial tomography of the brain; 3 had pneumoencephalograms or ventriculograms.

The endocrinological investigations consisted of detailed evaluation of the pituitary-hypothalamic axis in 7 cases. Five others had normal growth rates and normal thyroid function tests and were therefore not more fully evaluated. One patient was growing normally but had no endocrine tests. Two others had such severe brain damage that full endocrine evaluation was not considered justified. Detailed endocrine tests included T_3 resin, T_4 serum thyroxine, free-thyroxine and TSH levels; arginine-insulin tolerance tests with growth hormone estimation; TRH and LHRH stimulation tests and serum cortisol estimations, sometimes with tetracosactrin stimulation.

Water deprivation tests with vasopressin injection were performed in 2 cases. The clinical, endocrinological and neuroradiological findings are summarised in table I. Formal psychometric evaluations were not performed, the assessment of intellect was based on clinical observation.

Results and Discussion

Clinical Features

1. Ophthalmic

As noted, ophthalmic disturbances were the presenting feature in 12 of the patients. All cases in the present series had severe visual defects ranging from total blindness to a measured acuity of 3/24 bilaterally. There was, however, a tendency for apparent improvement in vision with increasing age. Several children were thought to be blind in infancy but subsequently were found to have useful vision. The optic discs were bilaterally involved in all cases, with obvious reduction in disc size but there was often asymmetry of disc involvement. The colour of the disc varied from extremely pale to relatively normal in a few cases. In no case was accurate visual field charting possible.

Table I. Details of the present series of cases of optic nerve hypoplasia

Patient	Date of birth	Sex	Birth rank	Associated clinical features	Endocrine evaluation	Neuro-radiology	Intellectual development
1	5.4.69	F	1	Neonatal fits Growth retardation	GH TRH	Absent septum pellucidum	MR +
2	14.12.71	F	1		O (T normal)	Slight ventricular dilation Absent septum pellucidum	N
3	5.11.73	F	1	Neonatal sepsis Hypoglycaemic fits Growth retardation Portal hypertension Died aet. 4 yrs. Inhalation	GH	Absent septum pellucidum	MR +
4	13.3.74	F	1	Neonatal jaundice Development delay	DI PP LHRH	Absent septum pellucidum	MR + +
5	22.3.74	F	2	Growth retardation	GH A T TRH	N	MR +
6	30.8.74	F	3	Apnoeic spells Seizures Microcephaly Developmental delay Spasticity Died aet. 23 mths Pneumonia	O	Ventricular dilatation Left porencephaly	MR + +
7	7.12.74	F	1	Growth deceleration aet. 2yrs	N (LHRH)	N	N

8	22.12.75	M	1	Neonatal hypoglycaemia Micropenis Growth retardation	T TRF A	N	MR +
9	6.6.77	F	2		O	N	N
10	2.6.79	M	1		O (T normal)	N	N
11	16.6.79	F	Unknown, adopted	Infantile spasms Developmental delay	O (T normal)	Absent septum pellucidum	MR + +
12	7.12.79	M	6	Neonatal sepsis Developmental delay Micropenis	T TRH DI GH	Agenesis of corpus callosum	MR +
13	18.1.80	M	1	Microcephaly Seizures Spasticity Developmental delay	O (T normal)	Agenesis of corpus callosum Hypoplasia of cerebellum	MR + +
14	14.6.80	F	1	Dysmaturity Irritability Microcephaly Spasticity	O (T normal)	Moderate ventricular dilatation	MR +
15	26.8.80	M	4	Neonatal apnoea and seizures Developmental delay	O	Hydrocephalus Porencephaly Agenesis of corpus callosum	MR + +

A = Abnormal adrenal function studies
GH = Growth hormone disturbance
T = Thyroid deficiency
TRH = Abnormality of thyroid releasing hormone test
LHRF = Abnormality of luteinising hormone releasing hormone test
DI = Diabetes insipidus
PP = Precocious puberty

N = Normal
O = Not investigated in detail
MR = Mental retardation
+ = Mild
+ + = Moderate or severe
(T normal) = Normal thyroid function test

According to the literature, visual acuity is usually decreased in the disorder, often to the point of blindness. However, recent publications have stressed the presence, at times, of good visual acuity despite optic nerve hypoplasia (Petersen and Walton, 1977; Frisen and Holmegaard, 1978; Bjork et al., 1978). In the present series, visual field defects were difficult to evaluate. According to Bjork et al. (1978), nasal defects are the most common. Inferior altitudinal defects, as well as unilateral temporal and bitemporal hemianopias, general constriction of the fields and cecocentral scotomas, have also been reported (Seely and Smith, 1972). It is apparent that failure to recognise the associated hypoplasia of the optic nerve head may result in such cases being over-investigated for intracranial pathology.

A variety of ophthalmic conditions has been associated with optic nerve hypoplasia — Duane syndrome (Denslow and Sims, 1980), choroidal coloboma (Hotchkiss and Green, 1979), micro-cornea, partial 4th and 6th nerve palsies, blepharophimosis and dacryostenosis (Petersen and Walton, 1977). Aniridia, microphthalmia and ptosis have also been reported (Zion, 1976).

2. General

Those general manifestations previously reported with optic nerve hypoplasia and confirmed in the present study have pertained mostly to the neurological observations and to certain common abnormalities in early life. Patel and his colleagues (1975) have pointed out that in the new-born period there may be apnoea, hypotonia, hypoglycaemia with or without seizures and hyperbilirubinaemia. Such features were present in 6 of the Royal Alexandra Hospital for Children patients.

Prolonged neonatal jaundice has been noted in several studies (Patel et al., 1975; Thomsett, 1977; Frisch and Schober, 1980). After several months of life, patients may show hypo- or hypertonia, psychomotor retardation, defective visual fixation and seizures. Hepatomegaly may persist. A receding lower jaw and occasionally a high-arched palate have been described (Patel et al., 1975). With increasing age, psychomotor retardation may become evident and growth failure, originally absent, may appear.

Of the 15 present cases, 8 showed neurological deficits — seizures (4), spasticity (3), microcephaly (3). Four were estimated to be of normal or near normal intelligence, 6 were mildly and 5 were severely retarded intellectually.

Rarely mentioned in the literature, but present in 2 of our cases, was early death, in one case occurring suddenly and unexpectedly in a mildly retarded and growth hormone deficient child.

3. Endocrine

The important association between optic nerve hypoplasia and hypopituitarism was first reported by Hoyt et al. (1970). Though initially noted in classical septo-optic dysplasia, hypopituitarism was subsequently documented in cases of bilateral optic nerve hypoplasia with intact septum pellucidum (Billson, 1975; Patel et al., 1975), and other cerebral anomalies (Greenfield et al., 1980; Billson, 1975; Huseman et al., 1978) as well as in unilateral optic nerve hypoplasia (Patel et al., 1975). Thus hypopituitarism may accompany unilateral or bilateral hypoplasia of the optic nerves, with or without demonstrable cerebral anatomical disturbances.

Because of the tendency to report cases with endocrine disturbances in the general literature and cases without such disorders in the ophthalmic literature, it is difficult to determine the frequency of endocrine deficits. Of the 43 reported cases of optic nerve hypoplasia with associated endocrine deficiencies, 5 had hypopituitarism (often not fully described), 40 had documented growth hormone deficiency, 15 had adrenal insufficiency, 6 had hypothyroidism and 2 borderline thyroid dysfunction. Twenty had anti-diuretic hormone deficiency. There were 2 cases of early sexual maturation (Huseman et al., 1978) and one of 'small male genitalia' (Krause-Bruchner, 1980). Septo-optic dysplasia has been cited elsewhere as a cause of micropenis (Lee et al., 1980). The case of Wilson et al. (1978) was hypogonadal at the age of 21 years. It should be noted that with the exception of the latter, and 2 other cases (Ellenberger and Runyan, 1970; Lovrencic et al., 1978), all patients reported were less than 13 years of age. The true frequency of hypogonadism may prove to be much higher.

In the present series of 15 cases, at least 7 had some evidence of hypopituitary-hypothalamic dysfunction. In one of these the defect was minimal (a prolonged elevation of luteinising hormone levels after LHRF stimulation). There was documented deficiency of growth hormone production in 4 cases. Two received growth hormone therapy. One has grown normally so far, despite the abnormal tests, and one is currently awaiting therapy. Four patients had evidence of hypothyroidism and 3 are receiving thyroid replacement therapy. Two patients had evidence of adrenal insufficiency, 2 of diabetes insipidus and one girl had precocious puberty. Two boys had micropenis (length less than 2 standard deviations below the mean for age). One had received testosterone therapy for this. It seems likely that gonadotrophin deficiencies will become more apparent as these patients are followed into the second and third decades of life. As Brook et al. (1972) have pointed out that there may be initially a normal growth rate with subsequent fall-off and demonstration of growth hormone deficiency, full endocrine workup is often better delayed until there is evidence of growth failure or other endocrine disturbance.

Neuroradiology

Routine skull roentgenograms are generally normal (Walton and Robb, 1970). Although the optic foramina may be small (Billson, 1975), they are usually normal (Edwards and Layden, 1970; Walton and Robb, 1970).

The pneumoencephalographic and computerised tomographic findings have been discussed in several publications (Kaplan et al., 1970; Reeves, 1941; Manelfe and Rochiccioli, 1979; Rush and Bajandas, 1978). The typical features of septo-optic dysplasia include absence of the septum pellucidum (giving the inverted school-bell sign), thin optic nerves and chiasm, abnormal fornices, irregular lamina terminalis and an abnormally shaped third ventricle with a small inferiorly pointing diverticulum from the optic recess. It is rare to demonstrate all these features. In our experience, the optic nerves usually appear normal on CT scan.

It should be stressed that the majority of cases of bilateral optic nerve hypoplasia do not have septo-optic dysplasia. Of the 15 Royal Alexandra Hospital for Children

cases, 5 had septo-optic dysplasia, 5 had normal scans and 5 had major CNS abnormalities, including agenesis of the corpus callosum (3), hypoplasia of the cerebellum and porencephaly (1), with left parietal porencephaly in the fifth.

Prognosis

The outlook for cases of bilateral optic nerve hypoplasia is largely dependent on the severity of associated cerebral malformations and on the avoidance of complications such as hypoglycaemia, adrenal crises and seizures.

Hypoglycaemia due to growth hormone deficiency may occur in the neonatal period or at any age subsequently. The stress of anaesthesia or fasting for special investigation has sometimes precipitated hypoglycaemia, justifying caution in the workup of such patients.

Major cerebral malformations carry a poor prognosis but mental retardation has been observed in patients with normal cerebral anatomy on pneumoencephalography or CT scan.

As previously noted, early prognostication with regard to vision is often incorrect, apparently blind infants sometimes developing useful vision later in life.

Many of the endocrine deficiencies are treatable but full endocrine evaluation is usually unnecessary in the first few years of life provided growth rate and thyroid function are carefully monitored.

Of the 15 Royal Alexandra Hospital for Children patients seen in the past 10 years, 2 are dead, 1 from terminal pneumonia in a severely disabled child and 1 from sudden unexpected death in a mildly retarded girl. In the latter case, autopsy revealed inhalation pneumonia as the probable cause of death.

Summary

In the past 10 years, 15 children with bilateral optic nerve hypoplasia have been studied at the Royal Alexandra Hospital for Children. There were 5 boys and 10 girls. Nine were first-born and they presented at a mean age of 5 months (range: 4 days to 25 months). Five presented with suspected blindness and 7 with abnormal eye movements (nystagmus or less commonly squint). The other 3 presented because of fits or developmental delay. Eight showed evidence of neural damage — microcephaly, seizures and/or abnormalities of tone. Four appeared to be of normal or near normal intelligence, 6 were mildly retarded and 5 severely so. Two patients had already died, one suddenly.

Six of the 7 cases investigated in detail had evidence of hypothalamic pituitary dysfunction. Another one had a minimal hypothalamic abnormality. Four were severely growth retarded and 2 were receiving growth hormone replacement. Two males had micropenis and a girl had precocious puberty with partial diabetes insipidus. Neuroradiological investigations showed an absent septum pellucidum in only 5 cases. Five patients had other major CNS malformations.

Five patients had normal CT scans; 3 of these 5 appeared of normal intelligence and all 5 had normal neurological examinations.

Bilateral optic nerve hypoplasia is frequently associated with serious brain and endocrine abnormalities.

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Acetylcholine Receptor Antibodies in the Diagnosis and Management of Myasthenia Gravis

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After the first descriptions of the finding of an antibody to the acetylcholine receptor (AchR) in about 50% of myasthenia gravis (MG) patients (Almon and Appel, 1974) there have been gradual improvements in the assay so that with better AchR preparations antibody is found in the serum of up to 90% of patients with generalised MG (Elias and Appel, 1979a). The AchR antibody is specific for MG; passive transfer of the antibody can produce a myasthenia-like syndrome and the antibody can reduce the number of acetylcholine receptors by a number of mechanisms (Drachman et al., 1980). Although there is a general correlation of antibody level with disease activity, various investigators have noted the lack of direct correlation of the antibody level with clinical progress (Appel et al., 1975; Elias and Appel, 1979b). Some reports suggest antibody levels correlate better with clinical features in individual patients (Bradley et al., 1978). With the advent of plasmapheresis therapy for MG some studies have reported correlation of antibody levels and early clinical response to plasmapheresis (Newsom-Davis et al., 1978).

Because of the generally poor correlation of antibody levels with clinical state, the existence of MG patients with no detectable serum antibody and the converse, the existence of animals with experimental MG with amounts of antibody in excess of that sufficient to bind every AchR in their body (Lindstrom et al., 1976), the role of the antibody in the pathogenesis of the disease has been questioned.

In order to examine the relationship of antibody levels to clinical characteristics of MG we have compared antibody levels with clinical classification of MG, disease activity, relationship to thymoma, response to conventional modes of therapy and to plasmapheresis, in a population of myasthenic patients which had not been previously studied.

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Materials and Methods

Reagents

^{125}I-α-bungarotoxin, specific activity >200Ci/mmol, was obtained from the Radiochemical Centre, Amersham. Goat anti-human gammaglobulin was purchased from Kallestad Pharmaceuticals. Benzoquinonium was a gift from Sterling-Winthrop Pharmaceuticals.

Methods

AchR antibodies were measured by the method described by McAdams and Roses (1980).

Acetylcholine Receptor Preparation

AchR was prepared from human skeletal muscle obtained from leg amputations for peripheral vascular disease. Muscle was kept at 4°C for less than 2 hours before the receptor was extracted according to the method described by Lindstrom (1977) with the exception that the homogenate pellet was resuspended in 4 volumes of 2% Triton buffer.

After ultracentrifugation the receptor was stored in liquid nitrogen. Receptor stored in liquid nitrogen retained activity for at least 6 months. AchR was initially quantitated by Skatchard analysis using Sephacryl S200 columns, using a modification of the method of McAdams and Roses (1980) and later by employing a high titre MG serum in the radioimmunoassay described below.

Optimum Conditions

The radioimmunoassay was carried out by the double antibody method as described by McAdams and Roses (1980). Assays were done in duplicate. Specific binding was determined by difference from duplicate estimations carried out in the presence and absence of 1mmol benzoquinonium.

In our assay 8nM ^{125}I-bungarotoxin was required to saturate the receptor and the optimal amount of myasthenic serum in the assay was found to be 5μL in a total reaction volume of 150μL with 100μL of a second antibody (goat anti-human gamma-globulin). Antibody estimations were expressed as nanomoles of AchR precipitated per litre of serum (nmol/L).

Radioimmunoassay Parameters

Reproducibility: Ten replicates of a MG serum yielded values from 6.80 to 8.46nmol/L with a mean of 7.70nmol/L and a standard deviation of 0.50. Ten replicates of a normal serum yielded values from −0.48 to 0.56nmol/L with a mean of 0.07 and a standard deviation of 0.27, indicating random fluctuations around zero, findings approximately within the values for the normal range (see below).

Interassay variation: High reference sera tested in 11 separate assays had a mean of 9.06nmol/L and a standard deviation of 1.59. Low reference sera tested in 16 assays had a mean of 0.15nmol/L and a standard deviation of 0.20.

Normal values: 28 sera from healthy donors ranged from − 0.45 to 0.47 with a mean of 0.08 and standard deviation of 0.24. Negative values arise when the mean of the duplicate tubes with benzoquinonium are greater than the mean of the duplicate tubes without benzoquinonium.

Results

Clinical Classification

Most patients with generalised MG, or generalised and ocular MG (24/25), had raised antibody levels. Six out of 10 patients with purely ocular MG had raised antibody levels. Two subjects with familial or congenital MG had no detectable antibody to the AchR. No subjects with other diseases or with generalised tiredness without other features of MG had detectable AchR antibody (fig. 1).

There was a slight trend for patients without thymoma to have lower antibody levels (fig. 2), but this trend did not reach statistical significance ($p < 0.1$).

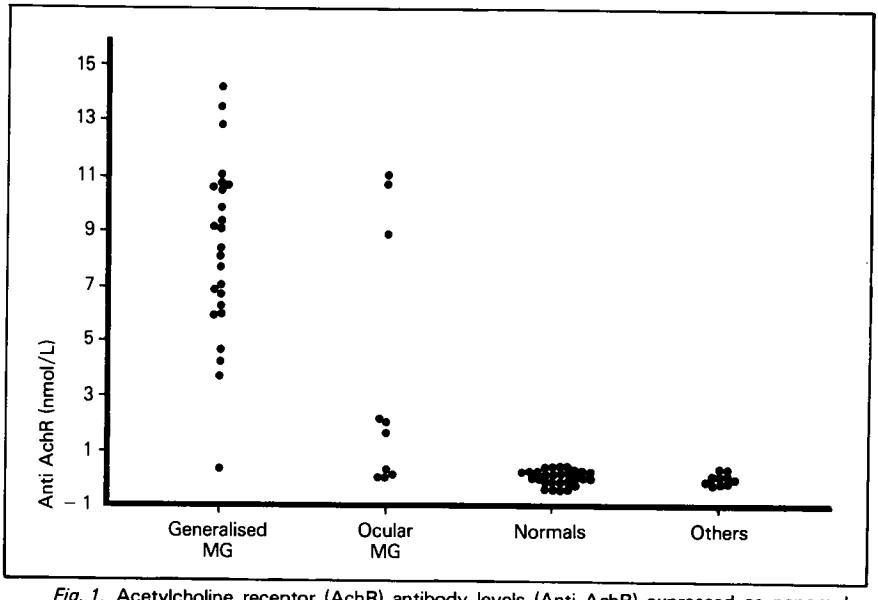


Fig. 1. Acetylcholine receptor (AchR) antibody levels (Anti-AchR) expressed as nanomoles (nmol) of ^{125}I-α-bungarotoxin precipitated per litre of serum, in patients with generalised and purely ocular myasthenia gravis (MG), normal subjects (normals) and patients with other diseases or complaints of weakness or tiredness with no objective evidence of MG (others).

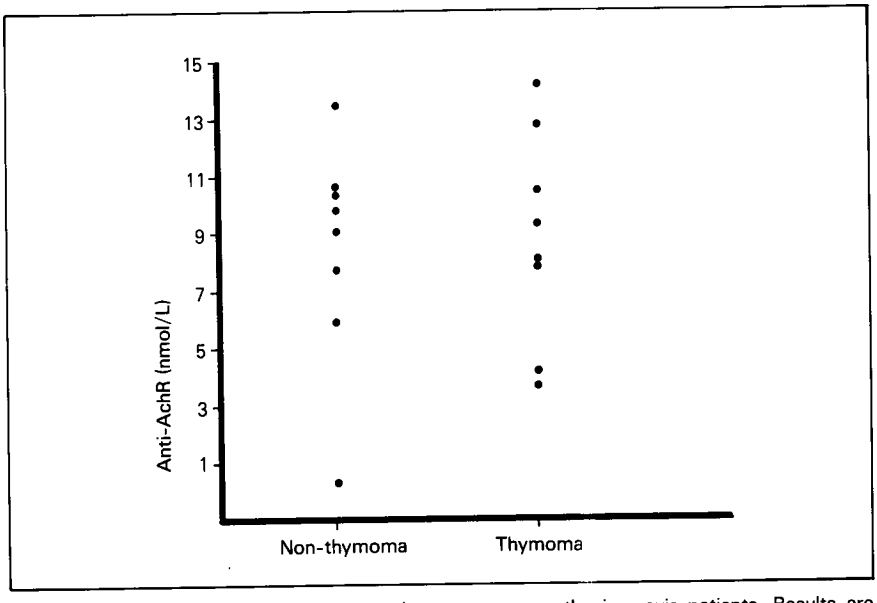


Fig. 2. AchR antibody levels in post-thymectomy myasthenia gravis patients. Results are plotted according to thymus pathology.

Response to Treatment

Medical Therapy

When patients in remission (as defined by ability to live a relatively normal life without anticholinesterase, steroid, or antimetabolite medication) were compared to patients with active disease there was only a slight difference in antibody levels which was not statistically significant ($p < 0.1$) (fig. 3). However, the few patients in remission had long-standing disease compared to patients with active disease.

Thymectomy

Three patients had pre- and post-thymectomy AchR antibody estimations. There was no immediate fall in antibody levels, although all patients improved clinically postoperatively (fig. 4).

Plasmapheresis

A number of antibody assays were performed on pre- and post-plasmapheresis samples in 5 patients receiving constant dosages of steroids and antimetabolites. All samples were analysed in the one assay to avoid inter-assay variations. Variations in antibody levels of the order of 25 to 30% of the pre-plasmapheresis levels were found

in accordance with a 2 litre plasma exchange. In some patients there was immediate symptomatic improvement. Objective evidence of improvement was only demonstrated over a period of weeks. However, there was no decrease in the mean AchR antibody level. Results from representative patients are shown in figures 5 and 6.

Discussion

The lack of direct correlation of AchR antibody levels and clinical state reported in this study is similar to some previous reports (Appel et al., 1975; Roses et al., 1981). It appears that in the early years of application of the AchR antibody assay, more was expected from the assay than could reasonably be expected.

The AchR antibody assay is an indirect measurement of antibody 'levels' and is a measure of the ability of MG antibodies to bind to the AchR, permitting precipitation of the receptor by anti-human gammaglobulin. The amount of binding does not directly represent the number of antibody molecules in the assay but is dependent on the affinity of the antibody for the receptor. MG serum contains a mixture of antibodies to various antigenic regions of the receptor, with different binding affinities,

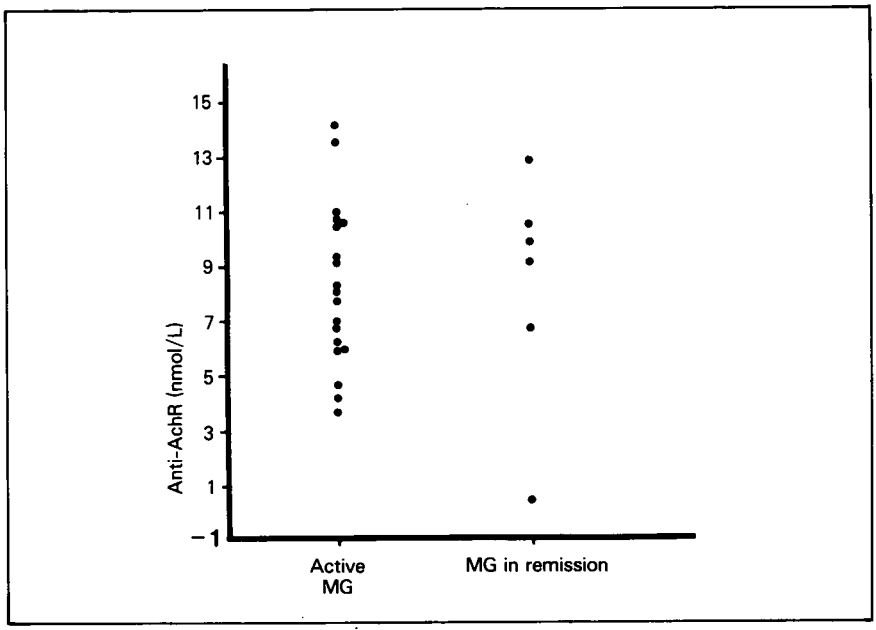


Fig. 3. AchR antibody levels in myasthenia gravis patients with active disease (defined as still requiring active treatment, either drug therapy or plasmapheresis) compared to patients in remission, defined as those not requiring active drug treatment.

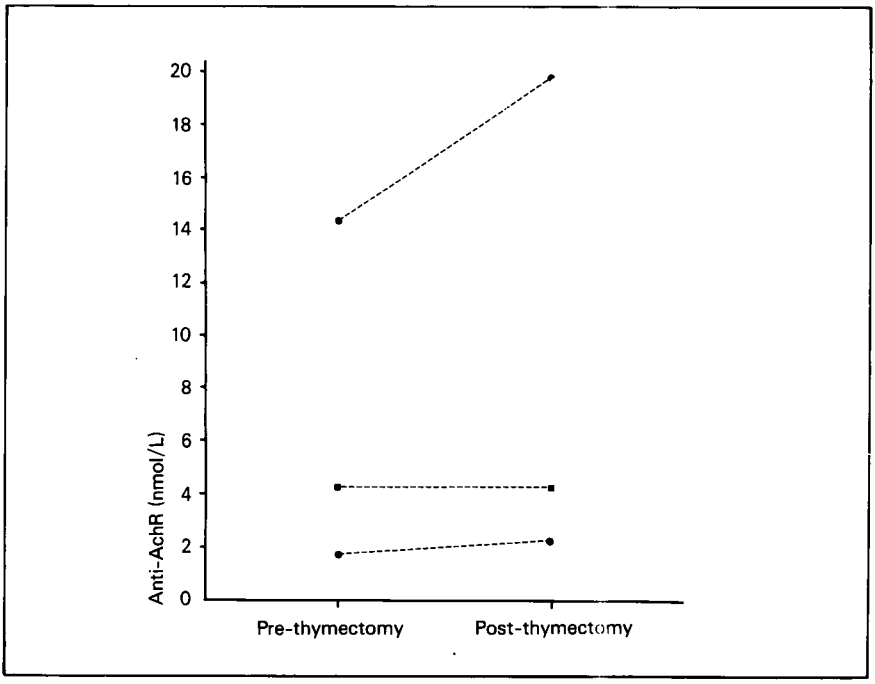
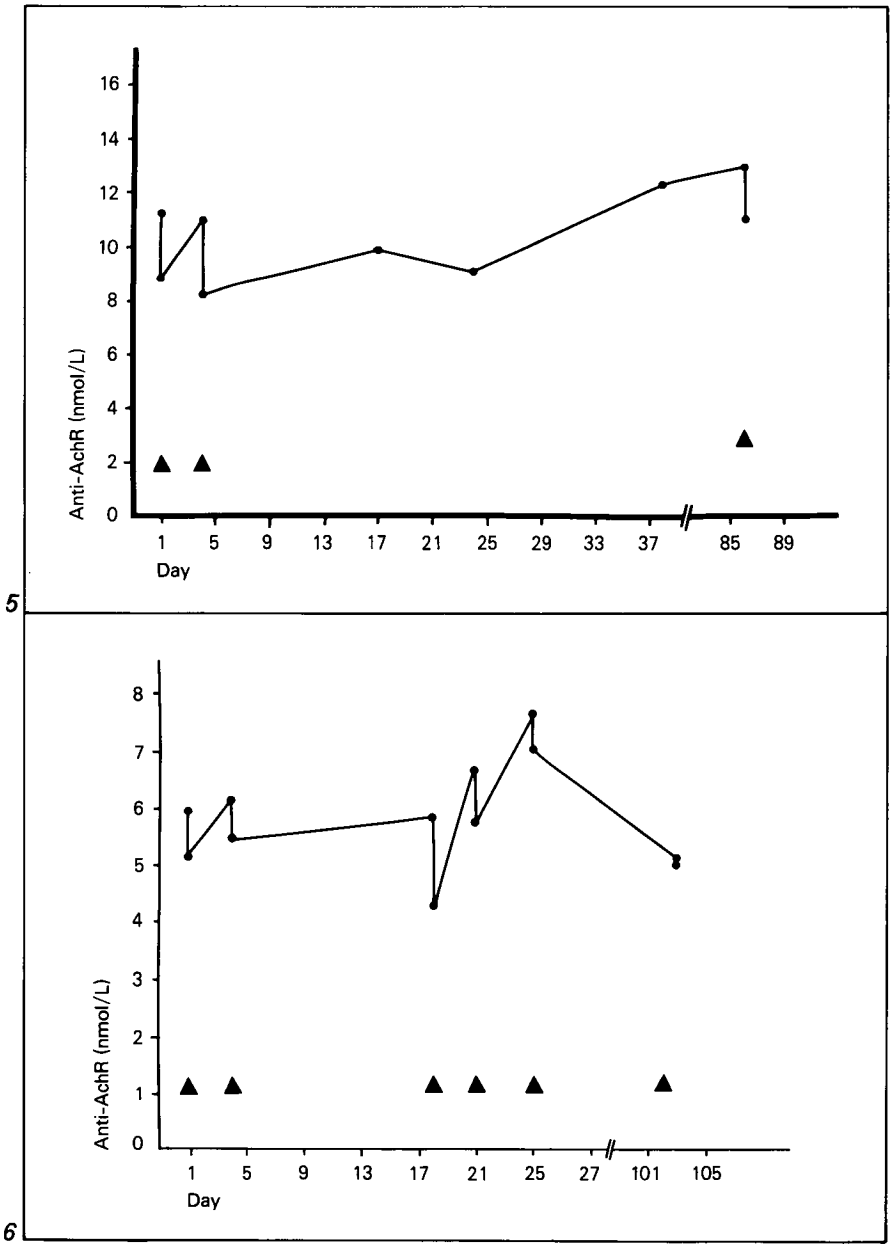


Fig. 4. AchR antibody levels obtained before and after thymectomy in 3 myasthenia gravis patients. Serum samples were obtained immediately pre-operatively and 1 or more weeks postoperatively. Points for individual patients are connected by broken lines.

and even antibodies to the same antigenic site with a range of binding affinities (Elias and Appel, 1979a). Because of this heterogeneous mixture of antibodies involved in the assay, receptor precipitation is not directly related to the number of antibody molecules present. For this reason it would perhaps be surprising if antibody 'level' did directly correlate with clinical parameters.

Acetylcholine receptor antibody subpopulations with various antigenic specificities in different individuals could provide an additional explanation for the lack of direct correlation of clinical state with antibody level. Evidence in support of this possibility has been reported by Savage-Marengo et al. (1980). These authors noted individual patterns of AchR antibody specificity.

From a theoretical standpoint, if AchR antibody does play an essential role in the MG disease process, it should be present in all cases of generalised MG. All investigators agree that some definite MG patients have no detectable AchR antibody; conversely some patients with thymoma but without MG have AchR antibody (Cuenoud et al., 1980). Acute experimental MG in mice can occur in the absence of detectable AchR antibody (Granato et al., 1980). Improved antigen from human skeletal muscle AchR rather than from animal skeletal muscle has increased the detection rate of antibody in generalised MG. Further, if human extra-ocular muscle AchR has some an-



Figs. 5 and 6. Variations in AchR antibody levels with time in 2 patients undergoing plasmapheresis, each plasmapheresis being indicated by a triangle. Both patients were receiving constant doses of both prednisone and antimetabolites (in fig. 5 cyclophosphamide and in fig. 6 azathioprine).

tigenic differences from skeletal muscle AchR this could explain why some ocular MG patients had no detectable antibody. This possibility was examined by Compston et al. (1980). However, AchR antigen from extra-ocular muscles still did not detect antibody in all generalised MG patients.

Another unresolved problem with the AchR antibody theory of the pathogenesis of MG is that the theory does not provide a simple explanation for the beneficial effect of thymectomy. Although antigenic material which cross-reacts with AchR has been demonstrated in thymus tissue (Lindstrom et al., 1976; Aharonov et al., 1975), there is no direct evidence that there is any material with the physical characteristics of AchR in the thymus (Nicholson and Appel, 1977). As an explanation for thymic involvement in MG, Goldstein (1975) has proposed that a thymic hormone, thymopoietin, causes the neuromuscular block and that the AchR antibody is an epiphenomenon. Twomey et al. (1979) suggest that there is a correlation between clinical improvement from thymectomy and sustained lowering of serum thymic hormone activity.

In conclusion, AchR antibodies are present in most but not all patients with generalised MG. There was no direct correlation of antibody level and clinical parameters. These findings may be partly explained by the assay system which is not capable of accurate quantitation of total AchR antibody or of AchR antibody subpopulations. Investigations of other factors such as antibody subpopulations, other antigens, the cellular immune response, complement and thymic factors is required to define the underlying disease mechanism, before any test can be devised which can accurately reflect the clinical progression of the disease.

Summary

The relationship of acetylcholine receptor (AchR) antibodies to disease activity in myasthenia gravis (MG) is controversial. Some authors claim a direct correlation with disease activity and treatment, in particular plasmapheresis therapy, whereas others have commented on the poor overall correlation of antibody levels with clinical state.

Antibody levels were examined in a population of MG patients and correlated with disease activity and response to treatment. Antibodies to skeletal muscle AchR were found in most patients with generalised MG (24/25) and in about half of the patients with purely ocular MG (6/10) and in neither of 2 patients with congenital MG. There was scant correlation with disease activity or response to treatment. It is concluded that the assay is more useful for diagnosis than for management of MG.

Acknowledgements

This work was carried out with the aid of grants from the Clive and Vera Ramaciotti Foundations. The assistance of Dr A.D. Roses and Ms M. McAdams in the development of the assay and the inspiration and stimulation of Dr Almon and Dr S. Appel who originally introduced one of the authors (G.A.N.) to this area of research, is gratefully acknowledged.

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Serum-induced Demyelination: An Electrophysiological and Histological Study

*J.D. Pollard, B. Harrison and P. Gatenby**

There has not been complete agreement concerning the role of cellular or humoral immunity in demyelinating disease of the peripheral nervous system. Pathological studies of the Landry-Guillain-Barré syndrome or acute idiopathic polyneuropathy (AIP) and of the animal model for this condition, experimental allergic neuritis (EAN), have emphasised the role of cell mediated immunity (Lampert, 1969; Wisneiwski et al., 1969). However, recent evidence which has been summarised by Cook and Dowling (1981) suggests a role for humoral factors. This evidence includes the following points. A large number of workers using a number of different techniques have shown the presence of antineural antibodies in patients with AIP. Antibody binding to sural nerve of patients with AIP and chronic relapsing polyneuropathy (CRP) has been reported (Luitjen et al., 1972; Dalakas and Engel, 1980). the serum of animals with EAN has recently been shown to have potent demyelinating potential when injected intraneurally and this activity correlates well with antigalactocerebroside antibody level (Saida et al., 1979). Finally, there have been many reports of improvement in patients with AIP and CRP after plasmapheresis.

As earlier workers had concluded that demyelination in EAN was transferable by cells and not serum (Allt et al., 1971), we felt it important to confirm the work of Saida et al. (1978) and in this paper we describe attempts to produce demyelination in rat sciatic nerve by the injection of serum from rabbits with EAN. The results of these experiments led to an examination of serum from patients with demyelinating neuropathy.

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Methods

Induction of EAN

Five NZW rabbits were injected intradermally with homogenised bovine peripheral nerve (nerve roots) in an equal quantity of Freund's complete adjuvant. 0.25ml was injected into each hind foot pad and into 4 sites on the back. Four animals showed signs of disease between 16 and 30 days post-injection.

Blood was taken from rabbits within the first 3 days of definite signs of EAN. It was centrifuged and the serum used fresh.

Injection into Rats

EAN Serum

From the rabbit which had developed most severe disease, 20μL of serum was injected subperineurally into the right sciatic nerve of 5 hooded rats, using a micrometer syringe and 30 gauge disposable stainless steel needles; 20μL of fresh control rabbit serum was injected into the left sciatic nerve in identical fashion. The area of injection was marked by a 6.0 silk suture inserted into surrounding muscle bed.

Serum from Patients

Serum from each of 8 patients with Landry-Guillain-Barré syndrome and 3 patients with chronic relapsing polyneuropathy was injected into the sciatic nerves of 3 hooded rats in an identical manner to that for EAN serum. The serum from all patients was collected and injected during the acute phase of the illness, i.e. within 3 weeks of the initial episode or a relapse. Control human serum was injected into the left sciatic nerve of each rat.

Neurophysiological Studies

Motor conduction velocity was recorded in both sciatic nerves of all rats before injection and again at 4 days when the animals were sacrificed and prepared for histological studies. The compound muscle action potential was recorded from the small muscles of the feet through a pair of steel electrodes and the sciatic nerve trunk stimulated by another pair of steel electrodes inserted through the skin at the sciatic notch and above the ankle. Injection of the sciatic nerve had been performed between these stimulating sites. The technique used was similar to that previously described (Pollard and McLeod, 1980).

Electrophysiological evidence of demyelination was assessed by measurement of:

1) Motor conduction velocity.
2) Distal motor latency.

3) Conduction block — by comparison of the amplitude of the compound muscle action potential when the nerve was stimulated at sciatic notch and ankle.
4) Dispersion of the compound muscle action potential

Histological Studies

At the completion of the electrophysiological studies the rats were anaesthetised and left ventricular perfusion was performed by a technique previously described (Pollard and Fitzpatrick, 1973). 1cm lengths of nerve were removed from the area of

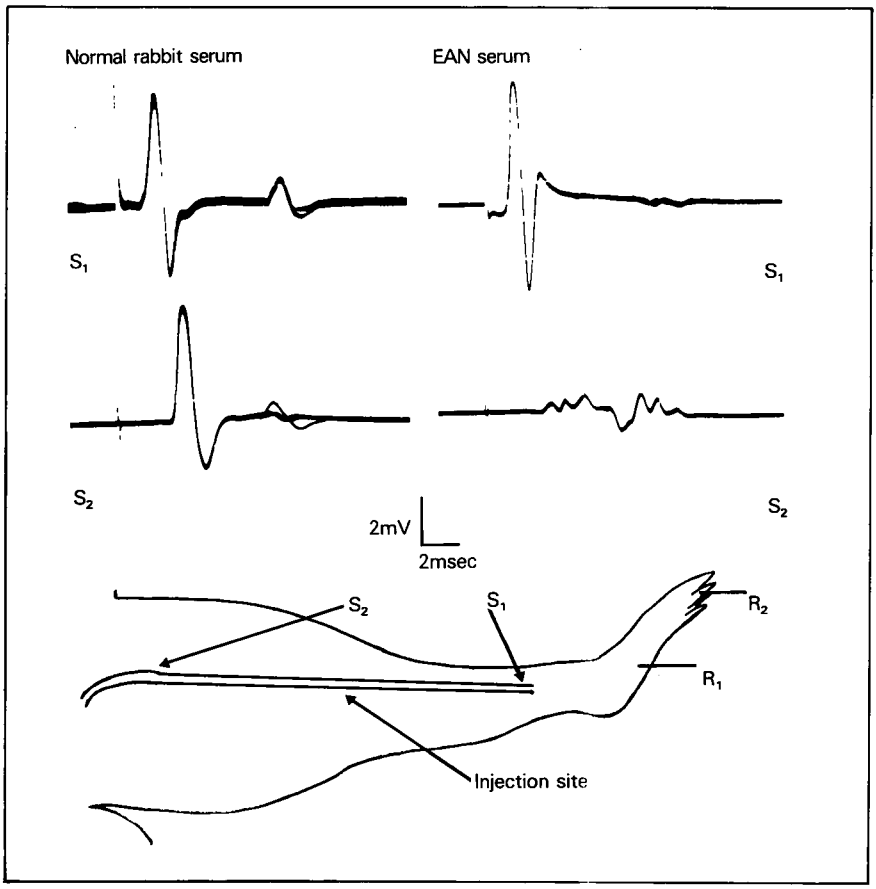

Fig. 1. Compound muscle action potential recorded from small muscle of the foot (R_1), R_2 a reference electrode. S_1 and S_2 are sites of stimulation at ankle and sciatic notch. Note pronounced conduction block with EAN serum and marked dispersion of action potential at 4 days post injection.

injection and post-fixed in either 2% osmic acid or cold Dalton's chrome-osmium solution, dehydrated in graded concentrations of ethanol and embedded in araldite/Spurr's resin. Ultra-thin sections were cut with glass or diamond knives on a LKB Ultratome III, mounted on copper grids coated with a nitrocellulose film and carbon, and stained sequentially with 5% aqueous uranyl acetate and lead citrate and examined with a Philips 200 electron microscope. Semi-thin sections 0.5 to 1μm thick were stained by toluidine blue and examined by light microscopy.

Results

Electrophysiology

The mean motor conduction velocity of rat sciatic nerves pre-operatively was 46.4 ± 5.3m/sec. The mean of the ratio of the compound muscle action potential obtained from the distal and proximal stimulating sites was 1.04 ± 0.02 pre-operatively.

The mean motor conduction velocity of the sciatic nerves injected with EAN serum was 39.5 ± 7.2m/sec 4 days post-injection, and of the nerves injected with control serum 44.7 ± 5.2m/sec. This difference was not significant. The ratio of compound muscle action potential was 4.8 ± 3.1 in the EAN injected nerves and 1.3 ± 0.2 on the control side. This difference was significant. Dispersion was observed only among those nerves injected with EAN serum and marked dispersion was observed in 30% of these nerves (fig. 1).

In rats injected with human serum the mean motor conduction velocity was 39.2 ± 9.4m/sec in the group given neuropathic serum and 43.5 ± 4.2m/sec in the control group. These differences in conduction velocity were not significant. The ratios of the compound muscle action potential ankle to sciatic notch were 1.22 ± 0.25 and 1.28 ± 0.21 in the control and neuropathic groups, respectively.

Clinical Observation

In two-thirds of the animals injected with EAN serum weakness of the foot on that side was observed. This sign was not found in any other animal.

Light Microscopy

In sciatic nerves injected with either rabbit or human control serum, relatively minor changes were found. These included crushing of occasional fibres along the needle tract, axonal degeneration in a few fibres below the site of injection, occasional demyelinated axons apparent in transverse sections, and in some nerves small groups of demyelinated fibres.

The changes in the nerves injected with EAN serum were very obvious. Diffuse demyelination, affecting one- to two-thirds of the nerve fascicle was observed (fig. 2). In rats injected with human neuropathic serum, small groups of demyelinated fibres

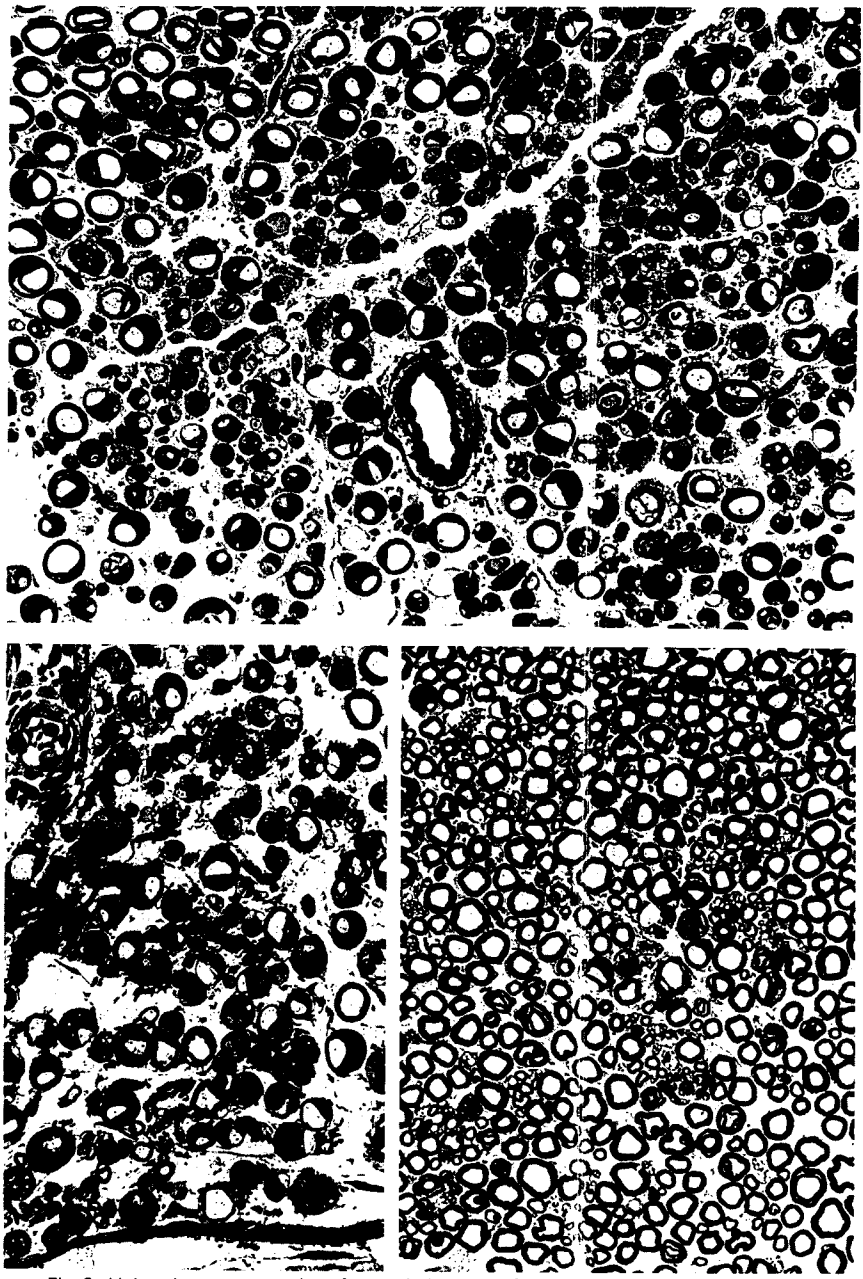

Fig. 2. Light microscope sections from sciatic nerve of a rat injected with EAN serum A and B, and from a rat injected with control rabbit serum C. Note extensive area of demyelination in EAN-injected nerve, whereas relatively few fibres are demyelinated in C. Toluidine blue ×250.

were found in subperineural regions in some nerves, but otherwise these nerves were indistinguishable from those injected with control sera.

Electron Microscopy

Changes on electron microscopy confirmed those seen by light microscopy. In animals given EAN serum, many fibres in the area of injection were completely demyelinated, and many were surrounded by macrophages (fig. 3). Myelin debris was still present within the cytoplasm of many macrophages, whether these were inside or outside neurilemmal tubes (fig. 3). Within some neurilemmal tubes a central axon lay naked without any surrounding myelin or even the usual investing Schwann cell cytoplasm (fig. 4). Degeneration of unmelinated fibres and the Schwann cells associated with these was noted in some areas.

In nerves injected with control rabbit serum, occasional demyelinated fibres were seen. The changes seen at 4 days in these animals differed only in extent of the lesion from the animals given EAN serum. This difference was, however, profound.

In the sciatic nerves injected with human serum no significant difference was found in rats given control serum or serum from patients with neuropathy. The changes were similar to those seen with control rabbit serum.

Discussion

The results of this study confirm the findings of Saida et al. (1978) that serum taken from animals with EAN in the acute phase of the illness has a potent demyelinating effect when injected into peripheral nerve. Some demyelination does follow the injection of control rabbit serum. Such damage could result from an increase in endoneurial pressure or from nonspecific immunoglobulin binding to myelin or Schwann cell membranes. Only the EAN serum, however, resulted in significant abnormalities of nerve conduction. Significant dispersion of muscle action potential and electrophysiological evidence of conduction block were seen only in the animals injected with EAN serum. The cause of the demyelination has not been elucidated by these studies. Saida et al. (1979) have produced evidence that the demyelinating effect of EAN serum parallels its content of antigalactocerebroside antibody. It is interesting, however, that in those nerves injected with EAN serum, damage to Schwann cells both in unmyelinated and myelinated fibres was apparent, as it is only in Schwann cells that have been induced to myelinatè that galactocerebroside is expressed (Mirsky et al., 1980).

In those nerves injected with human serum, results similar to control rabbit serum were found; small groups of fibres were demyelinated in some animals, but in none of these were electrophysiological abnormalities of significant degree recorded. This finding is at variance with that of Feasby et al. (1980) who found focal demyelination of rat sciatic nerve in a predominantly perivascular distribution with serum of 6 of 7 patients with Landry-Guillain-Barré syndrome.

However, Cook and Dowling (1981) who have injected 250 rats with serum from 21 patients and 48 controls failed to produce clear-cut results. Tandon et al.

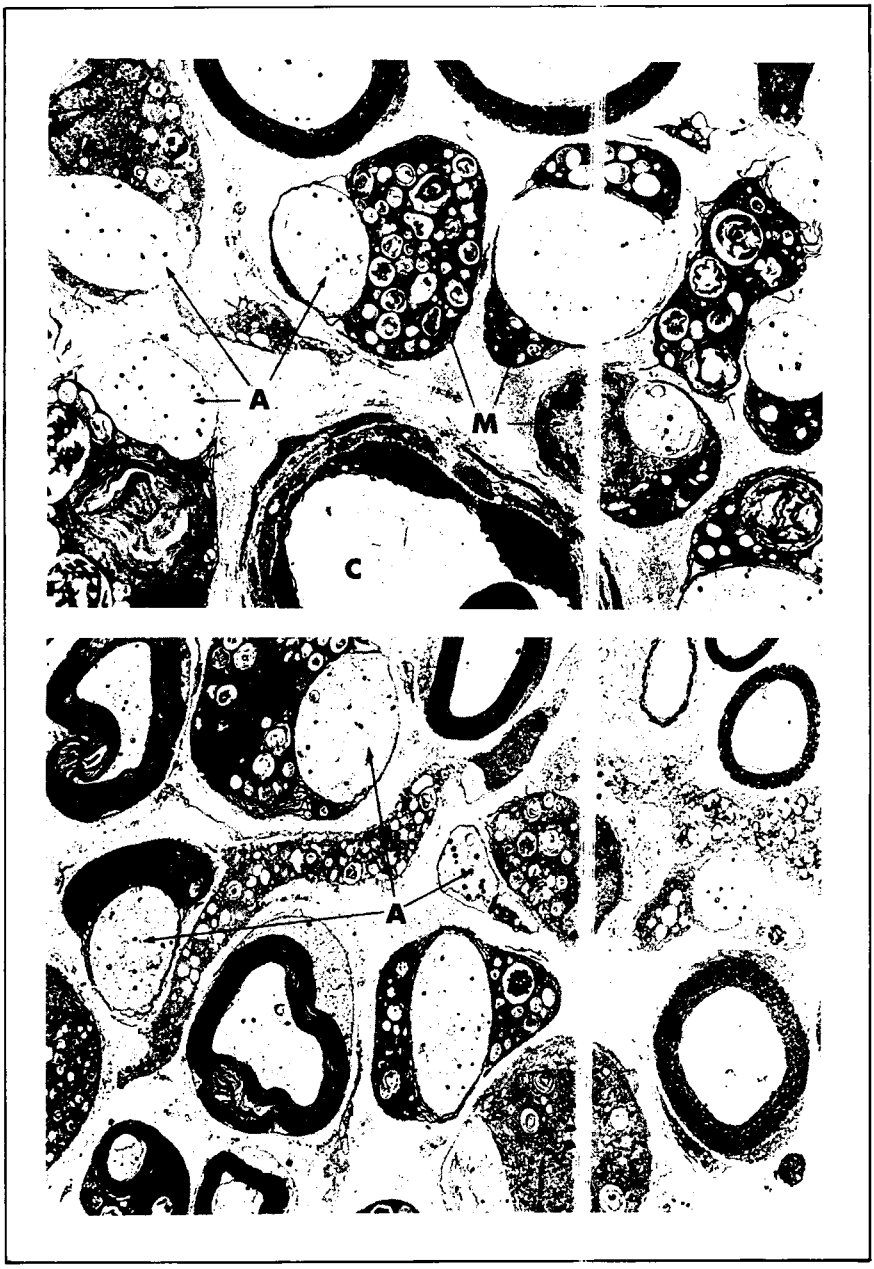

Fig. 3. Electron micrographs from the same nerve illustrated in figure 2a. Note numerous demyelinated fibres in perivascular distribution. A = axon. M = macrophage. C = cytoplasm. × 2900.

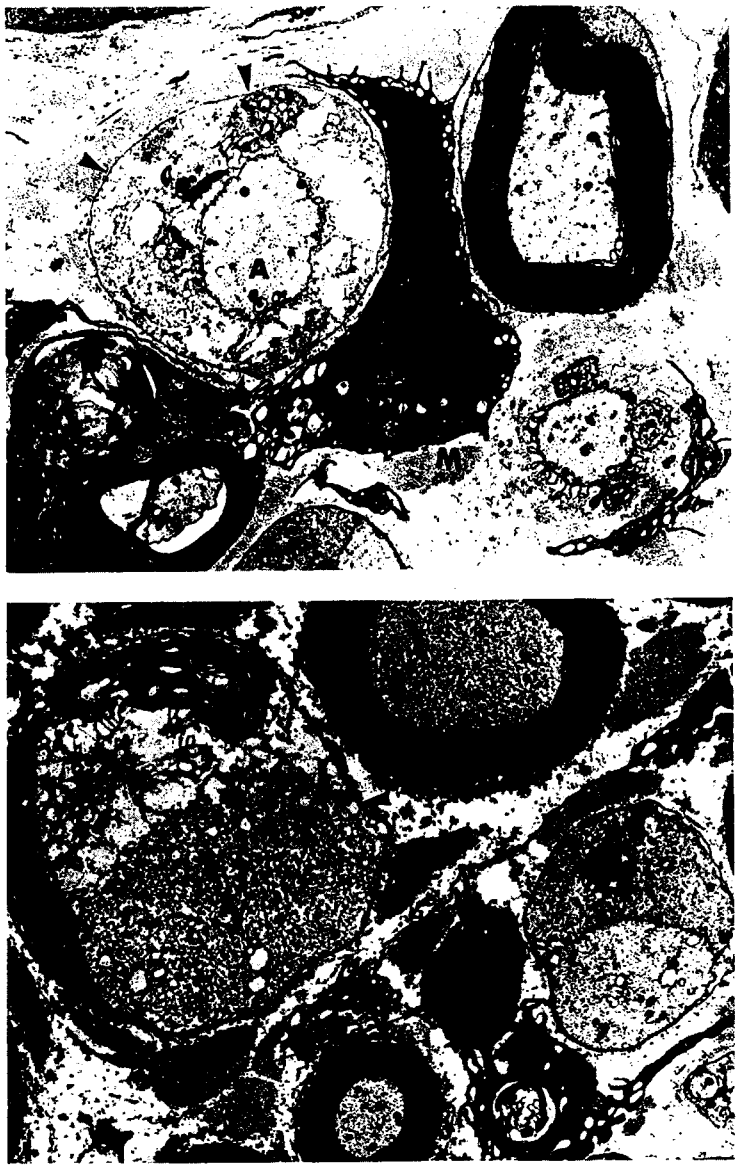

Fig. 4. Electron micrographs from rat nerve injected with EAN serum. Above, an axon A lies naked within original Schwann cell basement membrane (arrow heads). Only debris of original Schwann cell cytoplasm and myelin intervenes. M = macrophage. × 4400.

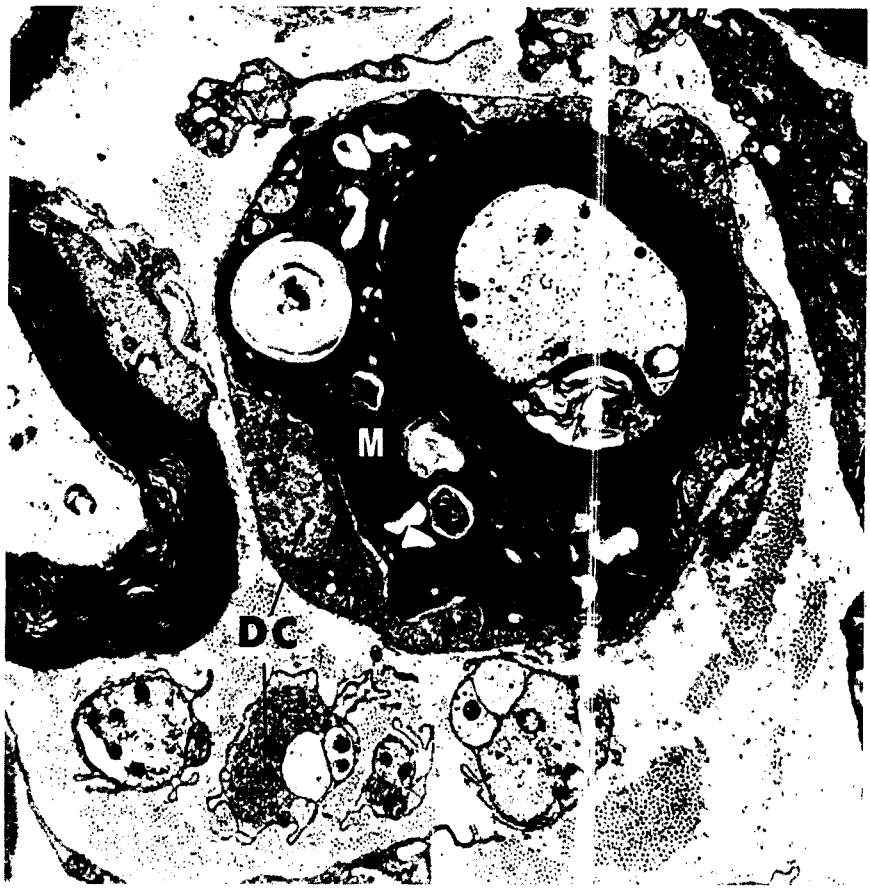

Fig. 5. Electron micrograph from same nerve as figure 4. A macrophage (M) is beginning to destroy this myelinated fibre. The original Schwann cell cytoplasm of this fibre appears to be degenerating (DC). Similar degenerative changes are apparent within the cytoplasm of a Schwann cell associated with an unmyelinated fibre. ×8544.

(1980) have also failed to produce definite demyelination after injection of serum from patients with inflammatory neuropathies.

Thus, a potent demyelinating potential in EAN serum has been readily demonstrated *in vivo*, by intraneural injection. Similar activity in human Landry-Guillain-Barré syndrome has yet to be confirmed. It may be that such factors are present in patients, but in reduced concentration or that their activity cannot be demonstrated by their transient presence within nerve after a single injection. We are currently exploring methods of exposing mouse peripheral nerve chronically to human neuropathic serum.

Summary

Serum from rabbits with EAN in the acute phase of the disease has been injected into rat sciatic nerve, and compared to control rabbit serum and serum from patients with demyelinating neuropathy and to normal human control serum. Electrophysiological studies were performed on all rat sciatic nerves so injected, and the nerve was then removed and examined histologically.

Control rabbit and human serum and neuropathic human serum, when injected in a 20μL quantity through a 30 gauge needle, did not produce significant electrophysiological abnormalities. EAN serum, however, produced significant dispersion of the muscle action potential and conduction block. All serum produced some histological evidence of demyelination but that seen with EAN serum was quite profound compared to all other sera. It is concluded that humoral factors are present within animals with EAN which has potent demyelinating potential. We were not able to demonstrate the same effect from patients with demyelinating neuropathy in this test system.

Acknowledgements

The authors are grateful to the Electron Microscopy Department of the University of Sydney for the use of EM facilities. Expert technical assistance was rendered by Virginia Mills. This work was supported by the National Health and Medical Research Council of Australia.

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Compression of the Tibial Nerve by the Tendinous Arch of Origin of the Soleus Muscle

*F.L. Mastaglia, J. Venerys, B.A. Stokes and R. Vaughan**

Compression of the tibial nerve in the popliteal fossa is uncommon. It may be due to a Baker's cyst in patients with rheumatoid arthritis or to other local compressive lesions but primary entrapment of the nerve by the tendinous arch of origin of the soleus muscle (fig. 1) is not mentioned in recent reviews (Nakano, 1978) or textbooks dealing with compression and entrapment neuropathies (Kopell and Thompson, 1976; Seddon, 1972; Sunderland, 1978). Since 1973 the authors have seen 3 such cases of entrapment of the tibial nerve and these, together with 2 other cases in which compression of the tibial nerve was associated with venous disturbances in the popliteal fossa, form the subject of this report.

Case Reports

Case 1

One month previously, a 28-year-old shearer noted discomfort behind the right knee after a day of strenuous physical activity. On the following morning, he noted a sensation of pins and needles in the right heel and over the next few days he noted numbness and pain in the sole of the foot. The popliteal pain subsequently increased in severity and was exacerbated by attempting to place the foot flat on the ground. He also noted sharp shooting pains in the heel and below the medial malleolus. On examination there was marked tenderness to palpation low in the popliteal fossa (fig. 2a) and the pain was increased by passive dorsiflexion of the foot. Pressure applied low in the popliteal fossa evoked a sharp pain below the medial malleolus and a tingling sensation in the sole of the foot. There was weakness of flexion and abduction of the toes and impaired appreciation of tactile and painful stimuli in an area extending from below the medial malleolus and including the heel, the sole of the foot and the ventral surface of the toes (fig. 2a). Electromyography showed fibrillations and positive sharp waves in the abductor hallucis brevis (AHB) muscle with a reduced interference pattern, and occasional fibrillations in both heads of the

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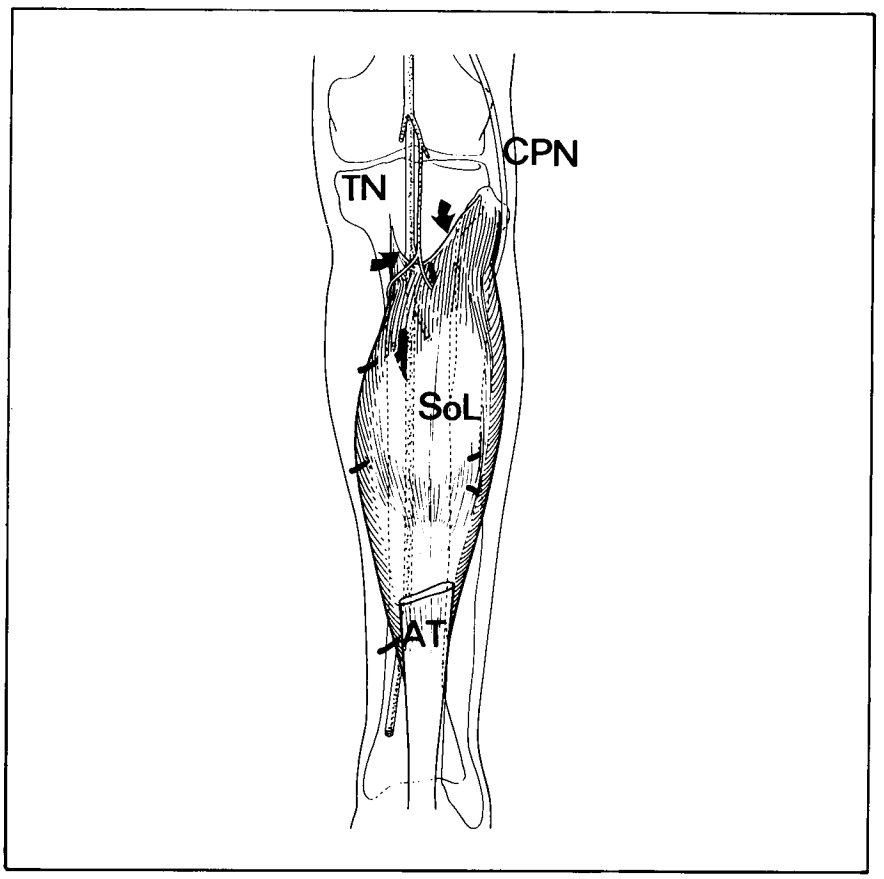

Fig. 1. Schematic drawing of the right popliteal region and leg showing the tibial nerve (TN) leaving the popliteal fossa by passing deep to the tendinous arch of origin (arrows) of the soleus (SoL) muscle and emerging medial to the Achilles tendon (AT). Branches of the tibial nerve to the soleus muscle are shown arising at the level of the knee joint. CPN = common peroneal nerve.

gastrocnemius muscle. The motor conduction velocity (MCV) in the right tibial nerve was normal (49m/sec, terminal latency 6.3msec) but the amplitude of the compound muscle action potential recorded from the AHB was reduced to 1mV. He failed to improve during a 2½ week period of conservative treatment in hospital and the popliteal fossa was therefore explored. The tibial nerve was found to be compressed and flattened beneath the soleus arch with swelling of the nerve trunk proximal to the site of compression (fig. 3). The soleus arch was divided. His symptoms improved markedly in the postoperative period and there was a rapid recovery of sensation in the sole of the foot and of motor function.

Case 2

A 13-year-old schoolgirl who was a very active basketballer gave a 6-week history of pain behind the knee and in the calf and left ankle. This was exacerbated by walking, particularly when the foot was placed flat on the ground, and she had taken to walking on the toes of the left foot. During the preceding 3 weeks she had required full length crutches to walk. Examination showed marked tenderness of the left

calf muscles and in the popliteal fossa (fig. 2b). There was mild weakness of the left triceps surae and of the plantar intrinsic foot muscles, with mild impairment of tactile and pain sensation over the heel, the tendo Achilles and the sole of the foot (fig. 2b). Electromyography showed no evidence of denervation in the calf or foot muscles. The MCV in the left tibial nerve was normal (47m/sec, terminal latency 6.5msec) but was slower than in the left common peroneal nerve (58m/sec). Exploration of the left popliteal fossa was carried out as she failed to improve during a 2 week period of conservative treatment in hospital. As in Case 1, there was compression of the tibial nerve by the soleus arch which was divided. There was prompt improvement in the calf and heel pain and she was discharged essentially asymptomatic on the fourth postoperative day.

Case 3

A 28-year-old heavy transport driver presented with a 6-week history of severe pain behind the left knee and in the calf with the more recent onset of tingling and numbness in the sole of the left foot. He failed to improve with conservative treatment and exploration of the popliteal fossa showed compression of the tibial nerve by the soleus arch, the nerve being flattened and pale at the site of compression and

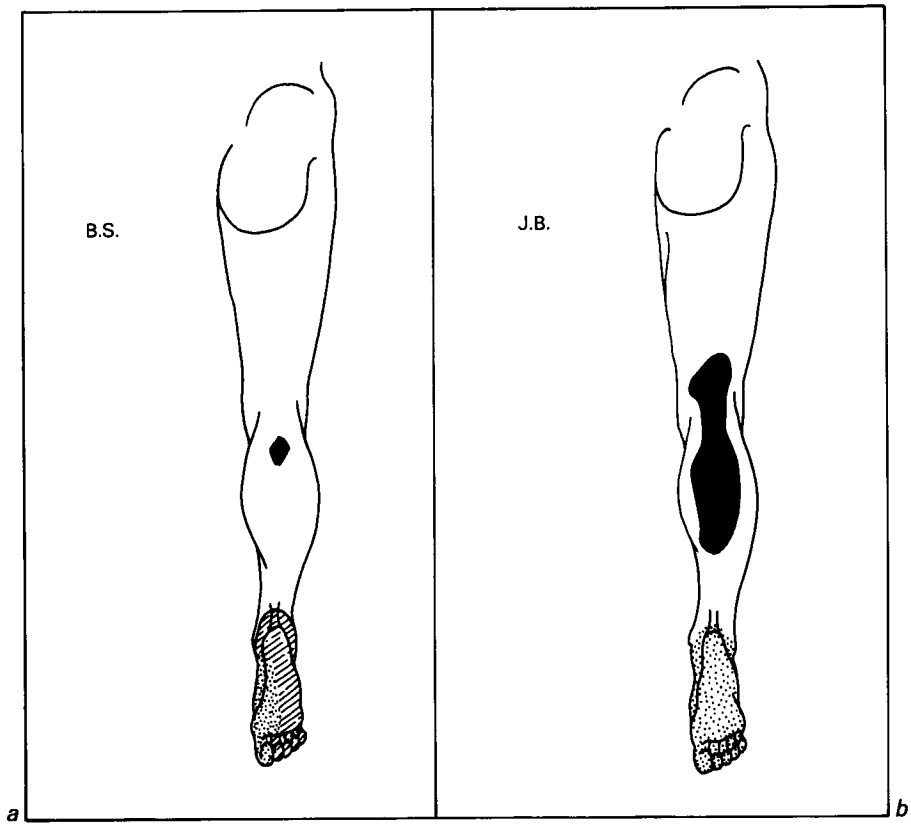

Fig. 2. Schematic drawings indicating the areas of tenderness (black) and of sensory impairment in the foot in Case 1 (a) and Case 2 (b). Sensory impairment was more severe in the cross-hatched area than in the stippled areas.

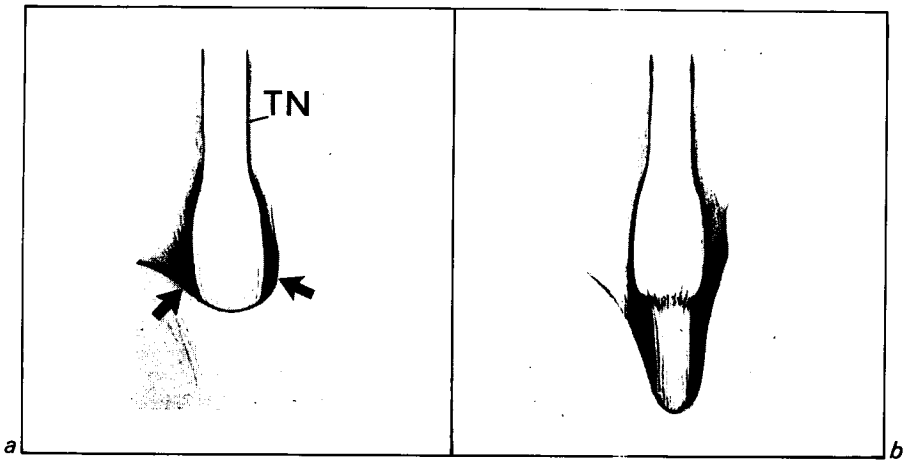

Fig. 3. Artist's impression of the surgical findings in Case 1. a) swelling of the tibial nerve (TN) proximal to the tendinous arch of the soleus muscle (arrows). b) after division of the soleus arch showing flattening of the tibial nerve at the site of compression.

swollen proximal to it. The arch was divided and there was prompt improvement of symptoms in the postoperative period.

Case 4

A 41-year-old transport driver presented with a 5-week history of pain behind the left knee and in the lower thigh and calf. He had developed a limp and found that the pain was made worse when he attempted to place the foot flat on the ground. He had also noted numbness of the lateral 2 toes and sole of the left foot. Examination showed marked tenderness particularly in the lower part of the popliteal fossa and passive dorsiflexion of the left foot gave rise to severe pain. There was impaired appreciation of pinprick over the left heel, tendo Achilles and ventral aspect of the lateral 2 toes and adjoining portion of the sole of the foot. There was weakness of flexion and abduction of the toes of the left foot. Electromyography showed fibrillation potentials in the medial head of the gastrocnemius and a reduced interference pattern with long duration motor unit potentials in this muscle and in the AHB. The MCV in the left tibial nerve was 47m/sec on the left (terminal latency 6.5msec), and 46m/sec on the right. He improved only slightly during a 2-week period in hospital and the popliteal fossa was therefore explored. The popliteal vein was compressed under the soleus arch and dilated above this point with the formation of a large varix anterior to the tibial nerve. The soleus arch was divided and on the following day, the calf pain and numbness in the foot had improved and he was able to abduct the toes of the left foot which he had not been able to do preoperatively.

Case 5

A 25-year-old female bank teller presented with a 1-month history of pain in the right calf and behind the knee and the more recent onset of a limp. On close questioning it was found that the pain had occurred episodically over the previous 10 months since she started her job as a teller. Three weeks previously her general practitioner had infiltrated local anaesthetic into the region of the fibular head and also more deeply into the popliteal fossa. This led to an increase in the calf pain and the onset of tingling and numbness in the heel and sole of the right foot, extending on to the outer aspect and dorsum of the foot. Examination showed impaired appreciation of tactile and painful stimuli over these areas but no definite muscle weakness. There was marked tenderness to palpation in the popliteal fossa and the pain was markedly exacerbated by passive dorsiflexion of the foot. Pressure applied low in the popliteal fossa and passive dorsiflexion of the foot gave rise to paraesthesiae along the outer border of the foot and the fifth

toe. Electromyography showed no evidence of denervation in the muscles of the calf, antero-lateral compartment or foot. The MCV in the right tibial nerve was normal (45m/sec, terminal latency 4msec) as compared to 50m/sec on the left side. MCV in the right common peroneal nerve was 63m/sec. She was treated conservatively but failed to improve and one month later the popliteal fossa was explored. Thrombosis of a large tributary of the popliteal vein in the medial head of the gastrocnemius muscle was found. There was oedema of the contents of the popliteal fossa and the tibial nerve was compressed beneath the soleus arch, which was divided. A postoperative venogram showed lack of filling of the posterior compartment veins but a patent deep venous system. She was anticoagulated and the pain and sensory disturbance in the leg and foot gradually resolved over the ensuing 3 weeks.

Discussion

The patients described presented a distinctive clinical syndrome characterised by pain and tenderness which was maximal in the popliteal fossa and which was markedly exacerbated by active or passive dorsiflexion of the foot and by weight bearing with the foot flat on the ground. These features, together with the motor and sensory deficits, pointed to involvement of the tibial nerve in the popliteal fossa. In each case exploration of the popliteal fossa was carried out, because of failure to improve with conservative treatment, and showed that the tibial nerve was compressed. In 3 cases this was due to a primary entrapment of the nerve by the tendinous arch of origin of the soleus muscle; in the other 2 cases, compression of the nerve was secondary to venous compression or obstruction.

A number of factors may be important aetiologically in causing this type of entrapment neuropathy. In each case the patients were physically fit individuals engaged in occupations or pastimes involving strenuous or sustained muscular activity of the lower limbs and in the 3 with primary entrapment of the nerve, the condition appeared to have developed relatively acutely after periods of particularly strenuous physical activity. A further factor to be considered is the size of the hiatus formed by the soleus arch through which the tibial nerve passes. It is likely that as in the case of other fibromuscular or fibro-osseus compartments the size of the aperture varies. It is possible that certain individuals with smaller soleus canals are more likely to develop compression of the tibial nerve particularly when the calf muscles are well developed and particularly following periods of strenuous physical activity.

Summary

Details of 5 cases of surgically confirmed entrapment of the tibial nerve in the popliteal fossa are presented. In 4 cases the nerve was compressed beneath the tendinous arch of the origin of the soleus muscle. In 1 of these cases, thrombosis of a tributary of the popliteal vein with oedema of structures in the popliteal fossa and secondary compression of the nerve was found. In the fifth case the popliteal vein was compressed by the soleus arch with secondary compression of the nerve. The clinical presentation in these cases was characterised by severe pain and tenderness in the popliteal fossa, aggravated by active and passive dorsiflexion of the foot, inability to

weight bear, and numbness and pain in the sole of the foot and heel. In each case, surgical exploration and division of the soleus arch led to prompt relief of symptoms.

Acknowledgements

The authors are grateful to Mr H. Upenieks who prepared the illustrations and to Mrs P. McBryde for secretarial assistance.

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Hypokalaemic Periodic Paralysis Unresponsive to Acetazolamide

*R.H. Rischbieth**

Hypokalaemic periodic paralysis was first distinguished from the wider group of the familial periodic paralyses, which includes cases of periodic paralysis with normal and with elevated serum potassium, in 1951. Subsequently the distinctive differences in the clinical syndromes associated with each of these disorders were delineated (Gamstorp et al., 1957; Pearson, 1966; Poskanzer and Kerr, 1961), with *adynamia episodica hereditaria* becoming recognised as the classical presentation of the hyperkalaemic group, while carbohydrate, post-exercise, and/or cold precipitated periodic paralysis was associated with a lowering of the serum potassium.

In 1968 acetazolamide, a carbonic anhydrase inhibitor, was reported by Resnik et al. (1968) to be successful in the treatment of 2 patients with hypokalaemic periodic paralysis, and became and remains the treatment of choice for that disorder. Incidentally, these workers also used triamterene, believed to be predominantly a natriuretic drug, without benefit, almost daily attacks of muscle weakness ensuing. They used acetazolamide to treat additional patients with hypokalaemic periodic paralysis and found improvement in 3 and no benefit in 2. They commented on the apparent paradox that acetazolamide seemed prophylactic for both hypokalaemic and hyperkalaemic periodic paralysis. The drug appeared not to affect serum potassium, total body potassium, or total body sodium, or blood pH, nor did it affect muscle excitability directly.

However, Riggs and his co-workers (1980) studied the effect of acetazolamide in 13 normal subjects and found a significant lowering of the plasma potassium ion concentration. They also achieved correction of the sustained hyperkalaemia in a patient with hyperkalaemic periodic paralysis. Further, Riggs et al. (1980) reported a father and son with the hypokalaemic variety of periodic paralysis, who did not respond to acetazolamide, and Dalakos and Engel (1980) also reported failure of acetazolamide therapy in 3 unrelated patients with hypokalaemic periodic paralysis.

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The subject of this report, a 14-year-old farm labourer, appears to be yet another example of non-acetazolamide-responsive hypokalaemic periodic paralysis.

Case Report

S.R.D., a 14-year-old farm labourer, was admitted to The Queen Elizabeth Hospital on 19/4/79, with a story that a week previously he had run a sheep down, requiring more than his usual exercise. That evening his muscles were more sore than usual, and in the early hours of the morning he was unable to lift his blankets with his legs, having to pull them up with his arms. He fell out of bed and could only put himself back again by using his arms. Next morning when working with his father, he had to lift his legs into the car with his hands. He rested at home that day, and regained his strength in the afternoon, his muscles remaining slightly sore.

On the night before admission, while at football training, his legs became unusually sore after running 2 laps. At the end of training he became cold and noticed, on returning to run, that his legs would not work as well, so that he had to retire early. In the early hours of the following morning he woke unable to move his legs, and again fell out of bed, on this occasion being unable to pull himself back with his hands and requiring his mother's assistance. By 7 o'clock in the morning he was able to walk, but fell on a polished floor and had difficulty in standing up again. He was able to eat breakfast without difficulty in swallowing, and improved after a period of rest. However, during the afternoon he became severely weak, was admitted to a country hospital and referred to The Queen Elizabeth Hospital as a possible case of the Guillain-Barré syndrome. He had had mild asthma for 10 years, but his previous health had otherwise been good. There was no family history of similar disorder.

Clinical examination disclosed a cheerful boy with a reduced movement of the right lower face. The limbs were hypotonic. There was marked weakness of all limbs, more severe in the proximal muscles than the distal, so that his hand grips were strong, as were his finger extensors and abductors.

He could twiddle his toes, but was unable to lift his lower limbs from the bed. The knee jerks were brisk, the ankle jerks sluggish. His pulse was 102 per minute and regular. His blood pressure was 150/40mm Hg. There were capillary pulsations in the nail beds, an ejection systolic murmur in the aortic area radiating to the neck, and a short diastolic murmur at the left sternal edge. His ECG showed sinus rhythm with a prolonged QT and flattened T wave and U wave, consistent with hypokalaemia, his serum potassium being 1.8mmol/L. His ALP was 152u/L consistent with age, his CPK 710u/L. He was given 5.4g of oral potassium chloride (sustained release) in the night of his admission, and on the following day had greatly improved with only moderate weakness involving the proximal muscles, although the calf muscles remained slightly tender. The serum potassium was then 4.6mmol/L, and his ECG had returned to normal. A diagnosis of hypokalaemic periodic paralysis was made, but only after a plasma aldosterone test was demonstrated to be normal. The 24-hour urine showed normal potassium excretion, thyroid function tests were normal, as were plasma renin tests. An ischaemic muscle test revealed normal lactate production, and attempts over the next 4 days to provoke further incidents by exercise were unsuccessful. He was discharged with a supply of potassium chloride (sustained release) to take if he developed soreness or weakness, beginning with a dose of 3g.

Nevertheless, over the next 12 months he continued to suffer mild attacks of limb weakness, usually in the early hours of the morning after strenuous activity, either on the farm or at football training on the previous day.

In May 1980 acetazolamide 500mg daily was prescribed, and 2 days later on the morning after a football game, he wakened with a severe attack of weakness, though not as profound as that of his previous admission. However, weakness prevented him from lifting himself off the bed, the hands on this occasion being weaker than the arms. Initially, his knees would not support him to stand, but he then began to improve spontaneously so that he was able to walk to get his potassium tablets and return to bed.

Little improvement occurred in the next 2 hours, but by the time he had travelled the 60 miles to The Queen Elizabeth Hospital he had only slight asymmetrical weakness of proximal and distal upper limb muscles, with only mild residual weakness of knee flexion, but otherwise normal lower limb power,

some 4 or 5 hours after the onset. The serum potassium by this time was 4.1mmol/L. He was admitted to hospital and challenged with further doses of acetazolamide. These provoked subsequent attacks of proximal muscle weakness, particularly involving the shoulder girdles, despite the use of supplementary potassium, the serum potassium falling to 2.3mmol/L during one of his worse attacks of weakness. In view of encouraging reports of the use of dichlorphenamide he was started on this, the dose being increased to 50mg twice daily, but this appeared to precipitate further attacks of hypokalaemia associated with muscle weakness, and the drug was therefore ceased. After an interval of 3 days, triamterene 100mg was instituted daily. Muscle power was then observed over the next 3 days and remained perfectly normal without the use of supplementary potassium, serum potassium levels ranging between 4 and 4.5mmol/L. He was therefore discharged on triamterene alone, and has been followed as an outpatient since that time. He has participated in football games and in training in competitive tennis in the summer, as well as working hard in the sheep yards. Serum potassium levels have remained satisfactory and no clinical incidents have been recorded since May 1980.

Discussion

Familial hypokalaemic periodic paralysis is usually inherited as an autosomal dominant, although males are more often affected than females. Attacks usually appear in the second and third decades and diminish after 35 years of age, but permanent myopathy and weakness may develop in some patients after years of paralytic attacks. Thus it is important that the most effective prophylaxis against acute attacks be instituted as early after the diagnosis has been made as is possible.

In this young man, in order not to limit physical activity, as a farm labourer, as a footballer or as a tennis player, an attempt was made to prevent further damaging attacks by medication in the face of unrestricted physical activity.

Dalakos and Engel (1980) reported 3 patients who were or became unresponsive to acetazolamide, but who responded to dichlorphenamide 50mg, which is also a carbonic anhydrase inhibitor. There is no carbonic anhydrase in skeletal muscle, and the authors therefore postulated an alternative mechanism of action, perhaps involving chloride or bicarbonate ion re-absorption in the renal tubules. McArdle (1962) had also found considerable improvement in most of a group treated with dichlorphenamide. Torres et al. (1980) reported a father and son with hypokalaemic periodic paralysis occurring spontaneously, and also induced by hypoglycaemia, in each of whom an attack of weakness occurred within 2 days of beginning therapy with acetazolamide. Two subsequent single-blind trials in one patient confirmed that attacks were increased in frequency and severity in response to acetazolamide despite prophylaxis with K^+ and spironolactone. However, triamterene 2mg/kg/day virtually abolished attacks during 4 trials over a 12-month period, serum potassium rising significantly while the patient was on triamterene, whereas it had fallen in response to acetazolamide to a degree similar to that found when spontaneous and glucose-induced attacks of weakness had occurred.

It would seem that within the hypokalaemic periodic paralyses there are several sub-groups, some responsive to acetazolamide and not at all to triamterene, others responsive to the latter but not to the former, and others to dichlorphenamide but not to triamterene.

Summary

The case of a 14-year-old farm labourer is presented as a further example of non-acetazolamide responsive hypokalaemic periodic paralysis. The family history was negative, the clinical picture classical, with prompt reversal of symptoms after the use of potassium salts. However, the administration of acetazolamide led to precipitation of an attack within a few days. The use of triamterene 100mg daily resulted in complete cessation of the attacks for the last 12 months with the maintenance of normal serum potassium levels without the use of supplementary potassium.

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A Case of Cortical Deafness

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The auditory cortex in man is located in the posterior superior temporal lobe, particularly in the transverse gyrus of Heschl. Hearing is represented bilaterally although each auditory cortex receives a greater input from the contralateral ear.

Unilateral lesions of the auditory cortex produce no symptomatic hearing loss but several studies have shown subtle auditory deficits. In particular, there may be loss of discrimination of distorted, interrupted or accelerated speech in the contralateral ear (Bocca et al., 1955; Bocca, 1958; Jerger, 1964) or difficulty in localisation of sounds in the contralateral auditory field (Sanchez-Longo et al., 1957).

Judging from the reported cases, bilateral temporal lobe lesions producing auditory deficits are rare, and the study of such cases has often been made difficult by the presence of co-existing dysphasia.

The auditory disorders which have been attributed to bilateral temporal lobe lesions have been due to either impaired perception of sound (cortical deafness) or impaired recognition of sound (auditory agnosia).

The term cortical deafness has been applied to cases in which there is total bilateral loss of hearing. It is, however, more generally applied to those patients whose daily activities and auditory behaviour indicate an extreme lack of awareness of auditory stimuli of any kind and whose audiometric pure tone thresholds are markedly abnormal (Rubens, 1979).

The term auditory agnosia implies the impaired capacity to recognise sounds in the presence of otherwise adequate hearing. The agnosia may be restricted to certain types of sound such as speech (pure word deafness), non-verbal sounds (sound agnosia) or music (sensory amusia).

We wish to describe a patient who presented with the sudden onset of cortical deafness with mild aphasia coinciding with a left temporo-parietal infarction, having previously had a right hemisphere infarction. The nature of the deficits seen during his recovery highlights the difficulty in using the terms described above.

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Case Report

A 70-year-old right-handed man was admitted to hospital on the night of 12th February 1980. His significant past medical history consisted of an uncomplicated inferior myocardial infarction in 1960. After this, he had 1 to 2 syncopal episodes each year related to bradycardia and attributed to the sick sinus syndrome. In January 1976 he had a permanent pacemaker implanted. In 1977 he suffered a right hemisphere cerebrovascular accident resulting in a left hemiplegia, without sensory, visual field or hearing loss. Over subsequent months he made a full recovery.

On the night of admission to hospital the history given by his family was that he had collapsed in his garden that afternoon. He had not lost consciousness but had fallen to the ground and appeared confused and unable to communicate. On arrival at hospital he was unable to respond to commands. There was occasional spontaneous speech which was fluent but nonsense. He made no response of any kind to questions directed to him or to any noise. As far as it was possible to examine him the remainder of the neurological examination was normal.

The following day he was more alert and it was apparent that he was totally deaf. There was no startle response to sudden loud noises made behind him and he made no response to surreptitiously shouted orders or to conversation taking place around him. He made no attempt to understand verbal questions directed at him and at this stage there was no attempt to lip-read. When given a written question or instruction, however, he would respond appropriately. He would read it aloud several times and then either answer verbally or in writing.

He initially misnamed objects and, although he could read a passage of prose fluently, interrogation revealed that he had incompletely comprehended it. He could simultaneously obey 2 written instructions but not 3. He thus demonstrated a mild disturbance of comprehension of written material. Clinical testing of calculation, verbal memory and visual fields revealed no abnormality. There was no other sensory loss.

He spoke in a loud voice without inflexion. He was able to whisper on request but relied on the examiner for feedback. He was also able to make non-verbal sounds such as animal or machine noises. He made paraphasic errors and occasionally errors of syntax in both written and spoken language. He would often repeat the terminal syllable of longer words several times. His answers to questions would also contain superfluous detail. For example, when asked what had happened to him he wrote '... in the back garden on 12th was hot mid after a stroke seized me on the lawn and this has left my hearing senses and I have been left stone deaf and I cannot hear any noises or sounds after this serious collapse.'

The patient continued to complain of complete deafness for 1 week. He then began to hear occasional sounds which seemed distant and muffled. He was not able to identify any of these sounds. Over subsequent days, however, he began to hear sounds more consistently and clearly but could only recognise occasional sounds in the ward such as a telephone ringing. After a further week he began to pick up occasional words in conversation. At the time of discharge from hospital 3 weeks after admission he was able, with the assistance of visual cues, to understand most of a conversation directed at him. He would usually repeat the statement to himself as if this were necessary for him to comprehend it.

Two months after the onset, his major complaints were that he was unable to understand a telephone conversation or voices on the radio or television. He was also unable to appreciate music which he said all sounded the same to him.

After 12 months his comprehension of speech had improved considerably but he was unable to understand distorted speech or normal speech when he was distracted. His inability to recognise music persisted.

CT scans were performed 3 days and 3 months after admission. These showed a large area of infarction in the right temporo-parietal region and a small area of infarction in the same region on the left (fig. 1).

Pure tone audiometry was performed 9 days after admission (fig. 2). This was at a time when partial return of hearing had occurred. It was noted that his reliability was very poor and that he performed better on a descending approach and made no response when ascending. Speech discrimination tests revealed that he was aware of a voice at 80 decibels bilaterally although he could not tell that it was a voice.

Brain stem and cortical evoked responses were performed 8 days after admission and the cortical evoked responses were repeated after 14 months (figs. 3 and 4). These showed that the brain stem evoked potentials were present initially, indicating an intact peripheral pathway. The cortical evoked responses, however, were absent initially but had returned by the time of the repeat examination with responses recorded down to a 30 decibel binaural click.

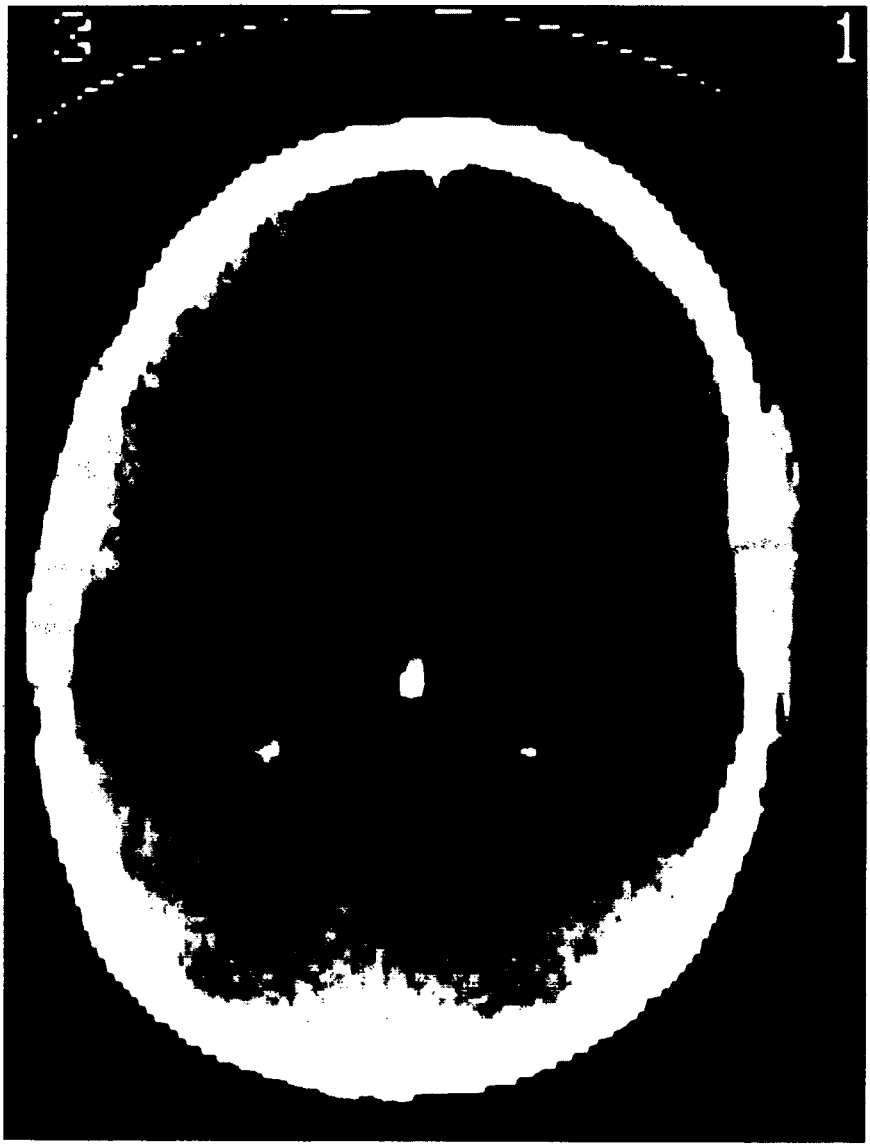

Fig. 1. A representative CT scan showing bilateral temporal lobe infarction. (By courtesy, Dr Sage.)

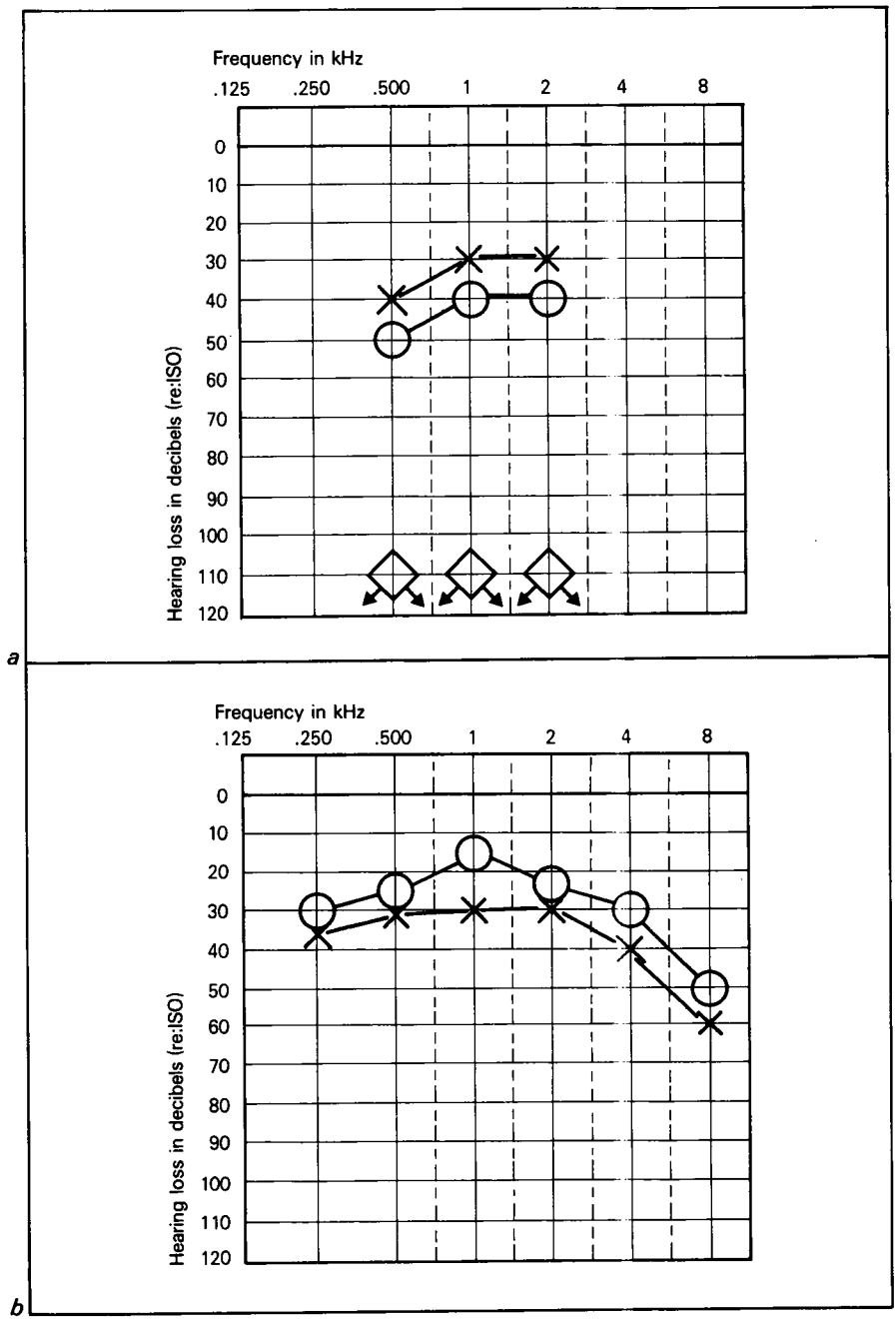

Fig. 2. a) Initial audiogram 21/2/80, b) Repeat audiogram 1/8/80. X = left, O = right.

Discussion

This case is of interest for several reasons. There have been very few cases in which CT scanning and cortical evoked responses have been performed. It is, to our knowledge, the only case in which the cortical evoked responses have been absent and subsequently returned. Furthermore, during the various stages of recovery this case demonstrated a spectrum of auditory and associative disturbances.

It is clear from the history and mild dysphasia present on admission that the onset of deafness coincided with the left temporo-parietal infarction seen on the CT

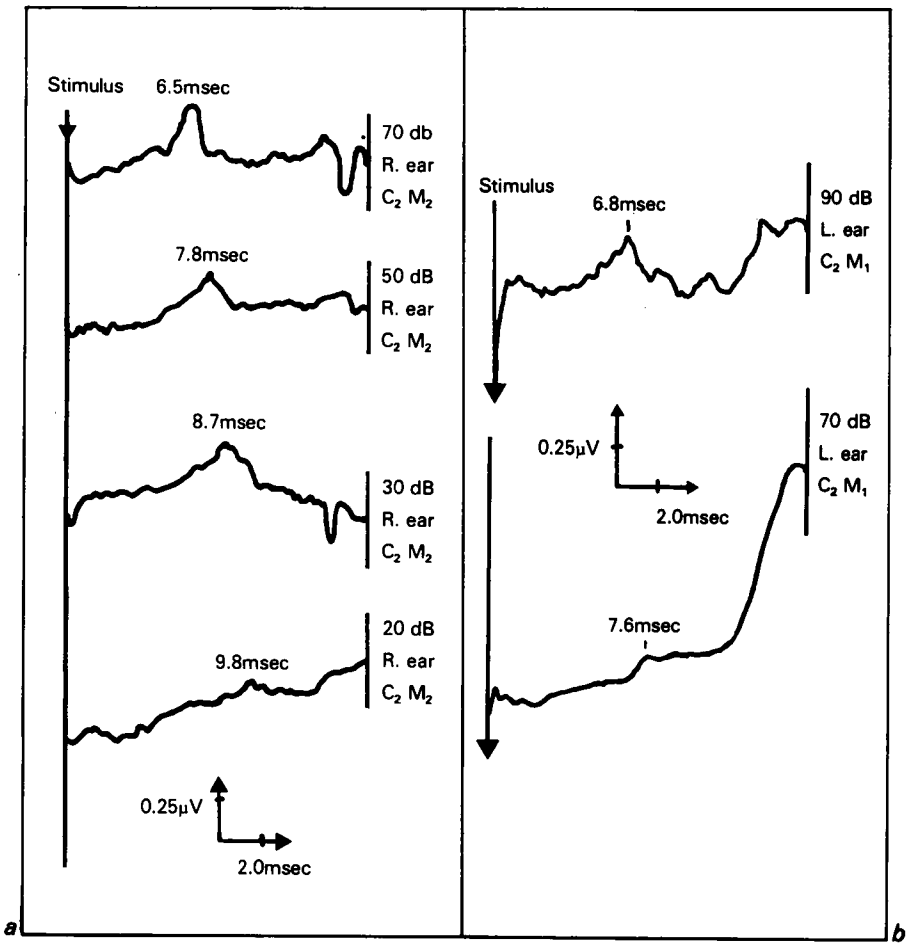

Fig. 3. a) Right ear brain stem evoked responses 20.2.81. b) Left ear brain stem evoked responses 20.2.81.

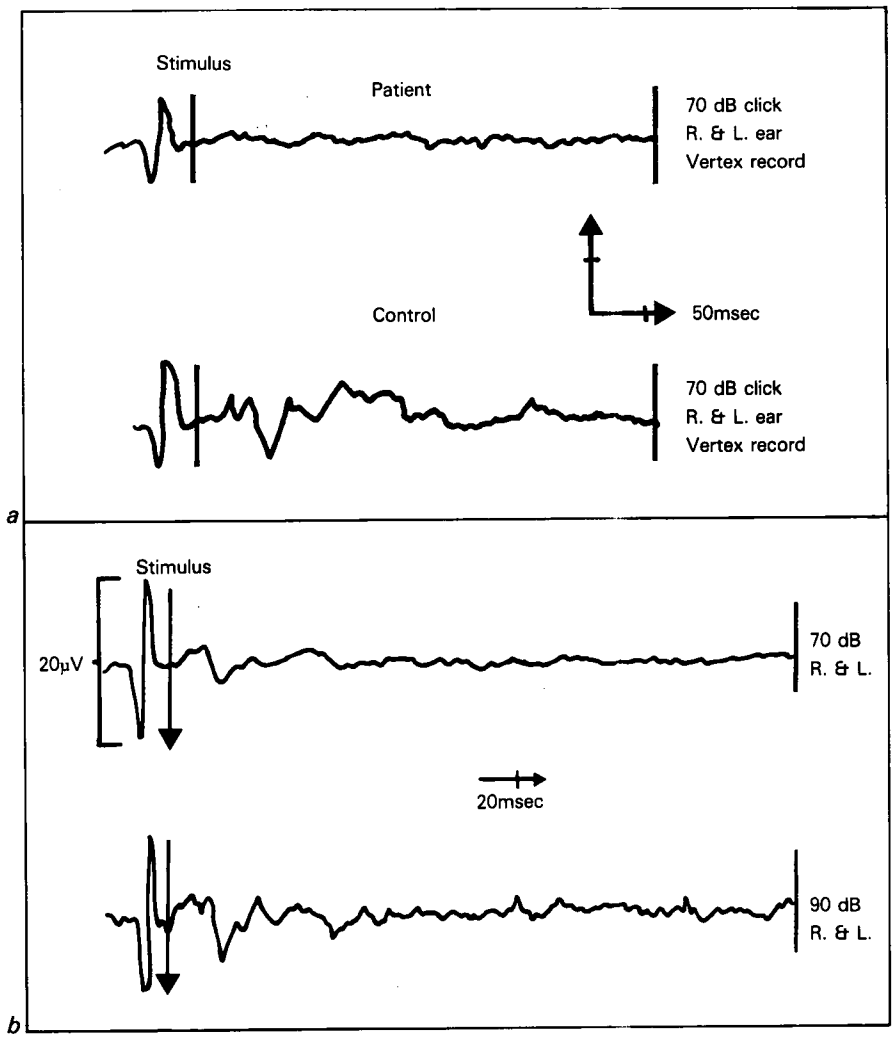

Fig. 4. Cortical auditory evoked potentials 20.2.81 (a) and 4.3.81 (b).

scan and that the larger right temporo-parietal infarct was related to the episode of left hemiplegia 3 years earlier.

As the patient's hearing was recovering he was initially unable to identify any sound. It would seem likely that this was due to an auditory agnosia but it is difficult to know to what extent his persisting cortical hearing loss was contributing. Similarly, if it were not for this, one might have easily labelled him as having pure word deafness during the phase when he was recognising sounds but not speech. There seems little doubt, however, that his persisting amusia is an agnosic deficit.

This highlights the problem associated with the use of conventional terminology to describe these disorders. As Kanshepolsky et al. (1973) note, pure syndromes are seldom encountered and more commonly a combination of auditory and perceptive deficits results from destruction of cortical auditory areas. This led to the suggestion of using the more general terms of a cortical auditory disorder which would seem appropriate in this case.

Summary

The presentation of cortical deafness, associated with mild dysphasia due to bilateral temporo-parietal infarction in a 70-year-old man, is described. Partial return of hearing occurred and associated with this a more complex cortical hearing disorder was seen with elements of both decreased auditory acuity and auditory agnosia.

After 1 year a mild hearing loss persisted with difficulty in speech discrimination and an inability to recognise music.

Bilateral temporo-parietal infarction was confirmed by CT scan. The cortical auditory evoked responses were initially absent despite intact brain stem auditory evoked responses. After a year, however, the cortical evoked responses had returned.

Acknowledgements

Thanks are due to Drs J. Manson and P. Weston, Adelaide Children's Hospital, for performing the auditory evoked responses; to Dr D. Beaumont, Flinders Medical Centre, for the ENT and audiometric assessments and to the Department of Radiology, Flinders Medical Centre, for the CT scan.

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Metachromatic Leucodystrophy in Children

*Peter G. Procopis**

Metachromatic leucodystrophy (MLD) is a metabolic disorder characterised by the deficiency of the enzyme cerebroside sulphatase, which is known as aryl-sulphatase A when an artificial substrate is used for its determination in the laboratory. As a result of this deficiency, the complex lipid cerebroside sulphate (also known as 'sulphatide') accumulates in central nervous system white matter, peripheral nerves and other organs (e.g. kidney). This leads to a degenerative disease characterised by progressive spasticity, peripheral neuropathy and dementia.

Since 1974, 9 patients with an enzymologically-proven diagnosis of MLD have been seen at the Royal Alexandra Hospital for Children. This paper summarises the findings in these children.

Clinical Features

Of the 9 children, 4 were boys. Their age of presentation was from birth to 8.8 years. However, 6 of the 9 presented between the ages of 2 and 4 years, reflecting the fact that the so-called 'late infantile' form of the disease is most commonly seen.

Onset

The initial manifestation of the disease was most commonly regression in motor milestones (7/9). One of these children presented with ataxia which was at first thought to be due to one of the spinocerebellar degenerations until leucocyte enzyme analysis showed the characteristic deficiency of cerebroside sulphatase. Another patient (J.G.), who is described below, presented with loss of previously acquired

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language whereas in another, speech deterioration accompanied motor regression. A seizure was the initial manifestation in another child.

Peripheral Neuropathy

Signs of a peripheral neuropathy were present in 6 children at presentation and in 7 at some time in their illness. These signs consisted of muscle wasting and the absence of some, or all, of the deep tendon reflexes. In 1 patient the deep tendon reflexes were absent on presentation but as the disease became more advanced they returned and became increased, presumably because of progressive demyelination of the pyramidal tracts. Sensory signs attributable to a peripheral neuropathy were not found probably because of the ages of the patients and their dementia.

Pyramidal Tract Signs

These were present in 8 of the 9 patients at some time. Usually a combination of pyramidal tract signs and signs of a peripheral neuropathy developed, e.g. increased muscle tone, muscle wasting, brisk knee jerks, absent ankle jerks and bilateral extensor plantar responses.

Cerebellar Signs

Ataxia not explained by a clinical peripheral neuropathy or a pyramidal tract deficit, was present in 1 patient. An action tremor was observed in 2 children. Two had nystagmus late in their course.

Dementia

Dementia of a progressive nature was present in 8/9 patients.

Seizures

Seizures occurred in 4 patients. They were either generalised or partial, occurred relatively infrequently and were easily controlled with standard anticonvulsant therapy.

One patient (J.G.) had none of the above features.

Course

Four of the children in this series have died. The duration of their clinical disease before death ranged from 9 months to 3 1/2 years. Three of the survivors have shown a progressive degenerative course and one (J.G.) has shown only slight intellectual deterioration without deterioration in motor abilities. One child has been lost to follow-up.

Genetics

MLD is inherited as an autosomal recessive characteristic. This is reflected by the fact that 5 of the patients in this series were the product of a consanguineous marriage.

Investigations

Enzyme Analysis

The diagnosis of MLD was confirmed in all patients in this series by the finding of the characteristic enzyme deficiency in both leucocytes and skin fibroblasts. Both natural and artificial substrates were used.

Nerve Conduction Studies

These were abnormal at presentation in all patients except J.G. Motor conduction velocities ranged from 13 to 58m/sec. Sensory potentials were studied in 5 patients and were absent in all except J.G.

Sural Nerve Biopsy

Biopsies were performed in 4 patients. Three had definite demyelination and Schwann cell inclusions by light or electron microscopy. In the biopsy from patient J.G. the nerve was normal on light microscopy but on electron microscopy one Schwann cell was found containing a typical 'tuff-stone' inclusion.

CT Scan

The CT scan findings in the leucodystrophies have been reported previously (Procopis, 1980). A scan was done on 6 of the children in this series and showed white matter degeneration in all except J.G. One child, in whom an enzymological diagnosis had been made at birth because of an affected sibling, had a normal CT scan at the age of 9 months. At the age of 2 1/2 years her scan showed the typical changes of a leucodystrophy.

CSF Protein

The CSF protein level ranged from 0.03 to 0.14g/L (normal — up to 0.04g/L). Two patients had normal levels and whereas neither had clinical signs of a peripheral neuropathy at the time, both had slow motor nerve conduction velocities.

Case Report

J.G., male, presented at the age of 3 years with progressive loss of previously acquired language skills and hyperactivity. Neurological and general physical examination were normal apart from marked aphasia. Investigations including audiogram and electroencephalogram were normal. However, the typical enzyme deficiency of MLD was found repeatedly in both leucocyte and skin fibroblast assay. Furthermore, the 24-hour urine excretion of cerebroside sulphate was markedly elevated at 246μg (normal — < 5μg). However, nerve conduction studies and a CT scan were normal. A sural nerve biopsy was normal to light microscopy and only one Schwann cell inclusion was present on electron microscopy.

This boy has been followed for 5 years. Although he requires special schooling and is without meaningful speech, only mild intellectual deterioration has otherwise occurred. His motor abilities have not deteriorated and in fact the school has reported that he has become more agile recently. No signs of peripheral neuropathy or pyramidal tract deficit have yet appeared.

Summary

Nine children with a proven enzymological diagnosis of metachromatic leucodystrophy are described. All except one have shown a progressive course with the clinical features of peripheral neuropathy, corticospinal tract involvement and dementia. Seizures and cerebellar signs also may occur. Abnormalities in nerve conduction, CSF, sural nerve biopsy and CT scan are described. One patient presented with language regression but after 5 years still had not developed other features of MLD.

Acknowledgements

The author wishes to thank Dr A.C. Pollard, Department of Chemical Pathology, Adelaide Children's Hospital, for enzyme assays and his continuing interest in these patients.

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Preservation of Acquired Music Performance Functions with a Dominant Hemisphere Lesion: A Case Report

D. Erdonmez and J.B. Morley

There is increasing interest in the differentiation of functions, for speech and music, for the dominant and non-dominant hemispheres. Henschen (1920), after recording several cases of motor amusia without aphasia, proposed different cerebral systems for speech and music functions. However, Feuchtwanger (1930) asserted that there was no significant difference between amusia and aphasia. Lately, Deutsch (1970) has presented experimental evidence supporting Henschen's view. Contemporary views are that musical memory functions depend more on the non-dominant hemisphere in musically naive subjects, with greater dominant hemisphere involvement in musically proficient persons (Damásio and Damásio, 1977; Wyke, 1977; Gates and Bradshaw, 1977; Wertheim, 1977).

It has been known for almost 250 years that aphasic persons may still be able to sing the melody and words of familiar songs (Dalin, 1745). Henschen (1920) examined the relationship between aphasias and amusias, and for the latter he proposed the traditional dual classification of motor and sensory, with specific subvarieties. Ustvedt (1937) examined a number of aphasic patients who had had musical training, and also distinguished perceptive and expressive disorders of musical function.

This case report, of the effects of an extensive left cerebral hemisphere lesion in a competent musician, is presented for the following reasons:

1) To document his preserved and disturbed musical functions.
2) To outline the correlations and contrasts with his speech disturbances.
3) To demonstrate the role of music therapy in his rehabilitation.

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Case Report

A 54-year-old, right-handed professional man suffered a left parieto-temporal infarct in December 1978. He was rendered aphasic, with a total right hemiplegia. CT scan confirmed the diagnosis, and the massive extent of his lesion (fig. 1).

He had been polyglot: he had learnt Latin at school, and Italian and German as an adult. He was musically competent on the piano and organ, with a broad classical repertoire.

With physiotherapy, occupational therapy, speech therapy and music therapy, he has gradually partly improved. His right arm remains paralysed. He can walk unaided despite a residual spastic right leg paresis. He has no facial weakness. Light touch, pain and thermal perceptions are moderately impaired down his right side, sparing the face. Vibration sense is normal in both right extremities. Joint position sense is normal in the right toes, and reduced in the right fingers. Tactile localisation and graphaesthesia are markedly impaired in both right limbs. He has right-left disorientation. He has a right homonymous hemianopia.

On speech testing, he can utter short phrases, characterised by literal and verbal paraphasia. He still has moderately severe receptive dysphasia. He can translate brief Latin phrases, but has lost all of the more recently acquired Italian and German language skills. On processing of auditory information, he can cope only with 3 units. He can read only single words, yet has minimal impairment of automised sequences such as singing in tune and tapping rhythms, although the rhythms used were repetitious.

On neuropsychological testing (WAIS), his performance IQ is 117, considered consistent with his premorbid IQ. Memory testing was restricted to visual memory tasks, and on the Benton Visual Retention Test his scores are normal. He is well oriented in time and place, can count backwards from 20 to 1, and can count in 3s from 1 to 40. He cannot recite the alphabet past G, and his immediate memory span is only 3 digits forwards. The latter is consistent with his auditory processing limitations; his inability to recite past the letter G may be coincidental with the names of music notes which span A to G.

On music testing, although dyslexic, he reads music fluently. In singing skills, he retains melodic and rhythmic memory for known songs, but the lyrical content is sporadic. He is highly motivated and eager to adapt his left hand to playing in the treble clef.

Music therapy began 10 months after his stroke. The patient chose all music himself, playing the treble with his left hand, and the therapist playing the bass with her left hand. Much of the music chosen had already been learnt in the premorbid state.

Initially he chose chordal pieces in simple keys. He was unable to name the notes of the piano, or the notes of the music, yet he interpreted the music information accurately. He was unable to name the symbols 'sharp', 'flat', or 'natural', yet he executed them correctly. He retained the key framework throughout the piece.

Although it is customary to mark music with fingering to aid in learning, our patient is unable to associate the numbers 1 to 5 with the fingers of his left hand. He therefore learns by repetition and by rote. He encounters difficulties where the score demands repetition of a single note, but this is not true of chords. He experiences difficulty in correct timing where there are notes of long duration.

After 12 months of music therapy, our patient had turned his attention to the Bach 2-part and 3-part Inventions (fig. 2). These works are recognised as difficult in several aspects:

1) The melodic line can not be anticipated, so that each note has to be read as a separate entity.
2) The melodic contour is interwoven and linear in concept, rather than the vertical concept of chordal music.
3) There is greater use of accidentals.
4) There is a greater demand for finger dexterity, which is additionally arduous for the left hand (e.g. scale passages written for the right hand are considerably more difficult when played with the left hand, as this requires crossing the midline of the body and a resulting imbalance).

While the 2-part inventions require the left hand to play one linear pattern, the 3-part inventions require interweaving 2 strands together. This process demands sequencing skills which are not apparent in his speech, indicating different neurological specialisation.

On the Botez-Wertheim battery (1959), the following sub-test results were obtained.

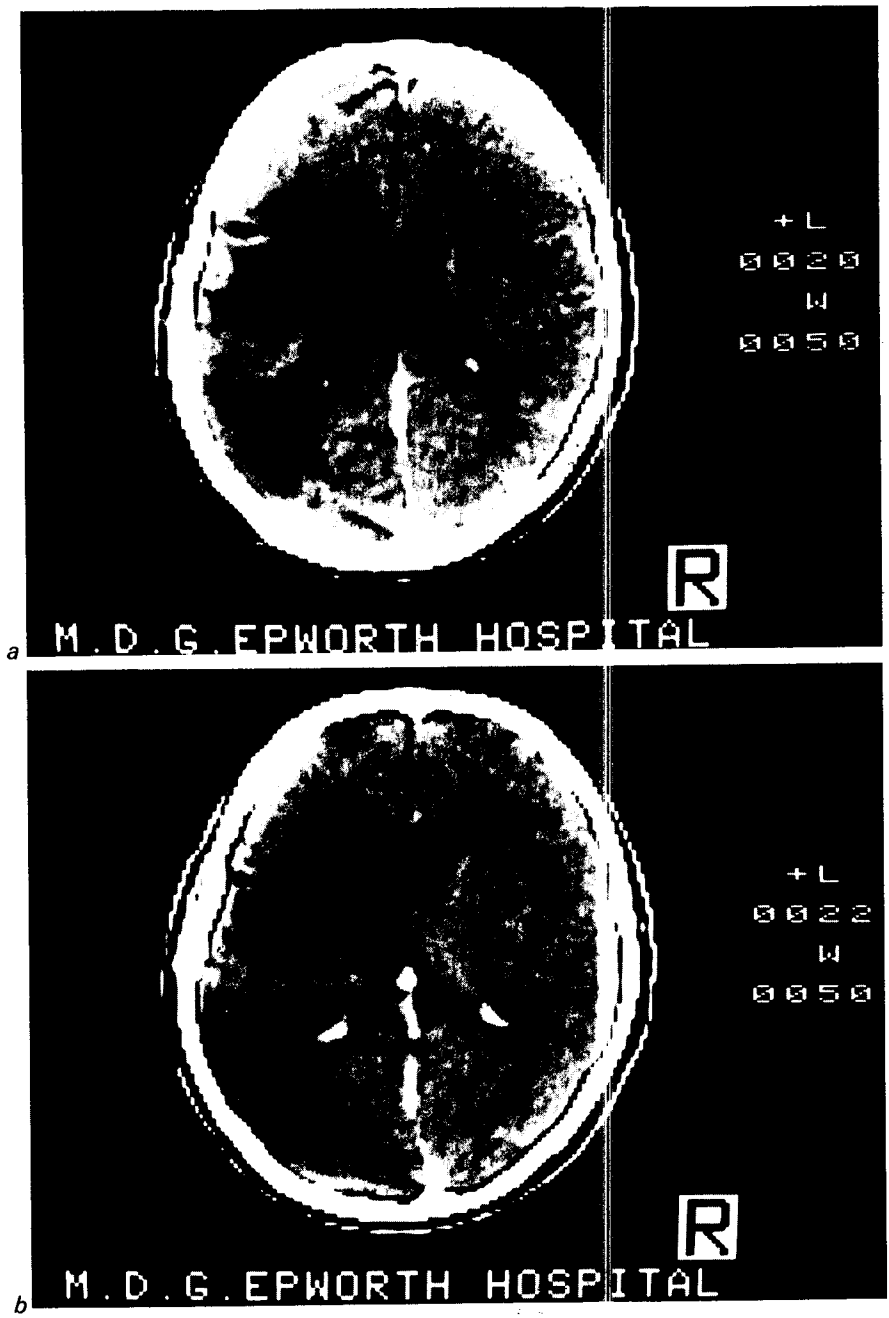

Fig. 1a,b. CT brain scan views, nearly two and a half years after the cerebral infarct.

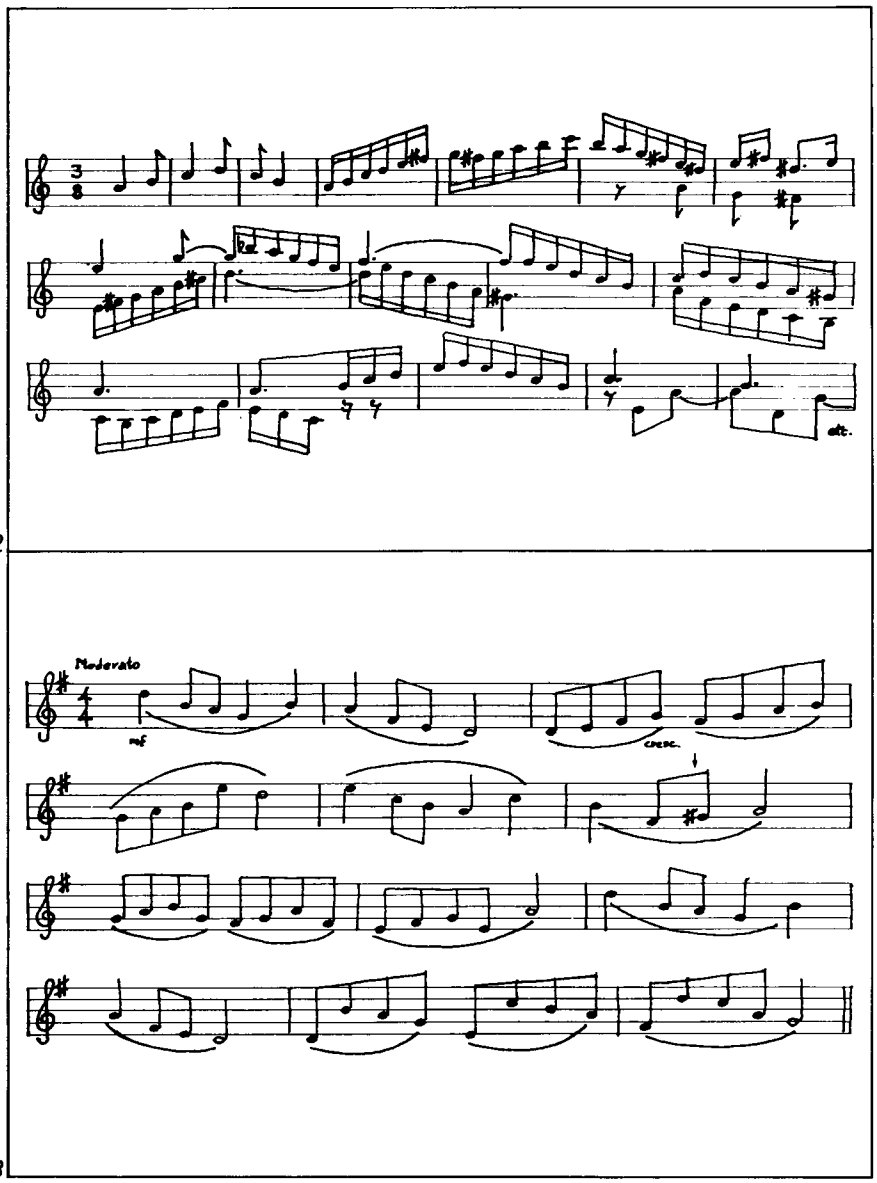

Fig. 2. Bach 3-part Invention Number 13 in A minor, reproduced to show the two linear melodic lines played in the left hand by the subject.

Fig. 3. Reproduction of a piece played at sight by the subject. All notes 'f' were correctly played as 'f sharp' in accordance with the key signature. The arrow indicates an accidental requiring the 'g' to be played as 'g sharp'. The accidental is in effect for the duration of that bar only. The patient made a mistake at this point, but immediately indicated this having concluded playing the piece.

Melodic and Harmonic Elements

The results of this sub-test were consistent with observations made above. Our patient could reproduce separate sounds, continue a known melody, recognise melodies and recognise faults played intentionally by the music therapist.

He had difficulty differentiating major from minor chords, and was unable to grasp the directions to identify the number of notes in a chord until the music therapist simplified the task, viz. 'are there 2 or 3 notes in this chord'.

Expressive tasks relating to the naming of notes played, and the playing of notes named, were the most difficult tasks. The patient was very slow to answer, and in some instances named a note by counting up from the previously named one. Recognition of intervals (e.g. 3rd, 5th octave) was totally beyond him. He could neither understand the directions given, nor could he choose if an option was given.

Rhythmic Elements

Our patient showed considerable loss in this area. He could identify the metre of a piece (3/4, 2/4 or 4/4), but was unable to reproduce a rhythm when presented as a melody or as a single note rhythm, unless the pattern was simple. This finding is consistent with the 3-unit memory mentioned in the speech pathology report and in the neuropsychological report.

Lexic Elements

The patient was asked to play at sight a piece which he could not have seen before. This was to test for the ability to read music, despite an inability to name notes. The piece was played at speed, and the rhythm was correct throughout.

Melodic accuracy was almost correct throughout — a few mistakes were made at the modulation point where accidentals are introduced. On finishing the piece, he identified the mistakes made (fig. 3). He could not name the clef, or key signature, but noted there was one sharp. He could not name which sharp it was, but executed the piece correctly. He correctly translated the Italian terms 'moderato' and 'allegro' (giving text book translations), but the symbol 'mf' was interpreted as 'slow but loud and soft and then hit big'; concepts of loud-soft and slow-fast are obviously confused and there is evidence of nominal aphasia.

Overall there appear to be difficulties in both the receptive and expressive areas. Some tasks could be completed if they were simple, but other complex tasks like sight reading were well executed.

Discussion

This patient exhibits a musical alexia, being unable to name notes or verbally interpret musical symbols, but he can read these correctly in sight reading for musical performance. One explanation of this is that, for a practised musician, the reading of music is automatic; it is unnecessary for the subject to 'translate' musical symbols into names before being able to perform them.

With regard to the conflicting results of the rhythm tests, where the patient did well in the speech test, but poorly in the music test, the possible explanation may lie in the different processes involved in simple and complex tasks. Where the rhythmic pattern was repetitive, but no more than 4 notes, he responded accurately. Longer patterns, or patterns presented melodically, or notes of longer value, tended to confuse the patient, indicating different neurological functioning. Yet his sight reading of an unseen piece indicated accurate rhythmic execution.

It thus appears that the music score is necessary as a constant cueing support in this case. An additional interpretation is that melodic rhythms are processed differently to non-melodic rhythms.

There is little known about the localisation of rhythmic functions in the brain. However, we have already cited references, pertaining to the steadily enlarging body of evidence, that melodic musical functions depend upon intact non-dominant hemisphere activity. Our observations support these propositions.

Conclusions

Our observations accord with the current view that many music memory functions rely on non-dominant hemisphere activity. However, it also is clear that there are fundamental systems which are common to both verbal and music memories, which have been disrupted by the massive lesion in this subject.

In this case, one of the roles of the music therapist has been to make it possible to define some of the contrasts and similarities in his aphasic and amusic patterns. Bearing in mind that he has been a competent musician for years, his music therapy would appear to have been of tangible benefit in his rehabilitation.

Summary

This paper presents evidence of preservation of acquired music performance functions in a right-handed man with a large dominant hemisphere lesion.

Results of music testing, speech pathology testing, neuropsychological testing and neurological examination are presented, with evidence of intact music skills (melodic perception and an ability to read at sight) being compared with lost skills (auditory processing span of 3 digits forward, and impairment of complex rhythmic tasks).

Interpretations are offered in light of contemporary theories suggesting that brain processes for musical memory involve different cerebral systems to those for verbal memory.

Acknowledgements

We gratefully acknowledge the assistance of Mrs J. Blomley, Speech Pathologist, Mrs M. Molloy, Neuropsychologist, and the Melbourne Diagnostic Group, for their valuable time and cooperation in testing for this case.

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Changes in Peripheral and Central Nerve Conduction with Aging

*R.A. Mackenzie and L.H. Phillips II**

Magladery et al. (1951) first described the recording of a thoraco-lumbar potential in man. They stimulated the posterior tibial nerve at the ankle and recorded from the subdural space. Since the introduction of averaging techniques to record cerebral evoked potentials (Halliday and Wakefield, 1963), lower limb nerves have been stimulated and surface potentials recorded over lumbar spine (Liberson et al., 1963, 1966; Cracco, 1973; Cracco et al., 1975) and central sensory cortex (Jones and Small, 1978; Eisen and Nudleman, 1979; Eisen and Odusote, 1980). By comparing the latencies of somatosensory evoked potentials (SEPs) recorded simultaneously from the scalp and the spine, a measure of conduction time in central pathways may be obtained (Hume and Cant, 1978). The 'central conduction time' of median nerve pathways has been determined in normal and healthy aged subjects (Desmedt and Cheron, 1980) but similar controls have not previously been established for lower limb nerves. The present study was undertaken to establish age- and height-corrected values for spinal and scalp recorded SEPs evoked by stimulation of the posterior tibial nerve in man.

Methods

Thirty adult paid volunteers (8 males and 22 females) aged 21 to 70 years (mean 42.9 years) were used in this study. None had a history or examination to suggest the presence of any peripheral or central disorder of the nervous system. Tests were carried out in a warm room, and a skin temperature of 31°C was maintained with radiant heat when necessary. Electrical stimuli were square wave pulses 0.2msec in duration applied through a stimulus isolation unit and surface electrodes. Supramax-

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Table I. Age changes in peripheral potentials (posterior tibial nerve) in 2 groups, each of 10 patients

Feature	Age group (years)		Significance
	21 to 33	50 to 70	
Motor amplitude	16.6 ± 3.1	10.9 ± 4.6	$p < 0.01$
Sensory amplitude (μV)	22.3 ± 8.1	7.3 ± 3.6	$p < 0.02$
Motor latency (msec)	3.6 ± 0.4	3.5 ± 0.4	NSD
Sensory latency (msec)	3.0 ± 0.5	3.0 ± 0.4	NSD
F wave latency (msec)	46.0 ± 5.0	49.0 ± 6.0	NSD

imal stimuli were used for peripheral nerve conduction studies; SEPs were obtained by 3/sec stimuli delivered to the right posterior tibial nerve at the ankle (cathode proximal) which produced a visible twitch of the abductor hallucis muscle. Recording electrodes were 5mm tin discs secured to the skin by plastic tape and filled with an electrolytic salt gel to give interelectrode impedence of less than 2000ohms. Posterior tibial nerve motor conduction studies were carried out using standard techniques; a nerve action potential was obtained at the ankle by stimulating the medial plantar nerve 14cm distal to the active recording electrode. The thoraco-lumbar spinal SEP was recorded from an active electrode over L1 spinous process and a reference electrode over right iliac crest. Cervical spinal SEP was recorded from an active electrode over C5 spinous process and cortical SEP from an active electrode at CZ; common FZ reference was used for both these sites. All recordings were made with standard electromyographic equipment. Frequency response of the system for SEP recording was linear, with less than 3dB rolloff over a range from 32Hz to 1.6KHz. SEP recordings were made at a gain setting of 20μV per cm and amplified 4 times after averaging. Signal averaging was performed with a digital averager with 512 or 1024 addresses at a sampling interval of 39 or 49μsec (25,600 or 20,480Hz). Two trials of each SEP recording were photographically superimposed.

Results

Age Changes in Peripheral Potentials (table I)

The mean amplitude of the motor potential evoked by stimulation at the knee was 13.3mV and declined with age. However, distal motor latency (mean 3.5msec), motor conduction velocity (mean 51.4m/sec) and F wave latency (mean 47.2m/sec) did not change significantly. The amplitude of the nerve action potential evoked by stimulation of the medial plantar nerve was 13.8μV and declined with age; mean peak latency was 3.0msec and there was no significant change with age.

Table II. Age changes in central potentials in 2 groups, each of 10 patients

Feature	Age group (years)		Significance
	21 to 33	50 to 70	
Thoraco-lumbar amplitude (μV)	1.5 ± 0.6	0.7 ± 0.3	$p < 0.001$
Cervical ampitude (μV)	0.9 ±0.3	0.7 ± 0.2	NSD
Central amplitude (μV)	1.6 ± 0.9	1.3 ± 0.9	NSD
Thoraco-lumbar latency (msec)	21.1 ± 1.7	23.7 ± 1.9	$p < 0.01$
Cervical latency (msec)	28.4 ± 2.3	31.9 ± 2.5	$p < 0.02$
Central latency (msec)	36.1 ± 2.2	41.2 ± 2.5	$p < 0.001$

Age Changes in Central Potentials (fig. 1, table II)

Consistent potentials were obtained at all 3 recording sites in all subjects; 512 stimuli were sufficient in most subjects, but 1024 were required on 6 occasions, usually to highlight a lower amplitude thoraco-lumbar potential in an older subject. The amplitude of the thoraco-lumbar potential (mean 1.1μV) decreased significantly with age, and the change correlated well with the decline in the amplitude of the peripheral posterior tibial nerve action potential (Pearson r co-efficient = 0.60). The mean amplitude of the cervical (0.8μV) and the central potentials also fell with age, but the changes did not reach the level of statistical significance.

All latency values listed in tables II and III have been multiplied by a correction factor for variation in height between subjects; this was done to enable assessment of the effect of age alone on conduction time.

$$\text{The corrected latency} = \text{the absolute latency} \times \frac{\text{mean height of sample}}{\text{height of subject}}$$

The mean height of the sample was 169.6cm.

The peak latency of the thoraco-lumbar potential was 22.1 ± 2.2msec (mean ± SD). It can be seen from table II that the increase with age was significant. Analysis of the raw figures also revealed a significant correlation of latency with height (r = 0.80), distance from cathode to L1 (r = 0.83) and F wave latency (r = 0.85) in the younger patients (age 21 to 41 years).

The peak latency of the cervical potential was 29.8 ± 2.2msec and increased significantly with age; there was also a significant correlation with height in the younger subjects (r = 0.84).

Scalp recorded responses consisted of an initial negative wave of low amplitude (in about half the subjects) followed (in all subjects) by a larger positive wave and then 2 negative waves. The latency to the peak of the initial positive wave was 38.3 ±

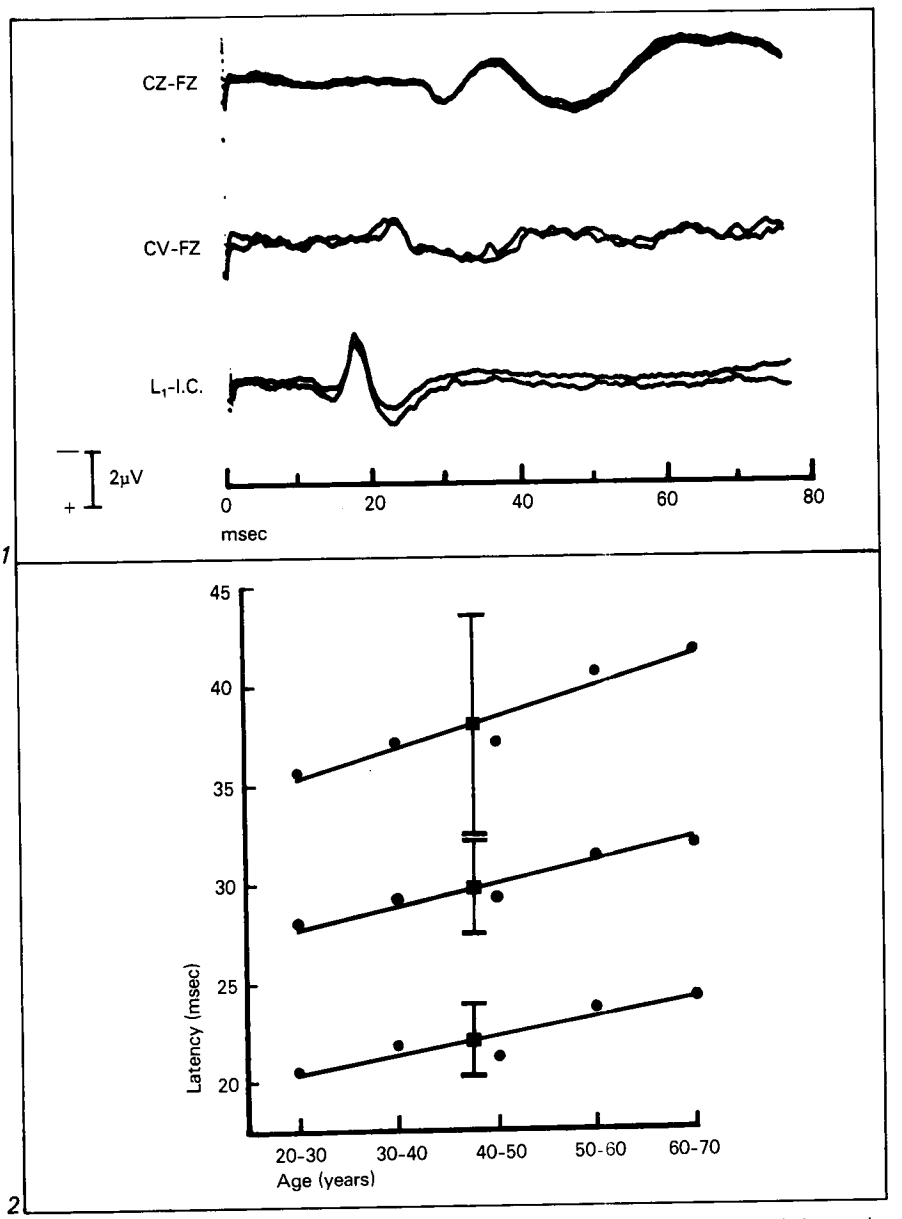

Fig. 1. SEPs recorded simultaneously at 3 sites after posterior tibial nerve stimulation at the ankle. Electrode placements are shown for each site; 2 separate runs are photographically superimposed.

Fig. 2. Mean latencies in age groups indicated for thoraco-lumbar (bottom), cervical (middle) and scalp (top) SEPs. Linear regression lines and 95% confidence limits are shown.

Table III. Age changes in central conduction time in 2 groups, each of 10 patients

Region	Age group (years)		Significance
	21 to 33	50 to 70	
Spinal cord alone	7.2 ± 0.8	7.9 ± 0.9	NSD
Brain stem to cortex	7.9 ± 1.0	9.4 ± 1.2	$p < 0.01$
Spinal cord to cortex	15.1 ± 1.2	17.3 ± 1.3	$p < 0.01$

3.3msec. Table II shows that the increase in latency with age was statistically significant. Correlation with height was again significant ($r = 0.69$).

Figure 2 shows mean latencies of the various central potentials calculated for subjects in 5 age groups and corrected to the mean height. The linear regression line ± 2SD for the samples are also shown. The bottom line represents change in thoraco-lumbar peak latency with age ($r = 0.57$), the middle line peak cervical potential latency ($r = 0.52$) and the top line scalp recorded initial positive peak latency ($r = 0.69$).

Age Changes in Central Conduction Time (table III)

The time difference between the latency to peak of thoraco-lumbar and cervical recorded potentials was 7.7 ± 1.1msec, and the increase with age did not reach statistical significance. However, both the time difference between cervical and scalp recorded (positive) potential (8.6 ± 1.5msec) and between thoraco-lumbar and scalp recorded (positive) potential (16.2 ± 1.6msec) increased significantly with age. The correlation coefficient of these values with height did not reach statistical significance.

Figure 3 compares the increase with age of the 'peripheral conduction time' (thoraco-lumbar potential peak latency) (top line) with the 'central conduction time' from thoraco-lumbar peak to the scalp recorded initial positive potential (bottom line, $r = 0.57$). These results indicate increases of 112.3% and 114.6% respectively, changes which are not significantly different.

Discussion

Electrophysiological changes in peripheral nerve function with age have been well documented. As well as a progressive decline in motor and sensory amplitudes, conduction velocity slows by 1 to 2.2m/sec per 10 years (Behse and Buchthal, 1971; La Fratta and Zalis, 1973 a,b; Nielsen, 1973). In the present study there was a fall in sensory and motor amplitudes of the posterior tibial nerve with age; slowing of nerve conduction was not demonstrated by conventional techniques, but 'peripheral conduction time' to the thoraco-lumbar potential did increase significantly with age.

The latencies of the thoraco-lumbar and central potentials obtained in this study are similar to the results in control subjects reported by Jones and Small (1978) and

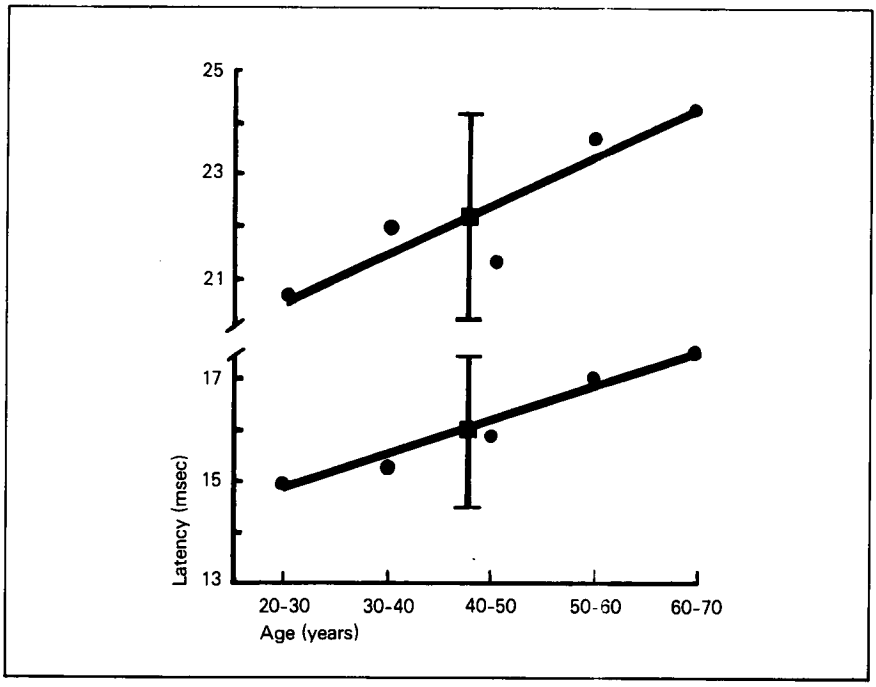

Fig. 3. Mean 'peripheral conduction time' (top) and 'central conduction time' (bottom) in the age groups indicated. Linear regression lines and 95% confidence limits are shown.

by Eisen and Odusote (1980); these authors did not consider age and height correction factors. Dorfman and Bosley (1979) measured the onset latencies of scalp SEPs from median and posterior tibial nerve stimulation and showed that there was significant prolongation with age. They used F wave latencies to extrapolate a 'spinal cord conduction velocity' (Dorfman, 1977) and claimed to show that there must be additional slowing with age in the central as opposed to the peripheral pathways. These calculations have been criticised by Desmedt and Cheron (1980) whose study of median nerve sensory conduction found no difference in central conduction velocity between young subjects and healthy octagenarians.

The present study confirmed the finding by Dorfman and Bosley (1979) of a significant increase with age in the latency of the scalp-recorded potentials evoked by posterior tibial nerve stimulation. Since the initial positive potential is thought to represent the arrival of impulses at the sensory cortex (A. M. Halliday, personal communication) the difference between this and thoraco-lumbar SEP latency was used to estimate 'central conduction time' from spinal cord to cortex. This increased by 14.6% between the third and seventh decades, and peripheral conduction time increased by 12.3%. Although not statistically significant in our small sample, it may well be that central conduction slowing is greater than that occurring peripherally, as suggested by Dorfman and Bosley (1979).

The recording of a cervical SEP after posterior tibial nerve stimulation was described by Jones and Small (1978). It is a negative potential of constant latency with midfrontal reference recordings; these authors suggested that it may be generated by an afferent nerve volley in second or third order neurones arising in the brain stem or thalamus. Whatever its origin, it was a consistent finding in all subjects in this study and was used to estimate 'spinal cord' and 'brain stem to cortex' conduction times in the different age groups. These calculations suggested that the age-related slowing of conduction occurred predominantly in the more rostral pathways.

Slowing of nerve conduction velocity is usually regarded as indicating segmental demyelination; within the central nervous system however, synaptic delay also needs to be considered. Recently, visual evoked potentials and median nerve SEPs have been shown to be delayed in Friedreich's ataxia (Carroll et al., 1980; Jones et al., 1980), a disorder known to be associated with widespread axonal degeneration. Slowing of nerve conduction in the peripheral and central nervous system with age may reflect a similar pathological process.

Summary

An electrophysiological study was made of 30 normal subjects aged 20 to 70 years. Routine methods were used to measure peripheral motor and sensory functions of the posterior tibial nerve. This nerve was then stimulated at the ankle and recordings made simultaneously over the thoraco-lumbar spine, cervical spine and central sensory cortex.

Peripheral and central potentials were reproducibly recorded at each site in all subjects. Peripheral nerve motor and sensory potential amplitudes fell significantly with age, as did the amplitude of the thoraco-lumbar potential. Cervical and central potential amplitudes did not change significantly with age.

The peak latencies of thoraco-lumbar, cervical and central potentials all showed a significant increase with age. In addition, when 'central conduction time' was calculated by subtracting thoraco-lumbar or cervical latency from the latency of the cortical potential, a significant prolongation with increasing age was still seen, especially in more rostral pathways.

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Evaluation of Therapists by Patients with Epilepsy

*C. Sutton and R.G. Beran**

A considerable amount of work has been undertaken exploring community attitudes towards people with epilepsy (Bagley, 1972; Caveness and Gallup, 1980). Little work has been done to gauge patients' attitudes to their illness and treatment. Information from patients should provide medical practitioners with guidelines as to how treatment of epilepsy could be more effective.

Lance (1977) has suggested that the attitudes of the doctor may be reflected in the perception that the patient has of himself and of his illness. Appolone et al. (1979) highlighted the need for health workers to relate favourably with the patient and to have the ability to dicuss major issues lucidly and comfortably.

The present paper reports the attitudes of a group of patients with epilepsy regarding the medical profession and includes patients' suggestions as to how management could be improved.

Method

A random sample of 50 general practitioners (GPs) was drawn from the Sydney metropolitan area (Beran and Read, in press). These GPs contacted those of their patients who were diagnosed as having epilepsy and asked them if they would be prepared to take part in a study of patients' attitudes.

Each patient was interviewed at home by a social worker, who completed a piloted questionnaire (Beran et al., 1981). To augment the 'closed question survey', the social worker conducted an 'open ended' interview, one purpose of which was to elicit the patient's perception of their medical attendant(s). As part of the questionnaire, patients were asked to identify the 'most important' therapist in the manage-

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ment of their epilepsy and to indicate their level of satisfaction with the various therapists involved in their care (using a scale from 1, 'most dissatisfied' to 7, 'most satisfied'). If a therapist was considered to be less than satisfactory, patients were asked to identify the basis of the dissatisfaction. Suggestions for improving management were also sought from each respondent, who was encouraged to speak freely and openly about the treatment he or she had received.

Results

At the time of preparing this paper, 53 patients had been interviewed. When asked to nominate the 'most important' person in the treatment of their epilepsy, 18 nominated their GP, 18 identified the neuro-specialist, 10 claimed that 'no-one' fulfilled this role and 6 cited 'others' (including themselves). Seventeen of the 53 patients rated the neuro-specialist negatively, compared with 4 who did so for their GP. A further 2 rated their neuro-specialist positively but made some negative comments.

The majority of comments suggested that lack of rapport between patient and neuro-specialist was the main cause of dissatisfaction. Statements included:

'Very abrupt'
'Scornful manner'
'Very rude and arrogant'
'I can't talk to him'
'He won't tell you anything'

Some comments related specifically to the lack of information given. Typical remarks were:

'He doesn't explain anything'
'You have to pump him for information'

Five patients commented on therapy: 2 were critical of dosage alterations without adequate explanation; 1 complained of 'breakthrough' seizures as a consequence of changed medication without prior warning of this possibility; 1 challenged that her daughter (aged 2) had outgrown medication and that the attending neurologist had neglected to warn either herself or her GP of this possibility; 1 suffered toxic sequelae from medication and was accused of 'attempted suicide' by junior hospital staff.

Two patients commented on diagnoses: 1 censured her neuro-specialist for misdiagnosing a 'brain tumour' and the other refused investigation for a suspected tumour some 14 years ago, without subsequent evidence of deficit.

Thirty-six of the 53 patients expressed views concerned with the improvement of treatment. Suggestions fell into the following categories:

(i) Information about epilepsy. The majority of comments (14) reflected a wish to know more about epilepsy. The desire for more information included such questions as:

What is epilepsy?

What precipitates a seizure?
What are the different 'types' of epilepsy?

(ii) Information about medication. Eight people indicated they would appreciate more information on medication and its possible side effects. Some intimated a need to know the mechanism by which medication is effective.

(iii) Awareness of the psycho-social needs of the patient. Five people volunteered the opinion that doctors should be more aware of the psycho-social aspects of epilepsy, saying that doctors should appear 'more concerned' and realise that 'people need help' in this area. Two patients advocated guidance concerning discussion of their condition with family and acquaintances and on what advice to give regarding seizure management.

(iv) Greater community awareness. Ten people advocated greater community education regarding epilepsy.

Discussion

Daly (1978) has noted that in the United States '. . . the Commission for the Control of Epilepsy and its Consequences has repeatedly heard complaints that physicians do not seem to understand, or at least cannot communicate to patients, basic information about the nature of epilepsy, the anticipated effects and side effects of drugs, the goals of treatment and the like . . .', a statement which is strongly borne out by this study.

Epilepsy is a chronic condition, bringing with it the challenge of continuity of care and the ability to deal with the psycho-social problems which many patients experience (Juul-Jensen, 1961). The high number of respondents who indicated that they were not receiving significant medical attention (16 people) suggests either that these people have fully accepted their condition and feel no further need for consultation or (as seems more likely) they have not found anyone to be of particular assistance in managing their condition.

Despite the one-third of respondents (18) nominating the neuro-specialist as the 'most important person' in treating their epilepsy, patients' comments on doctors evinced most criticism of neuro-specialists. The majority of these criticisms reflected a lack of rapport as the basis for dissatisfaction. A corollary to this was that those patients who held the specialist in high regard did so because they found it easy to communicate with him.

Freidson (1961) has indicated that patients use two criteria in evaluating their experience with medical care — 'technical competence' and 'personal interest'. There is evidence that those who nominated the GP as the 'most important person' did so because they felt that the GP was the person with whom they could most easily question and discuss their condition, rather than because they saw him as the therapist with the most technical expertise. In this sense, the GP could be regarded as the prime therapist 'by default'. Very few of the negative comments directed at the neuro-

specialist suggested technical incompetence, but the majority indicated a lack of personal interest as the basis for dissatisfaction.

In nominating the GP as the 'most important person' in the treatment of epilepsy, many people had difficulty in divorcing management of their condition from the GP's involvement with the overall health care of the patient and his or her family. GPs are often seen as old and trusted acquaintances, involved in a continuing and reciprocal relationship with the patient (Balint, 1968). Trust in the GP implies that he is seen as an empathic person, one who has an awareness of and sensitivity to the patient as a person in a unique social milieu. Empathy, rather than sympathy, has long been recognised as a critical skill in establishing a reciprocal relationship through which constructive communication can be developed (Keefe, 1976; Truax and Carkhuff, 1967). An important aspect of a reciprocal relationship is that the patient can feel free to ask questions or express concern while the doctor can use the flow of information to improve diagnosis and management.

The neuro-specialist's infrequent contact with the patient presents a particular challenge in establishing rapport. Failure to meet this challenge has underpinned the view of the specialist as an unknown, technical expert with whom the patient may regard himself more as a 'symptom' than as a person (Balint, 1968). This view is degrading for both patient and doctor and is ultimately counter-therapeutic. Marsh (1972) has indicated that the doctor may give the appearance of being remote, omniscient and a poor communicator by abrogating responsibility for communication to the patient. The inappropriateness of this is highlighted by the fact that the majority of suggestions for improving treatment implied that the patient sees the onus as being on the doctor to initiate and facilitate communication about epilepsy, medication and the psycho-social aspects of the condition.

Studies have shown that patients are often given little information (Stimson and Webb, 1975). It has been suggested that for some doctors, this represents an attempt to assume and retain power over the patient and to maintain an emotional distance (Byrne and Long, 1976). For the patient who has unexpressed fears about epilepsy or about medication and its effects, this 'distancing manoeuvre' may lead to a belief that the condition is particularly serious, thereby creating unwarranted fears and fantasies. Withholding information reinforces the social stigma which is attached to epilepsy since stigmata are perpetuated in part by ignorance (Goffman, 1968).

In this study, few patients were prepared to assert themselves with the specialist. Several respondents commented that they felt they were being 'rushed' or that the specialist had 'no time' for them. Generally, the educated, 'middle class' patients were more likely to feel that they had a 'right' to question the doctor and this group was more articulate in its criticisms. The literature supports our finding that those from the lower socio-economic groupings were more inclined to assume a submissive and accepting role with the doctor (Freidson, 1961).

The ability to relate to those of differing backgrounds is implicit in the concept of empathy and must be seen as essential to forming therapeutic relationships. It encompasses the ability to use language and explanations appropriate to those of varying social classes and cultural backgrounds (Day, 1972). It is significant that several respondents commented that the specialist used 'words which I did not understand', which increased feelings of alienation.

The diagnosis and prognosis of epilepsy may be, in many cases, uncertain. In our culture, which demands solutions, communicating the unknown or problematic can cause serious difficulties for the doctor (Davis, 1966). The failure to convey information in lay terms may reflect the doctor's anxiety with being asked a question to which he cannot give a definitive answer. This defensive manner may exacerbate communication problems between patient and doctor (Day, 1972). Often the patient is satisfied with knowing that 'no one knows the answer' rather than being offered jargon which may confuse rather than clarify the issue.

It has been said that doctors' training equips them poorly to take account of the influence of psycho-social factors on illness and that they are inadequately prepared for forming and maintaining a therapeutic relationship (Huntington, 1980). A lack of skill in this area engenders a tendence to judge, control and objectify the patient, leading to the same attempts on the part of the patient toward the doctor (Huntington, 1980). Although many doctors are highly successful in managing a relationship with the patient, success may be due to 'intuition' or 'personality' rather than to systematically acquired skills.

The specialist is often responsible for the long term management of chronic conditions such as epilepsy and it is therefore important to be able to institute and maintain a relationship which will maximise the patient's feeling of well-being.

Summary

Fifty-three patients were asked to nominate the most important person treating their epilepsy and asked to give suggestions for improving treatment. One-third of patients named the neuro-specialist as the prime therapist, although there was considerable dissatisfaction expressed concerning the neuro-specialists' manner of communicating.

The majority of suggestions for improving treatment reflected a desire for greater rapport between doctor and patient. More open communication would form the basis for increased patient knowledge of epilepsy and greater opportunity for the doctor to consider the important psycho-social aspects of his patients' condition.

Acknowledgements

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How Worthwhile is Plasma Primidone Level Measurement?

*M.J. Eadie, R. Heazlewood and J.H. Tyrer**

Primidone has been used in man as an anticonvulsant since 1952. In Australia it is one of the more widely used antiepileptic drugs. There were some 39,000 Pharmaceutical Benefits prescriptions written for it in 1979, compared with some 44,000 prescriptions for phenobarbitone, some 259,000 for phenytoin and some 110,000 for carbamazepine.

The molecular structures of primidone and phenobarbitone are very similar (fig. 1), and primidone is known to be metabolically transformed to phenobarbitone in man. Phenobarbitone is a well-established anticonvulsant. Therefore the question arises as to the extent to which primidone acts as an anticonvulsant in its own right, or even as to whether it merely serves as a prodrug for phenobarbitone. It is generally accepted that primidone has an independent anticonvulsant action, largely because of 2 pieces of evidence. Animal work has shown that primidone protects against certain forms of experimental epilepsy too soon after its administration for significant amounts of phenobarbitone to be expected to have formed (Goodman et al., 1953) although in such studies the absence of phenobarbitone formation has not been established by modern analytical methods. Secondly, in man it is known that occasional patients become exceedingly drowsy after their first dose of primidone, and several workers (Huisman, 1969; Booker et al., 1970; Gallagher and Baumel, 1972) have reported that phenobarbitone does not appear in humans until 2 to 4 days after the patient's first dose of primidone. It has therefore been accepted that primidone has at least an independent sedative action in man, and by analogy probably an independent anticonvulsant action. However, recent studies (Eadie and Tyrer, 1980) have shown measurable phenobarbitone levels in blood within the first few hours of initial primidone administration in some patients. Further, the studies of Frey and Hahn (1960) indicated that primidone did not protect against experimental epileptic seizures

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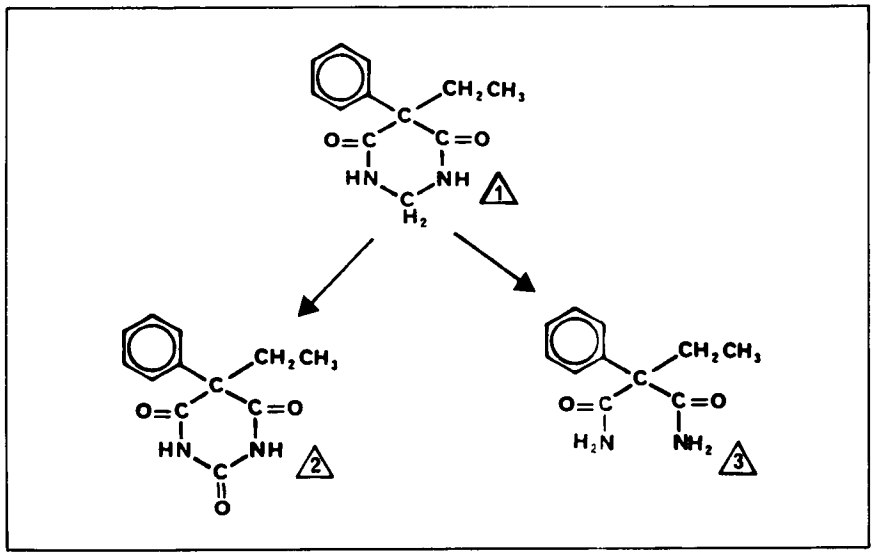

Fig. 1. Biotransformation of primidone; 1) primidone; 2) phenobarbitone; 3) phenylethylmalonamide.

in guinea pigs, a species which cannot metabolise primidone to phenobarbitone. Therefore the role of primidone as an anticonvulsant in its own right is not established with certainty. Despite this, and despite the fact that a proven anticonvulsant (phenobarbitone) is also present in the body whenever primidone is used for longer than 2 or 3 days (and as well another possible anticonvulsant, phenylethylmalonamide, a metabolite of primidone), the practice has developed in some places of using plasma primidone levels alone as a guide to the use of primidone as an anticonvulsant. Therapeutic ranges of plasma levels for primidone itself are sometimes quoted, not necessarily with any cross-reference to simultaneous plasma phenobarbitone levels.

This paper examines some aspects of the measurement of plasma primidone concentrations in a series of patients, in an attempt to ascertain how useful the measurements have been in relation to the measurement of simultaneous plasma phenobarbitone concentrations.

Materials and Methods

A computer printout was obtained of all plasma primidone levels measured at the Royal Brisbane Hospital from Janaury 1, 1979, to June 30, 1980. The primidone measurements were carried out in the Department of Medicine, University of Queensland, using a high performance liquid chromatographic assay that permitted the simultaneous measurement of phenobarbitone concentration. However, pheno-

barbitone levels were sometimes measured separately by gas liquid chromatography in the Royal Brisbane Hospital Pathology Department. Data from the printout were excluded from further consideration unless details of patient's age, sex, body weight and dosages of primidone and other drugs taken concurrently were all available. Data were also excluded if the patient was taking phenobarbitone or methylphenobarbitone simultaneously with primidone, as sometimes happened. In these circumstances it was impossible to know what contribution primidone made to the total phenobarbitone measurement. Multiple data points for a patient were not used, unless there had been some change in the dosage of primidone or of some other drug taken simultaneously, except when the question of fluctuation in plasma levels with time, in the presence of constant drug dosages, was considered. When the question of effect of age and sex on the relation between plasma primidone level and drug dose was considered, only one data point was accepted from each subject, regardless of how many measurements had been carried out on that subject and irrespective of any changes made in his drug doses.

In all, data from only 43 patients were suitable for study. Usually there was more than one data point for each patient. The 43 patients comprised 26 males and 17 females. Eight were under the age of 14 years, and 35 were 14 years of age or older.

The majority of the measurements were carried out on patients not under the authors' direct clinical control. Plasma level sampling had occurred at the times of

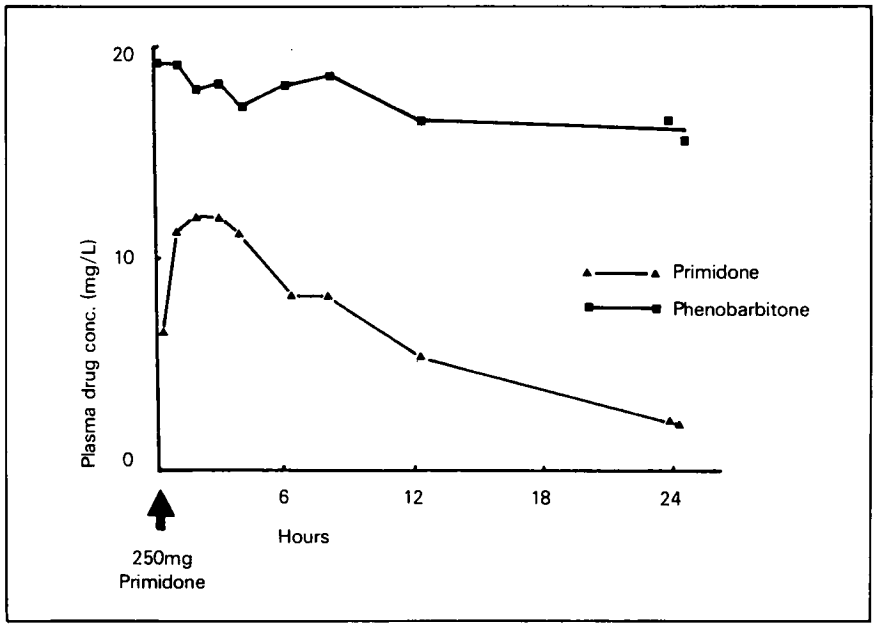

Fig. 2. Interdosage fluctuation in simultaneous steady-state plasma concentrations of primidone and phenobarbitone in one subject.

Table I. Variation in repeated simultaneous plasma primidone and phenobarbitone levels in selected patients taking constant primidone dosages

Anticonvulsant	Plasma level (mg/L)					Mean	SD	Fluctuation (%)
Subject 1								
Primidone	2	2	3	2	2			
Phenobarbitone	16	15	16	12	17			
	3	3	9	15	3	4.40	4.27	97
	14	17	16	18	17	15.80	1.75	11
Subject 2								
Primidone	18	13	12			14.33	3.21	22
Phenobarbitone	25	26	26			25.67	0.58	2
Subject 3								
Primidone	13	16	40	11	18	19.60	11.71	60
Phenobarbitone	19	22	29	23	26	23.80	3.83	16
Subject 4								
Primidone	2	7	8	20		9.25	7.63	83
Phenobarbitone	24	26	30	22		25.50	3.42	13
Subject 5								
Primidone	5	10	5	9		7.25	2.63	36
Phenobarbitone	21	17	18	18		18.50	1.73	9
Subject 6								
Primidone	5	3	4	9		5.25	2.63	50
Phenobarbitone	18	16	14	17		16.25	1.71	11

routine blood collection from inpatients and outpatients for various laboratory analyses, carried out as part of regular hospital practice. It seems likely that the great majority of the measurements were steady-state ones, as judged from the information regarding dosage and its duration supplied with the pathology request forms.

Results

Pharmacokinetic Considerations

Primidone has an elimination half-life of the order of 6 to 10 hours (Van der Kleijn et al., 1975; Booker et al., 1970; Gallagher and Baumel, 1972; Kauffman et al., 1977), and phenobarbitone has a half-life of the order of 3 to 4 days (Mark, 1963; Buchthal and Lennox-Buchthal, 1972). In view of this discrepancy in elimination rates of the 2 substances, one would expect substantially more interdosage fluctuation in steady-state plasma primidone levels over the conventional primidone dosage interval of 8 to 12 hours than in the steady-state concentrations of the derived phenobarbitone. That this theoretical prediction is borne out in practice is illustrated in figure

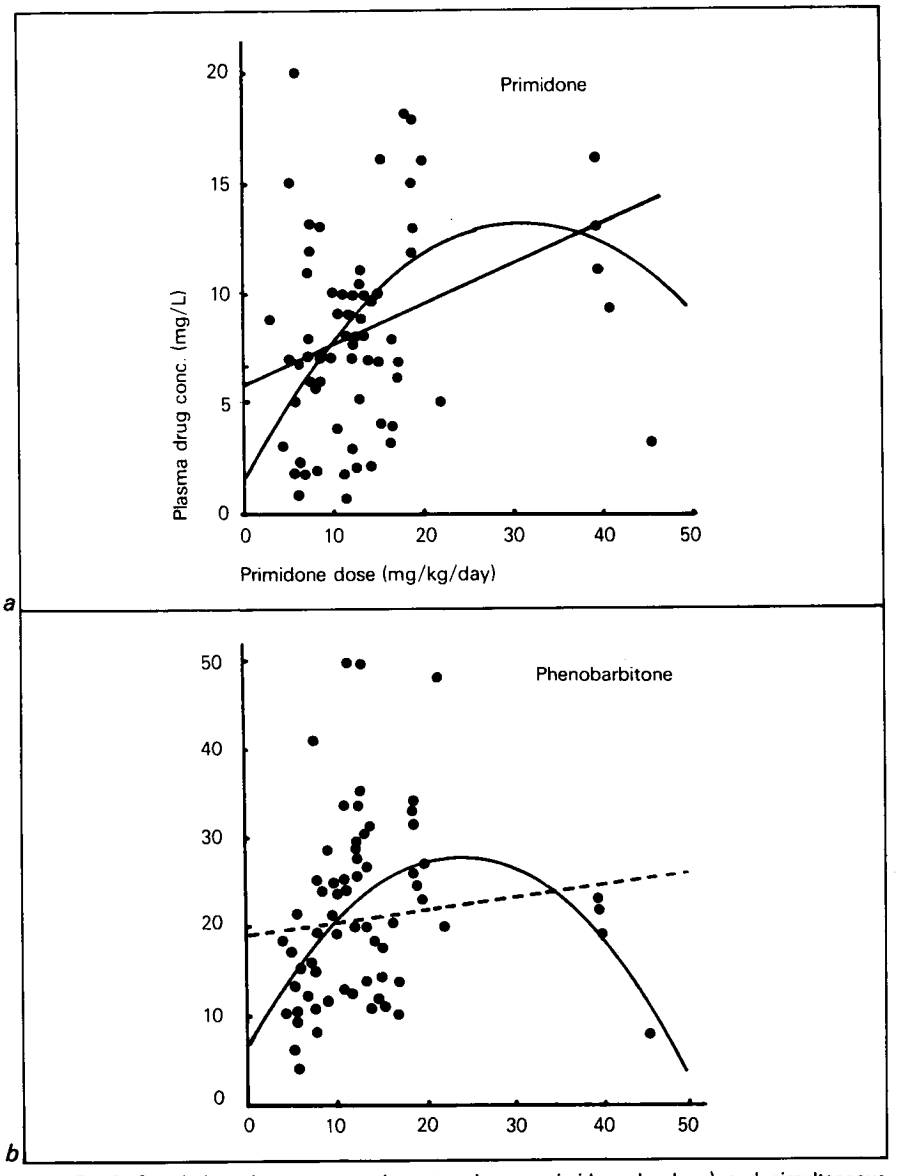

Fig. 3. Correlations between steady-state plasma primidone levels a) and simultaneous plasma phenobarbitone levels b) and primidone doses. Linear and parabolic regressions have been fitted to each set of data. The linear and parabolic regression equations for plasma primidone level (y) are

$y = 5.916 + 0.187x$ ($r^2 = 0.0675$)
$y = 1.253 + 0.763x - 0.013x^2$ ($r^2 = 0.1194$)

and for plasma phenobarbitone level (y)

$y = 19.703 + 0.101x$ ($r^2 = 0.0111$)
$y = 5.684 + 1.865x - 0.038x^2$ ($r^2 = 0.1674$)

where x = primidone dose in mg/kg/day.

2, which shows significantly more interdosage change in plasma primidone levels than in plasma phenobarbitone levels in the steady-state. for one patient.

Because of this interdosage fluctuation in plasma primidone levels, plasma primidone concentration measurements that are randomly timed relative to dosage (as plasma levels have often been in clinical practice) are likely to prove a good deal more variable than simultaneous phenobarbitone levels. This expectation is confirmed in table I, which sets out the results of serial simultaneous plasma primidone and plasma phenobarbitone levels in 6 patients from the present series who were taking constant primidone doses over the period of study. The standard deviations, relative to the mean values, are expressed as percentages. These percentages provide a measurement of variation between measurements. This variation is 5 to 10 times greater for plasma primidone measurements than for plasma phenobarbitone levels. In terms of absolute units, the fluctuation is also at least 50% greater for primidone than for simultaneous phenobarbitone levels.

Plasma Level-Dose Relationships

Simultaneous plasma primidone and phenobarbitone levels are plotted against primidone dose (expressed per unit body weight) in the 2 parts of figure 3. For both parent substance and active metabolite, a parabola fitted the plasma level-dose rela-

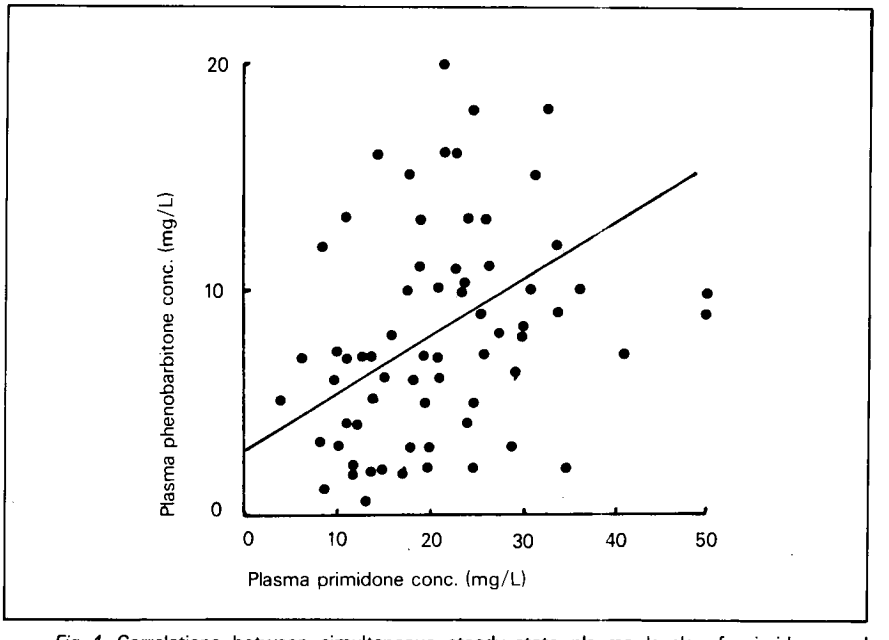

Fig. 4. Correlations between simultaneous steady-state plasma levels of primidone and phenobarbitone. The regression equation is: $y = 3.133 + 0.251x$ ($r^2 = 0.1884$).

Table II. Regressions for plasma primidone levels and plasma phenobarbitone levels and doses of anticonvulsant drugs taken concurrently

$$[\text{Primidone}] = 0.098 + 0.230\,x_1 - 0.384\,x_2 - 0.140\,x_3 + 0.190\,x_4 + 8.250\,x_5 + 0.129\,x_6 - 0.460\,x_7$$

and

$$[\text{Phenobarbitone}] = 22.814 + 0.173\,x_1 - 0.371\,x_2 - 0.274\,x_3 + 0.372\,x_4 - 30.508\,x_5 + 0.215\,x_6 - 0.294\,x_7$$

Where x_1 = primidone dose
x_2 = phenytoin dose
x_3 = carbamazepine dose
x_4 = ethosuximide dose
x_5 = clonazepam dose
x_6 = valproate dose
x_7 = sulthiane dose

} in mg/kg/day

[all r values > 0.05 for both equations]

tionship better than a lincar or other curvilinear regression. The parabola fitted the data points better in the case of phenobarbitone levels ($r^2 = 0.1674$) than of primidone levels ($r^2 = 0.1194$).

The relation between simultaneous plasma primidone levels and plasma phenobarbitone levels appeared a simple straight line, one over the concentration range studied (fig. 4). Multiple variable linear regression analyses showed no statistically significant effect of dosage of phenytoin, carbamazepine, ethosuximide, clonazepam, valproate or sulthiame on the linear relation between either plasma primidone level or plasma phenobarbitone level and primidone dose. The regression equations are shown in table II.

Analyses of covariance showed no statistically significant effect of sex, or of age (less than 14 years compared with 14 years and over) on the linear relation between plasma primidone level and primidone dose.

Discussion

The most valid answer to the question 'How worthwhile is measurement of plasma primidone levels?' would be obtained from a study correlating anticonvulsant and toxic effects of the drug with plasma concentration of drug and metabolite. Such a correlation could not be obtained from the material available to the present study, and suitable data do not appear to have been published in the literature. Therefore, given the known pharmacokinetic properties of primidone and phenobarbitone and the reasonably good relationship between plasma levels of the 2 substances demonstrated in figure 4, an answer to the question might be sought by considering if there are clinical situations where steady-state plasma primidone levels should yield information not available from plasma phenobarbitone levels. The main circumstance where this might be the case would be when temporary drug toxicity occurs soon

after a primidone dose. Here the relatively rapid changes in steady-state plasma primidone levels as compared with those of phenobarbitone may mean that such toxicity is associated with excessively high peak plasma primidone levels. Except for this circumstance, in the present state of knowledge it is hard to envisage a situation where plasma primidone level would be more informative to the clinician than plasma phenobarbitone level. Further, if primidone levels alone are measured, a major anticonvulsant is ignored. To cite a 'therapeutic range' for plasma primidone levels, without considering the therapeutic range of the phenobarbitone that is present, bespeaks ignorance of pharmacological realities.

Further, if plasma primidone levels alone are measured, and (as often happens) the measurements are not carried out in a consistent time relationship to drug dosage, it is possible that those who are unaware of the pharmacokinetic properties of primidone may be misled by variations in serial steady-state plasma primidone levels. They may unjustly accuse patients of non-compliance with prescribed dosages. Worse, they may make unnecessary dosage adjustments and thus further confuse the situation, and themselves.

The present study has provided no evidence of circumstances in which plasma primidone levels might be more useful than plasma phenobarbitone levels. It has shown that plasma primidone levels and plasma phenobarbitone levels were linearly related, also that steady-state plasma phenobarbitone levels correlated better with primidone dose than did plasma primidone levels, and that age, sex and the concurrent intake of other anticonvulsants did not alter the relationship between plasma primidone levels and drug dose. Therefore it would seem that in nearly all circumstances, knowledge of plasma primidone levels would appear to add little additional insight to that provided by the simultaneous plasma phenobarbitone levels. If there is opportunity to measure the level of only 1 of the 2 substances with the patient in the steady-state, in nearly all circumstances plasma phenobarbitone level is likely to be the more useful, and potentially the less misleading, estimation. Preferably, simultaneous measurement of both substances would be carried out, simply to have more complete information available. Even when this is done, in most circumstances therapeutic decisions will tend to be based on the plasma phenobarbitone levels, with the primidone levels adding little further to the clinician's insight into the situation.

Summary

Simultaneous steady-state plasma levels of primidone and phenobarbitone were studied in 43 patients receiving primidone therapy. Primidone and phenobarbitone levels in the individual appeared to be linearly related but steady-state plasma phenobarbitone levels correlated better with primidone dose than did steady-state plasma levels of primidone itself. This pattern of correlation is probably due to primidone being more rapidly eliminated than the phenobarbitone that is derived from it. Steady-state plasma primidone levels showed more inter-dosage fluctuation than steady-state plasma phenobarbitone levels in the same patients. In the subjects studied age, sex, and concurrent anticonvulsant therapy did not alter the relation between plasma levels of primidone or phenobarbitone and primidone dose. The study sug-

gested that knowledge of steady-state plasma primidone levels adds little to knowledge of plasma phenobarbitone levels in guiding the therapy of epilepsy with primidone.

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Stroke Syndromes in Young People

*B.R. Chambers, P.F. Bladin, K. McGrath and A.J. Goble**

The stimulus for the present study has been the recent interest in unusual causes of stroke in young people. These causes include conjugal disharmony with attempted strangulation (Milligan and Anderson, 1980), cervical chiropractic manipulation (Krueger and Okazaki, 1980), heavy alcoholic excess (Hillbom and Kaste, 1978), and mitral valve prolapse (Barnett et al., 1980; Grainger, 1981).

We have carefully evaluated all contributory factors in the patients less than 40 years of age admitted to the Stroke Unit of the Austin Hospital, Melbourne.

Patients and Methods

In the period from August 1977 to December 1980 there were 700 admissions to the Stroke Unit of the Austin Hospital. Of these, 14 patients were under the age of 40 years (2% of admissions). There were 7 males and 7 females, whose ages ranged from 17 to 38 years.

The protocol for investigation of patients admitted to the Stroke Unit has been described elsewhere (Chambers et al., in preparation). Particular attention was paid to the following aspects.

Vasculopathy

Each patient was screened for factors which might contribute to 'premature vascular disease' including hypertension, diabetes, smoking, obesity and hyperlipidaemia. In addition, the following tests were performed to exclude an arteritic process — full blood examination, ESR, protein electrophoresis, syphilis serology and the presence of antinuclear factor.

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Coagulopathy

A personal history of thromboembolic events or of illness which may predispose to these events was recorded, as was any relevant family history. The following protocol of investigations was completed in 12 of the 14 patients. The testing was performed at least 3 months after the stroke, except in 3 patients. Any abnormalities detected in these 3 patients were checked at a later date to exclude the possibility of reactive changes having been found.

1. Haemoglobin, haematocrit, white cell count and platelet count.
2. Clotting studies:
   a) Prothrombin time (PT), kaolin partial thromboplastin time (KPTT) and thrombin time (TT)
   b) Antithrombin III assay (ATIII)
   c) Factor VIII coagulant activity (FVIIIc), Factor VIII antigen (FVIIIAg) and Von Willebrand factor (FVIIIVW).
3. Tests of fibrinolysis. Pre- and post-venous occlusion euglobulin clot lysis time (ECLT) (Venous occlusion was performed using a sphygmomanometer cuff inflated to a pressure midway between systolic and diastolic blood pressure for 15 minutes. ECLT was performed using a Data-FI^R kit.)
4. Platelet aggregation studies:
   a) Platelet aggregation performed on a Chronolog Aggregometer for 5 minutes with no aggregating agent (spontaneous), and with low concentrations of ADP and adrenaline
   b) Platelet aggregate ratio — method of Wu and Hoak (1974)
   c) Betathromboglobulin (BTG) — enzyme released from platelets and measured by radioimmunoassay (modified Amersham technique) (Smith and Martin, 1981).

Cardiac Lesion

Thirteen patients were interviewed and examined by a cardiologist who also reviewed their electrocardiographs and chest radiographs. An M mode echocardiograph was performed on each of these 13 patients (by the same technician) and reported by a cardiologist who was not familiar with the details of the cases.

The criteria adopted for the diagnosis of mitral valve prolapse are in accordance with those of Hickey et al. (1981). Summarised briefly, positive diagnosis required the presence of typical ausculatatory findings and a positive echocardiographic recording.

Other Factors Possibly Implicated

Patients were interviewed carefully for a past history of migraine and for migrainous symptomatology at the onset of the stroke. Females were questioned concerning the use of oral contraceptives. Any relationship of stroke to trauma and alco-

Table I. Details of patients

Case	Sex, age	Clinical summary	Relevant predisposing factors
1 A.H.	F 37	Left cortical and subcortical infarction. Total occlusion of the extracranial internal carotid artery. Layered clot formed in Quattlebaum loop	Anomalous vessel. Maritial conflict with attempted strangulation
2 S.V.dO	F 32	Right cortical and subcortical infarction documented by CT scan. Narrowing arteries by arteritis with occlusion internal carotid artery by secondary thrombus. Takayasu's arteritis.	Takayasu's arteritis. Increased platelet aggregation. Blood loss anaemia due to carcinoma colon. Marital conflict stemming from frigidity and hand-washing neurosis
3 I.D.	F 20	Right cortical and subcortical infarction documented by CT scan. Embolus lodged at T junction	Congenital heart disease. Increased platelet aggregation. Recent illness and death in family
4 R.H.	M 27	Right cortical and subcortical infarction. Total occlusion of extracranial internal carotid with rat-tail appearance of in-situ thrombosis. On exploration, extracranial internal	Increased platelet aggregation. Deficient plasminogen activator release. Adultery on part of wife with marriage breakdown carotid normal and free of disease. Thrombus dislodged to middle cerebral artery
5 M.A.	F 31	Right cortical and subcortical infarction confirmed by CT scan. Total occlusion of internal carotid artery in siphon. At exploration, extracranial vessels normal	Prodromal symptoms suggestive of migraine but no past history of migraine. Major marital conflict
6 P.B.	M 17	Left frontal cortical and subcortical infarction confirmed by CT scan. Normal angiogram	Migrainous infarction. Past history and family history of migraine
7 J.B.	F 38	Left temporoparietal cortical infarction confirmed on CT scan. Normal angiogram	Migrainous infarction. Past history migraine. Oral contraceptive intake. Increased platelet aggregation
8 E.S.	M 38	Right fronto-parietal cortical infarction. CT scan demonstrated bilateral cortical infarcts. Right carotid angiogram ulcerated atheromatous disease carotid bifurcation	'Premature atherosclerotic disease' — obesity, hypertension, diabetes, smoking, hyperlipidaemia. Deficient plasminogen activator release and increased platelet aggregation. Gross personality disorder

9 L.N.	M 37	Left internal capsular infarction confirmed by CT scan	Hypertensive occlusive vascular disease. Smoking. Hyperlipidaemia. (Refused to cooperate with subsequent tests)
10 G.O.	M 35	Right lateral medullary syndrome preceded by vertebrodynia. Spasm of right vertebral artery and right posterior inferior cerebellar artery not visualised angiographically	? Migrainous infarction (Refused to cooperate with tests for hypercoagulability)
11 M.G.	F 26	Left lateral medullary syndrome. No radiological procedures	Pregnant. Deficient release of plasminogen activator and increased platelet aggregation. Husband convicted of embezzlement
12 L.H.	M 20	Post traumatic right occipital infarction. CT scan showed massive oedema of right parieto-occipital lobe. Follow up scan: infarction striate cortex	Alcohol intoxication. Bashing. Increased platelet aggregation. Traumatic cerebral oedema produced compression of posterior cerebral artery against tentorium cerebelli
13 J.D.	F 34	Massive infarction occipital lobes, thalamus and midbrain confirmed by CT scan. Basilar artery segmentally narrowed. Left posterior cerebral artery not visualised	Migrainous infarction. Oral contraceptive intake. Heavy smoker. Increased platelet aggregation
14 S.A.	M 32	Right amaurosis fugax, left frontal, right parieto-occipital and left occipital cortical infarctions. Serial CT scans confirmed multiple infarctions. Normal angiogram	Migrainous symptoms with some events. Increased platelet aggregation Deficient plasminogen activator release

hol intoxication was noted. Patients were asked to elaborate on significant emotional factors in the period leading to the stroke. The medical social worker and occupational therapist attached to the Unit were most helpful in eliciting this information.

Results

Each of the 14 patients suffered cerebral infarction. The selection protocol excluded patients with subarachnoid haemorrhage since these patients were admitted to the Neurosurgical Unit. However, there was no bias against primary intracerebral haemorrhage, which was not seen in this small series of young strokes'.

A summary of each case is presented in table I. In 9 patients (Cases 1 to 9) infarction occurred in the carotid territory of supply. Large cortical infarcts with or without subcortical involvement occurred in Cases 1 to 8, of whom 5 (Cases 1 to 5) had major vessel occlusion demonstrated angiographically and another (Case 8) had stenosing and ulcerative atheromatous disease at the extracranial carotid bifurcation. Of the 5 cases of major vessel occlusion, the appearances on angiography and at operation (where performed) were not those of occlusion superimposed upon pre-existing atheroma but rather the following — layered clot formed *in situ* in a Quattlebaum loop (Case 1), *de novo* thrombosis within apparently normal internal carotid artery (Cases 4 and 5), Takayasu's arteritis (Case 2) and embolism (Case 3) from the heart. Case 9 suffered internal capsular infarction.

In a further 4 patients, infarction occurred within the vertebrobasilar territory and was either confined to the brain stem (Cases 10 and 11), the occipital cortex (Case 12) or involved both (Case 13). Angiograms were performed in 2 of these patients and showed irregular narrowing of the vertebral artery which was interpreted as spasm (Case 10), and segmental narrowing of the basilar artery (Case 13).

The final patient (Case 14) had several ischaemic events which included right sided amaurosis fugax, and left frontal, right parieto-occipital and left occipital infarctions. Angiography was normal.

All patients survived the stroke and were able to go home. Of 8 patients who were working at the time of their stroke, 5 returned to their previous jobs and another returned to a less demanding position.

Vascular Disease

In 2 patients cerebral infarction was caused by atheromatous or hypertensive occlusive vascular disease. Embolism from an ulcerated stenosing plaque at the carotid bifurcation was implicated in Case 8, in whom obesity, diabetes, hypertension, smoking and hyperlipidaemia were predisposing risk factors. Hypertensive occlusive vascular disease was considered as the cause of the internal capsular infarction occurring in Case 9. Another patient (Case 10) was hypertensive and had hyperlipidaemia but mechanisms other than premature vascular disease were considered more likely in causing the stroke. Takayasu's arteritis produced narrowing of major arteries and secondary thrombotic occlusion of the internal carotid artery in Case 2.

Cardiac Lesion

In Case 3 an embolus occluded the middle cerebral artery. The patient had a form of congenital heart disorder characterised by globular cardiac enlargement and bradycardia although a precise diagnosis was not made.

There were 6 patients (Cases 1, 6, 7, 11, 12, 13) in whom echocardiography suggested mitral valve prolapse, but in only 1 patient (Case 1) were the full diagnostic criteria satisfied. In this patient the stroke was considered unrelated to the presence of mitral valve prolapse.

Trauma (and alcohol)

Case 1 (the sole patient with mitral valve prolapse) was the victim of 3 attempts at strangulation by her husband. The internal carotid artery was totally occluded by a layered clot arising *in situ* within a Quattlebaum loop. Presumably trauma to the artery, made more vulnerable by way of its looping course, produced an intimal tear followed by thrombus formation.

Case 12 sustained occipital infarction after a bashing by strangers while he was heavily intoxicated. Cerebral oedema was demonstrated by CT head scan. Presumably his posterior cerebral artery had been compressed against the tentorium cerebelli by the oedema.

Migraine (and oral contraceptives)

Infarction complicating migraine was diagnosed confidently in 4 patients (Cases 6, 7, 13, 14) on the basis of typical migrainous symptomatology in the past and ac-

Table II. Plasminogen activator release: results of post-venous occlusion euglobulin lysis time

Case	Time (minutes)
1	65
2	25
3	75
4	> 180*
5	30
6	15
7	55
8	> 180*
9	-
10	-
11	> 180*
12	25
13	50
14	135*

* These patients showed prolonged post-occlusion euglobulin clot lysis time (normal range < 90 mins)

Table III. Platelet aggregation ratio (Wu and Hoak) and betathromboglobulin levels in patients

Case	Platelet aggregation ratio[1]	Betathrombo-globulin level[2]
1	0.30*	155*
2	0.71*	217*
3	0.77*	450*
4	0.80	224*
5	0.81	49
6	0.90	-
7	1.00	1270*
8	0.81	189*
9	-	-
10	-	-
11	0.75*	224*
12	1.00	157*
13	0.33*	480*
14	0.50*	420*

1 Normal range 0.8-1.0 (abnormal value*).
2 Normal range 10-54ng/ml (abnormal value*).

companying the stroke. Two of the patients were female and both were taking oral contraceptives. Both had experienced an increased frequency and severity of migraine headaches before the infarction. All 4 patients were investigated angiographically. These studies were normal apart from Case 13 in whom segmental narrowing of the basilar artery was found.

Migrainous infarction was strongly suspected in Case 10 despite the absence of a history of previous migraine headache. He complained of occipital and nuchal pain for 2 days before brain stem infarction and vertebral angiography revealed changes suggestive of spasm.

Another patient (Case 5), without a history of migraine, presented twice during the prodrome of her stroke with what was regarded as typical migraine. Cerebral infarction followed and an angiogram demonstrated total occlusion of the internal carotid artery at the siphon. No satisfactory explanation for her stroke was determined.

Three other patients (Cases 1, 2, 8) gave a history of migraine headaches, but not at the time of the stroke, and other causes of the strokes were found.

Coagulopathy

Of the 12 patients fully evaluated, there were no cases of polycythaemia or thrombocytosis. Similarly, there were no abnormalities of the clotting factors. Disturbances of clot lysis and platelet aggregation were demonstrated as follows: 4 patients (Cases 4, 8, 11, 14) showed prolonged post-occlusion euglobulin clot lysis time indicating deficient plasminogen activator release from veins of the forearm (table II). Preocclusion ECLT was normal in all cases tested. Although spontaneous

platelet aggregation was not observed, there were 6 patients (Cases 1, 2, 3, 11, 13, 14) with circulating platelet aggregates (Wu and Hoak, 1975 method). In addition, BTG levels were elevated in these and another 4 patients (Cases 4, 7, 8, 12). These results suggest that 10 of the 12 patients tested had evidence of continuing platelet activation *in vivo* (table III).

It has not been determined whether the observed abnormalities were primary or related to underlying disease. For example, in one patient (Case 2) there were 2 possible mechanisms which could have produced platelet hyperaggregability — Takayasu's arteritis and carcinoma of the colon. Except for Cases 4 and 11, the observed abnormalities of coagulation occurred in association with other well-defined factors responsible for cerebral infarction which have already been mentioned.

It is interesting to note that 4 patients had a combined disorder with deficient plasminogen activator release and continuing platelet activation. One of these patients (Case 14) had a history of spontaneous deep venous thrombosis, solitary polycystic kidney and infertility and a family history of Werner's syndrome. Another patient (Case 11) was pregnant at the time of her stroke. Her hypercoagulability can not be attributed to pregnancy, however, since the tests were performed 14 months after the stroke and 8 months after childbirth.

Of the 2 patients on the 'pill' at the time of their strokes (Cases 7 and 13), increased platelet activation was demonstrated despite discontinuation of the 'pill.'

Emotional Trauma

Although almost every patient had some form of emotional upset, we were surprised by the number of patients with significant psychiatric illness and emotional problems of extreme magnitude (Cases 1, 2, 3, 4, 5, 8, 11). The problems included adultery by the marital partner, attempted strangulation, conviction of the spouse for embezzlement and death and illness in the family.

Discussion

The purpose of this small series has been to examine carefully many factors potentially implicated in the causation of stroke in the young patients studied, with a particular interest in hypercoagulability, migraine and mitral valve prolapse.

Hypercoagulability

The abnormalities found in the 12 patients fully investigated fall into two categories:

(i) Four patients had deficient plasminogen activator release from forearm veins. This enzyme, released from the walls of veins, promotes fibrinolysis by conversion of plasminogen to plasmin. Isaacson and Nilsson (1972) reported the relationship between deficient plasminogen activator content and release and venous thrombosis. Later studies showed that the abnormality could be corrected by therapy with phen-

formin and ethyloestrenol (Nilsson et al., 1975), but long term follow-up of patients with venous thrombosis receiving treatment with phenformin and ethyloestrenol is lacking. Consequently doubts have been cast upon the relevance of the findings. Apart from occasional reference to deficient plasminogen activator release from veins and associated arterial thrombo-embolism (Hedner et al., 1976), there have been no major studies examining the possible relationship with cerebral infarction.

(ii) The other abnormality was increased platelet aggregation. Elevated betathromboglobulin (BTG) levels provided evidence of continuing *in vivo* platelet activation in 10 patients, of whom 6 also had circulating platelet aggregates. The assertion that platelet hyperaggregability is implicated in cerebral ischaemia and infarction has been challenged on the basis of methodology. Previous investigators have relied on the reactivity of platelets to aggregating agents such as ADP and adrenaline (epinephrine), but the aggregability tests are insensitive. Current opinion suggests that the most sensitive techniques available for assessment of *in vivo* platelet aggregation are platelet survival studies, assays of betathromboglobulin and measurements of the platelet aggregate ratio by the method of Wu and Hoak. Wu and Hoak (1975) have demonstrated a significant difference between patients with transient ischaemic attacks and controls with respect to mean platelet aggregation ratios. A study by Cella et al. (1979) included assay of BTG in patients with a past history of stroke, but no significant deviation from the mean BTG level was found.

Hence the literature on this topic is confusing and the potential relationship between increased platelet aggregation and stroke in young people requires further investigation. It is likely that, in most cases, increased platelet aggregation is secondary to other pathology, e.g. atheroma (Case 8), vessel trauma (Case 1), arteritis (Case 2), and hyperplastic intimal change (Case 13). One problem concerning the interpretation of tests of hypercoagulability is that they are performed after the vascular event and no definite time interval has been ascertained which allows the investigator to know whether or not the abnormalities are reactive. Current opinion suggests that to wait 3 months before testing is sufficient.

Migraine

Although migraine has been recognised as a cause of persisting hemiplegia, aphasic, hemianopic and retinal sequelae, the incidence of migrainous brain infarction has probably been grossly underestimated. The CT scan has demonstrated that a significant proportion of patients with severe migraine have cerebral atrophy or focal infarctions (Cala and Mastaglia, 1976).

At least 4, and possibly 5, of the patients in the present series suffered migrainous infarction. The diagnosis was purely clinical and made only after exclusion of other causes including embolism from the heart and major vessel occlusions. The most popular explanation for migrainous infarction is that it is due to unusually prolonged vasospasm during a migraine attack. The diminished cerebral blood flow during the prodromal phase of migraine may merely represent sluggish flow rather than spasm. Several authors have demonstrated a relationship between migraine and increased platelet aggregation (Couch and Hassanein, 1977; Deshmukh and Meyer, 1977; Kalendovsky and Austin, 1977). An increase in circulating platelet aggregates

may contribute to sluggish flow during the prodromal phase of migraine. However, a more attractive hypothesis suggests that increased platelet aggregation is followed by release of vasoactive amines (including serotonin). The action of serotonin in intracranial arteries leads to vasoconstriction. As platelets are depleted of serotonin the plasma concentration of this substance falls, with accompanying vasodilatation and headache. The relationship of plasma serotonin levels to migraine attacks has been demonstrated by Anthony et al. (1967). Other vasoactive amines may be involved in the vessel wall inflammatory changes and the production of pain. If further studies confirm the relationship between migraine and platelet hyperaggregability, the tests might offer a simple measure of the effectiveness of interval migraine therapy. Perhaps aspirin or other antiplatelet agents may prove to be the most effective prophylactic therapy of migraine.

Oral Contraceptives

Since the introduction of the oral contraceptive pill, numerous case reports and studies, including those by the 'Collaborative Group for the Study of Stroke in Young Women' (1973, 1975) have established, with little doubt, that there is a significantly increased risk of 'thrombotic' and haemorrhagic stroke in women taking oral contraceptives. What is not well understood is by what mechanism(s) these strokes occur. Changes in clotting factors were earlier incriminated, but these changes are probably irrelevant (with the exception of antithrombin III deficiency) and amount to an adjustment of homeostasis. None of the clotting factors elevated are activators of the intrinsic or extrinsic coagulation pathways. Venous thrombi in oral contraceptive users arise from localised abnormalities of the venous intima. Recently Irey et al. (1978) have observed similar changes in cerebral arteries. Thrombus had developed on areas of intimal hyperplasia characterised by eccentric nodular intimal thickening and a variable increase in acid mucopolysaccaride content. Probably the most significant mechanism involves the effect oral contraceptives have on the pattern of migraine. In a controlled crossover study (Ryan, 1978) the overall frequency and severity of migraine headaches was increased in oral contraceptive users although in a few patients symptoms were actually lessened. The findings support the clinical observations made earlier by Gardner et al. (1968), who described a crescendo of headache in the 2 months before cerebral infarction in women taking the 'pill.'

There may be an inter-relationship between the pathological findings of Irey et al. (1978) and the effect the 'pill' has on migraine and this is relevant to Case 13. Sustained exposure to the 'pill' may produce the pathological changes described (visible as segmental narrowing angiographically). These changes in turn may lead to an increase in platelet aggregation. Migraine attacks could occur at times of heightened platelet aggregation and release of serotonin. Worsening arterial lesions might cause the crescendo pattern of migraine, culminating in migrainous infarction. The hypothesis is strengthened by analogy with variant angina. In patients with variant angina, coronary angiography sometimes reveals a proximal vascular lesion and distal spasm. Alternatively, infarction might be due to embolism of fragments of thrombus which had been adherent to the arterial lesions described.

Cardiac Source of Embolism

In the younger age group the heart must be considered as a likely source of embolism, although this was documented in only one patient (Case 3) of the present small series. Recent publications have suggested an association between mitral valve prolapse (MVP) and ischaemic events (Barnett et al., 1980; Grainger, 1981). Mechanisms suggested include bacterial endocarditis, paroxysmal atrial fibrillation and thromboembolism arising from fissures and thrombi which occur on a myxomatous valve. Although not disputing that these mechanisms may occur, we suggest that the finding of mitral valve prolapse needs to be considered carefully in the clinical context of each case. It is difficult to accept, for example, that recurrent unilateral amaurosis fugax may be related to MVP. The diagnosis of one patient with MVP (Case 1) in our series of 14 patients is consistent with the demonstration of a 4% prevalence rate of the valvular anomaly in Australia (Hickey et al., 1981). In this particular patient the stroke was related to factors other than MVP.

Miscellaneous Factors

Although this was a small series of patients, several unusual aetiological factors were encountered, emphasising the need for thorough evaluation of all young patients with strokes. Atheromatous and hypertensive occlusive disease in young people is uncommon and arteritis assumes greater importance. Milligan and Anderson (1980) drew attention to the relationship between conjugal disharmony, attempted strangulation and total occlusion of the internal carotid artery. This history should be sought by direct enquiry, as in our patient the information was only volunteered months after the stroke. Other causes of vascular trauma should be remembered, for example cervical chiropractic manipulation (Krueger and Okazaki, 1980). Vascular anomalies such as redundant looping extracranial carotid artery may also predispose to total occlusion (Quattlebaum et al., 1959). Head trauma is another unusual cause of cerebral infarction. In the patient here described, acute cerebral oedema was demonstrated by CT scan. Presumably the posterior cerebral artery was compressed against the tentorium. Follow-up scan has shown infarction of the striate cortex. The role of alcohol intoxication is uncertain although Hillbom and Kaste (1978) have suggested that stroke may occur due to associated cardiac arrhythmia, raised haematocrit or rebound thrombocytosis. The extraordinarily high rate of psychiatric illness and personal catastrophe in the present series must be relevant in some way, but to suggest mechanisms would be entirely speculative.

Conclusion

The present study has confirmed that cerebral infarction in young adults is uncommon (2% of stroke unit admissions) and that there is an excellent prognosis for survival. With a diligent search, mechanisms of infarction could be determined in most patients. Usually multiple causal factors were found. Since atheromatous and

hypertensive occlusive disease is uncommon in young people there was an over-representation of rare aetiologies of stroke in the series. Mitral valve prolapse was not responsible for stroke in any of our patients. Disorders of coagulation, particularly increased platelet aggregation, were found in most patients tested. Although the significance of these findings is uncertain at present, the abnormalities may help provide an explanation for stroke in seemingly healthy young people. In particular, an explanation has been offered for the observed relationship between oral contraceptive intake, platelet hyperaggregability, migraine and cerebral infarction.

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Carotid Endarterectomy at Royal Brisbane Hospital and Princess Alexandra Hospital, Brisbane

*G.D. Ohlrich and J.R. Kukums**

A retrospective study of public patients submitted to carotid endarterectomy at Royal Brisbane (RBH) and Princess Alexandra (PAH) Hospitals over a 5-year period has been carried out and morbidity and mortality figures for the procedure during this period at these hospitals have been determined. The results of the PAH survey have been reported previously (Ohlrich and Kukums, 1979). In the present study the results of both hospitals are presented. A local study of this nature is of limited value in considering the management of carotid stenosis and the value of carotid endarterectomy. Nevertheless it does highlight the importance of knowing precisely what the local major complication rate for this operation is before referring patients locally for such surgery.

Estimates vary as to the percentage of patients with transient ischaemic attacks who subsequently develop a completed stroke. Reliable authorities (Barnett, 1979; West et al., 1979) have quoted a stroke rate of 5 % per year in people who have had transient ischaemic attacks, with the greatest risk of stroke in the first 12 months (Whisnant et al., 1973). A high proportion of these strokes is directly related to the previous transient ischaemia (Marshall, 1964). If it can be established that there is a reasonable likelihood that the cerebral or ocular disturbance is originating from carotid stenosis, removal of the stenotic lesion could be expected to reduce substantially the risk of future stroke.

Apart from the question of whether the carotid stenosis is causing the patient's symptoms, other factors are important in deciding the likely benefit of surgery. The medical and neurological condition of the patient at the time of surgery is important in prognosis (Callow, 1980). The expertise of the vascular surgeon undoubtedly influences the outcome, and mortality and morbidity figures vary widely between differ-

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Table I. Details of patients undergoing carotid endarterectomy at 2 Brisbane hospitals over a 5-year period

		RBH	PAH
No. of operations		38	85
No. of patients		35	72
Sex —	male	28	60
	female	10	25
Operative site			
	Right	9	32
	Left	23	27
	Bilateral	3	13
Age (years)	41 to 50	4	2
	51 to 60	13	29
	61 to 70	16	42
	71 to 80	4	11
	81 to 90	1	1

RBH = Royal Brisbane Hospital; PAH = Princess Alexandra Hospital.

ent centres (West et al., 1979). The present study highlights this variability and emphasises the need for critical evaluation of local surgical results before recommending patients for this operation.

Methods

Records were studied of the public patients submitted to carotid endarterectomy at Royal Brisbane and Princess Alexandra Hospitals during the 5-year period from 1st July 1973 to 30th June 1978. A computer listing of patients who had undergone the operation was obtained. Additional patients missed by the computer listing were obtained from a search of the operating theatre books in which all operations performed during the relevant period were noted. At Royal Brisbane Hospital some of the operating theatre books could not be found. Therefore it is possible that more operations were performed at this hospital than recorded in this study. At Princess Alexandra Hospital all the operating theatre books during the study period were searched. However, the records of 2 patients identified from the operating theatre books could not be found. The surgeon who performed the operation on one of these patients could recall the case. Apparently the operation was performed without mishap and there were no major complications afterwards. Unfortunately no record of the second case could be found.

At Royal Brisbane Hospital each carotid endarterectomy was performed by 1 of 3 vascular surgeons, although 1 vascular surgeon performed 90% of all operations. At Princess Alexandra Hospital each endarterectomy was performed by 1 of 4 vascular surgeons. In all cases endarterectomy was performed at the bifurcation of the

Table II. Number of carotid endarterectomy operations performed in each 6-month period from 1 July 1973 to 30 June 1978

6-month period	No. of operations	
	RBH	PAH
July-Dec 1973	3	10
Jan-June 1974	1	5
July-Dec 1974	—	2
Jan-June 1975	1	5
July-Dec 1975	5	7
Jan-June 1976	2	9
July-Dec 1976	6	10
Jan-June 1977	4	8
July-Dec 1977	9	18
Jan-June 1978	7	11

RBH = Royal Brisbane Hospital; PAH = Princess Alexandra Hospital.

common carotid artery and an atheromatous stenotic lesion, sometimes with associated thrombus, was removed from this region in either the internal or common carotid artery, or both.

Results

Table I shows the number of operations, patient sex ratio, site of operation and the age range of patients at each hospital. Most patients at each hospital were in the 60- to 70-year age group, as expected. There were more operations performed in the second half of the study period than the first (table II).

Reference has already been made to the fact that the records of 2 patients operated on at PAH during the study period could not be found. Thus the information contained in tables III, IV and V and in the figure refers to the study of 83 operations on 70 patients at PAH.

Incomplete carotid stroke, where the neurological deficit lasted more than 24 hours, was the most frequent indication for surgery at RBH (table III). At PAH similar numbers of patients were operated on for carotid transient ischaemic attacks and incomplete carotid stroke, with the former indication being more frequent. In the cases of completed carotid stroke, endarterectomy was performed within hours after the onset of the episode. In 19% of operations at PAH, the major indication was ischaemia in vertebro-basilar territory. In 16% of operations at RBH and in 13% at PAH there were no cerebral ischaemic symptoms related to the carotid stenosis on the side of operation. In a number of cases where a significant stenosis was found on the asymptomatic side at angiography, this was operated on in addition to the symptomatic side, as a separate procedure. These cases are grouped in the category 'radiological finding' (table III). At PAH an asymptomatic carotid stenosis was operated on in 3 cases before another vascular procedure — carotico-subclavian bypass graft in 2 cases and a vascular procedure in the legs in 1 case.

Table III. Major indication for carotid endarterectomy and the number of operations performed for each type of indication

Indication	No. of operations (%)	
	RBH	PAH
Carotid transient ischaemic attack	10(26)	19(23)
Incomplete carotid stroke	16(42)	17(20)
Completed carotid stroke	1(3)	2(3)
Vertebrobasilar insufficiency	—	13(16)
Vertebrobasilar stroke (incomplete)	—	3(3)
Amaurosis fugax	5(13)	17(20)
Asymptomatic bruit	1(3)	3(3)
Radiological finding	5(13)	6(7)
Prelude to vascular surgery elsewhere	—	3(3)

RBH = Royal Brisbane Hospital; PAH = Princess Alexandra Hospital.

Figure 1 shows the delay from the time of referral to the hospital to the time of surgery. Asymptomatic cases are not included. More than two-thirds of operations at each hospital were performed more than 2 weeks after the time of referral. About half the operations were performed after a delay of more than 1 month. In some cases delay was desirable, e.g. some patients with neurological deficit were allowed to improve before surgery was undertaken. In many cases it should have been possible to overcome the delay. How many patients developed a completed stroke during their wait for surgery could not be calculated from this study.

Table IV shows the neurological deficits present immediately before surgery.

A shunt was used in most cases at each hospital during the operation. This allowed circulation through the internal carotid artery from the common carotid artery. At RBH a dacron patch graft was used in most cases, whereas at PAH a patch graft was used in only 2 cases and the artery was wrapped in dacron in 1 case.

Table IV. Neurological deficit immediately before surgery and the number of operations performed for each type of deficit

Neurological status	No. of operations (%)	
	RBH	PAH
No deficit	23(61)	62(75)
Minor deficit (mild dysphasia, mild limb weakness)	9(24)	10(12)
Moderate deficit (monoparesis, hemiparesis, confusion, mental impairment)	3(8)	7(8)
Major deficit (hemiplegia ± aphasia)	1(3)	2(2.5)
Uncertain	2(5)	2(2.5)

RBH = Royal Brisbane Hospital; PAH = Princess Alexandra Hospital.

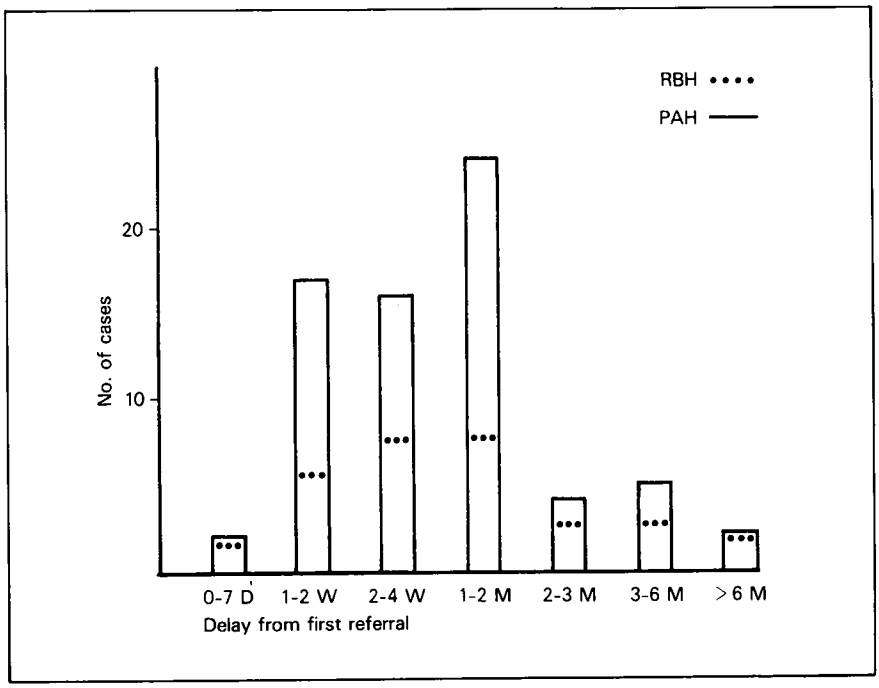

Fig. 1. Delay in days (D), weeks (W) and months (M) from first referral to hospital until endarterectomy was performed.

The complications resulting from the operation are shown in table V. At RBH there were 3 deaths from 38 operations, a mortality rate of 8%. There was also 1 completed stroke.

At PAH there was 1 death from 83 operations, and 3 completed strokes. Minor deficits occurred in some cases (e.g. temporary weakness or dysphasia or mental confusion). Thus there was a major complication rate of 11% at RBH and 5% at PAH. Other complications included wound haematoma needing to be drained in theatre, myocardial infarction, acute coronary insufficiency and cardiac failure. One patient suffered a haemorrhage from a chronic gastric ulcer 2 weeks after operation.

After angiography before operation there was 1 incomplete stroke at RBH. At PAH there was 1 completed stroke immediately after angiography and this patient was operated on some hours afterwards.There was also 1 incomplete stroke.

Discussion

In order for surgery to be considered the preferred therapy in carotid stenosis, the risk of operation must be considerably less than the natural risk of the disorder itself. It has already been stated that a reasonable assessment of the natural history of

Table V. Complications resulting from carotid endarterectomy operations

Complication	No. of operations (%)	
	RBH	PAH
Immediate neurological		
nil	29(76)	73(88)
incomplete stroke (minor)	5(13)	6(7.2)
completed stroke	1(3)	3(3.6)
death	3(8)	1(1.2)
Other		
wound haematoma	3	4
cardiac	2	2
gastrointestinal bleed	—	1

RBH = Royal Brisbane Hospital; PAH = Princess Alexandra Hospital

patients with transient ischaemic attacks is a stroke rate of 5% per year (Barnett, 1979; West et al., 1979) with the greatest risk of stroke in the first 12 months (Whisnant et al., 1973). Many centres provide morbidity and mortality figures for carotid endarterectomy which makes this operation a very successful procedure (Callow, 1980; West et al., 1979). However, in a review of published series of carotid endarterectomy cases from 1968 to 1977 by West et al. (1979), there was a range of surgical mortality from 0 to 11.2%, and of permanent neurological morbidity from 0.8% to 27%, indicating a great variability in results obtained. Although the numbers in the present study are small, it seems reasonable to consider that the 5% major complication rate from PAH is satisfactory. However, the major complication rate of 11% from RBH is probably not acceptable and needs to be improved. It should be emphasised again that the local risks of carotid endarterectomy should be known before referring patients for surgery.

Another important feature of this study is the delay from the time of initial referral to the time of operation. Marshall (1964) showed that many of the major strokes in carotid territory occurred within 1 month of the first transient ischaemic attack. Therefore, if an operation is indicated, it should be performed with some urgency.

Summary

A retrospective study was made of carotid endarterectomies performed at Royal Brisbane and Princess Alexandra Public Hospitals, the 2 major teaching hospitals in Brisbane, between 1st July 1973 and 30th June 1978. The case histories of the patients undergoing the procedure during the period were studied and the immediate mortality and morbidity associated with the procedure were determined. Records of 38 operations at Royal Brisbane Hospital were found. From these operations there were 3 deaths and 1 completed stroke, a major complication rate of 11%. From 83

operations at Princess Alexandra Hospital there was 1 death and 3 completed strokes, a major complication rate of 5%. Significant delays were noted from the time of referral to the hospitals to the time when endarterectomy was performed.

Acknowledgements

We are grateful to the vascular surgeons at Royal Brisbane and Princess Alexandra Hospitals for permission to study their cases.

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Retention of Urine and Sacral Paraesthesia in Anogenital Herpes Simplex Infection

*R.H. Edis**

It is well known that the herpes zoster virus causes an inflammation of sensory root ganglions, with manifestations of radicular pain, rash and paraesthesia. Sacral zoster may cause urinary retention and anorectal symptoms (Jellinek and Tulloch, 1976). However, it is less well known that anogenital herpes simplex virus can infect sacral root ganglia and cause back and leg pain, retention of urine, constipation and sacral paraesthesia (Oates and Greenhouse, 1978; Caplan et al., 1977). This syndrome is occurring more frequently as herpes genitalis now has a higher prevalence than any other sexually transmitted disease (Gardner, 1979).

Case Reports

Over a 2-year period, 2 definite and 2 probable cases of anogenital herpes simplex and sacral radiculitis were diagnosed. One patient had an overt history of recurrent herpes genitalis. In the other 3 patients, an association between the neurological symptoms and anogenital herpes was made only after specific enquiry. In no patient were herpetic lesions still present at the time of neurological consultation.

Case 1

This 33-year-old woman had suffered attacks of perineal herpes simplex every few months over a period of 5 years. Several days after one of her attacks, paraesthesia developed over both buttocks, up to the umbilicus and into the lateral and posterior aspects of the thighs. She also had difficulty initiating micturition, these symptoms resolving over 3 days. With some subsequent attacks of herpes genitalis, she was aware of a right thigh 'sensitivity', lasting several days. Herpes simplex type II was isolated from a vesicle scraping during one attack. At the time of presentation she was asymptomatic and the neurological examination was normal.

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Case 2

A 20-year-old girl presented with a 3-week history of right buttock and leg numbness. She also had abdominal pain and difficulty initiating micturition, being able only to pass small amounts of urine. Examination revealed decreased pin prick and light touch in the right S1, 2, 3 dermatomes. CSF examination showed 17 lymphocytes/mm^3, with a normal protein and sugar concentration. On direct enquiry, she admitted to having a right perineal vesicular rash 1 week before the onset of her symptoms. The sensory and bladder symptoms settled over a further 3 weeks. Micturition was aided by bethanechol chloride. Over subsequent months, further attacks of herpes genitalis occurred and her boyfriend also then began to suffer episodes of penile herpes.

Case 3

A 41-year-old homosexual male was seen after an L5 laminectomy and negative exploration for a possible extra-dural cauda equina compressive lesion. The CSF had shown 72 lymphocytes/mm^3 and a protein of 0.66g/L. He had a several-month history of back pain after a back injury for which he had been hospitalised. There was a recent history of proctitis, followed within days by bilateral buttock numbness, urinary retention and constipation. Examination revealed reduced pin prick and light touch appreciation bilaterally in an S2, 3, 4, 5 distribution and a lax anal sphincter. Catheterisation was required for 2 weeks and micturition was re-established with the use of bethanechol chloride and phenoxybenzamine hydrochloride for several days. Buttock numbness and reduced anal sphincter tone persisted for 2 months. The diagnosis of a recent anorectal herpes simplex infection was supported by the change in complement fixation titre which was negative at the time of the proctitis, rising to 1:80 two weeks later, and falling to 1:20 after a further 2 weeks. Anorectal and CSF cultures for herpes simplex were negative.

Case 4

This 21-year-old woman presented with urinary retention, constipation and bilateral peri-anal and leg numbness. Examination revealed a reduced sensation to pin prick and light touch in a left L5 to S3 distribution and right S2 dermatome, with a mild reduction in anal sphincter tone. There was a history of a painful anal ulcer 7 days previously, which had healed over 4 days. At this time, right leg numbness began and spread to the buttock and left leg over a period of 3 days, coincident with the appearance of constipation and difficulty with micturition. On specific enquiry, she admitted to anal intercourse several days before the appearance of the anal ulcer. Interview with the boyfriend revealed that he had herpes genitalis, although no active lesions at the time of the recent sexual contact. CSF showed 40 lymphocytes/mm^3 and a protein of 0.53g/L. Viral culture from anal, CSF and cervical swabs were negative. Urinary catheterisation was required for several days. The subjective peri-anal numbness persisted for 2 months.

Discussion

Herpes simplex virus type II has been cultured from sacral sensory ganglions obtained from cadavers shortly after death (Baringer, 1974). Experimentally, the herpes simplex virus has demonstrated neurotropism after inoculation at a peripheral site (Baringer and Swoveland, 1974). It is postulated that the virus may infect the sensory ganglions by ascending along nerves from the primary skin or mucosal site of infection. Recurrent peripheral infection may be the consequence of re-activation of virus in the ganglions, with subsequent progression down the axons to the skin (Baringer, 1974).

Genital herpes presents as a cluster of vesicles, which may involve the vulva, vagina, cervix, penis or anorectal area. Neuralgic pain and pruritis just before an attack are common. The vesicles soon burst to form erosions that heal in a few days. With the primary infection, fever, malaise, headache and inguinal lymphadenopathy are often present. Anogenital herpes infection may be due to either herpes simplex virus type I or II. It is transmitted sexually (even by asymptomatic carriers), and

genital auto-inoculation is also possible from labial herpes. Recurrent attacks have been reported in up to two-thirds of cases during the year after the first episode (Chang et al., 1974). The virus can readily be isolated from vesicular fluid by cell culture. Primary infections can be recognised by rising titres of complement fixation antibodies, but no characteristic serological change occurs in recurrent attacks (Belsey and Adler, 1979).

Most patients who develop sacral radiculitis and urinary retention appear to have a primary infection. This complication occurred in about 5% of patients with a probable primary infection in one large series (Oates and Greenhouse, 1978). The sacral radiculitis is manifest by pain, paraesthesia, difficulty with voiding urine, constipation, and decreased potency. Loss of anal tone, diminished bulbo-cavernosus reflex and cystometrographic evidence of lower motor neurone dysfunction can be demonstrated. There is an accompanying CSF pleocytosis which may include polymorphonuclear leucocytes (Caplan et al., 1977). This syndrome is self-limited, although micturition may need to be temporarily aided by cholinergic or parasympatholytic drugs, and intermittent or suprapubic catheterisation for up to 5 weeks may be required for urinary retention (Smith and Gordon, 1981). Topical antiviral treatment is of little use and there is no proved means of reducing the frequency of recurrence. A new systemic anti-viral agent, acycloguanosine, currently under investigation, may prove helpful (Selby et al., 1979).

These cases demonstrate that all young sexually active people who present with urinary retention should be evaluated by history and examination for occult anogenital herpes simplex infection. Recognition of this syndrome will prevent unnecessary myelography and misdiagnosis as multiple sclerosis or psychogenic urinary retention.

Summary

Two definite and 2 probable cases of anogenital herpes simplex and sacral radiculitis are described. Symptoms were typical and consisted of paraesthesia and neuralgic pain in the perineum and legs, urinary retention and constipation occurring within several days to a week after an anogenital herpetic eruption. However, at presentation only 1 case had an obvious history of anogenital herpes simplex. Neurological signs were not striking and consisted of a reduced appreciation of light touch and pin prick over the sacral dermatomes and in 2 cases reduced anal sphincter tone. CSF examination in 3 patients showed a lymphocytosis. Bladder catheterisation was required for up to 2 weeks in 2 patients. The paraesthesia persisted for weeks to months. It should be more widely recognised that anogenital herpes simplex, with sacral radiculitis, is probably the commonest cause of acute retention of urine in young sexually active people.

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Substance P in the Central Nervous System

*R.D. Helme and D.W. White**

Substance P, discovered in 1931 by von Euler and Gaddum, is an 11-amino acid peptide (Chang et al., 1971). A radioimmunoassay for substance P (or substance P-like material) was first developed in 1973 (Powell et al., 1973). Immunohistochemical studies have demonstrated that substance P is found in high concentrations in the outer layer of the dorsal horn of the spinal cord (Hokfelt et al., 1975). Substance P may therefore be a neurotransmitter of primary sensory neurones (Nicholl et al., 1980).

In this study central nervous system tissue samples from rats and humans were examined using radioimmunoassay and an immunofluorescence method established in our laboratory. Tissues were examined at various time intervals after death.

Methods

Antibody

Synthetic substance P (Sigma Chemical Company) was coupled to bovine serum albumin using 1-ethyl-3(3-dimethyl-aminopropyl) carbodiamide by the method of Harkins et al. (1978). A solution of the conjugate containing approximately 50μg of substance P was emulsified with an equal volume of Freund's complete adjuvant and female New Zealand white rabbits were given multiple subcutaneous injections every 3 weeks.

Radioimmunoassay

[Tyr^8]-substance P (Peninsula Laboratories) was iodinated with ^{125}I using the chloramine T method. The tracer was purified using a CM-Sephadex C25 ion ex-

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change column at 4°C. The specific activity for the tracer was 1017μCi/μg substance P. Standard curves were established using dextran 10-coated charcoal to separate free from bound label. The antibody for RIA was used at dilutions of 1 : 15,000 (Ab40) and 1 : 4,000 (Ab56). The assay sensitivity was 0.7fmoles of substance P for Ab40 estimated as the amount of substance P for which the corresponding change detected in free ^{125}I-substance P is 2 standard deviations removed from the mean response for zero substance P (fig. 1).

Cross-reactivity between extracted substance P, synthetic substance P and [Tyr^{8}]-substance P was examined for both antibodies and found to be parallel. Specificity of the antiserum was also examined using a variety of peptides. Physalaemin and eledoisin cross-reacted appreciably in the assay. C terminal penta-substance P and hepta-substance P also cross-reacted. Other peptides did not show cross-reactivity.

Tissue Extractions

Twelve female Sprague-Dawley rats were sacrificed using ether anaesthetic. Four were decapitated at each of 3 time intervals and spinal cords and brains were

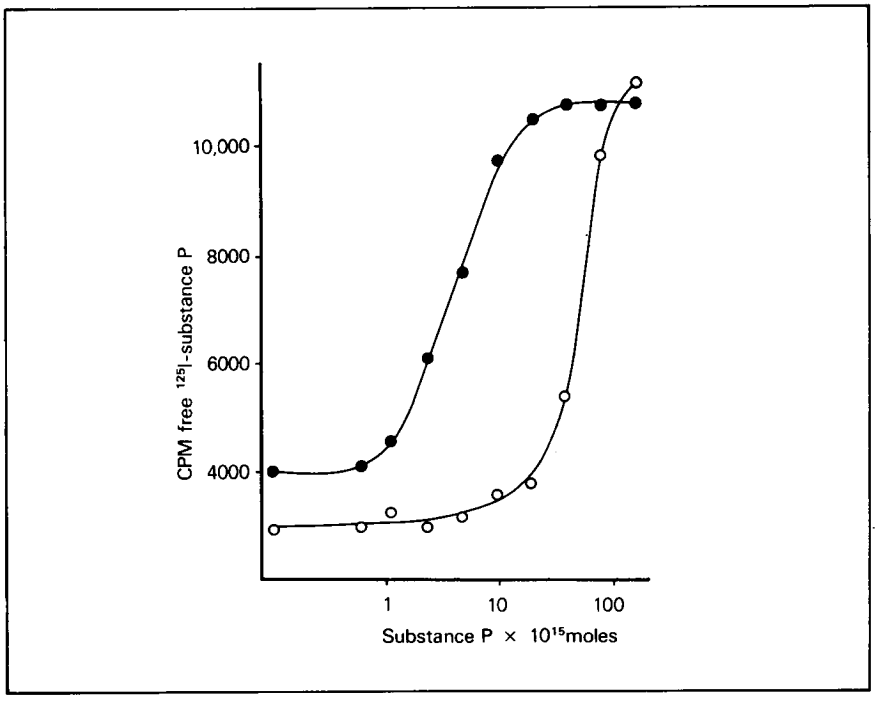

Fig. 1. Standard curve for substance P immunoreactivity. Ordinate : free ^{125}I-substance P. Abscissa: moles substance P on a log scale. Standard curve using antibody from rabbit No. 40 (closed circles) has a greater sensitivity than that using antibody from rabbit No. 56 (open circles).

Table I. Regional distribution of substance P in the brain and spinal cord of Sprague-Dawley rats

Region	Concentration of substance P ($\times 10^{-12}$moles/mg protein ± SEM[1])		
	0 hours	8 hours	24 hours
Spinal cord	1.7 ± 0.4	2.2 ± 0.5	1.0 ± 0.5
Brain stem	4.3 ± 0.9	2.5 ± 0.3	3.3 ± 0.9
Cerebellum	0.3 ± 0.1	0.4 ± 0.2	ND
Midbrain	2.0 ± 0.5	2.8 ± 0.9	2.4 ± 0.6
Cerebral cortex	0.1 ± 0.1	ND	ND
Striatum	0.8 ± 0.1	1.9 ± 0.6	0.4 ± 0.3
Hypothalamus	3.4 ± 0.6	3.9 ± 0.9	1.9 ± 0.7

4 specimens for every region.
ND = Not detectable.

removed. Dissection was performed 0 hours, 8 hours and 24 hours after death. Brain and spinal cord tissues were individually homogenised in 2N acetic acid. An aliquot of the supernatant was taken for protein estimation using Lowry's method. The extract was then lyophilised and reconstituted in casein buffer immediately before being assayed. Human spinal cord obtained 18 hours after death was similarly processed. Recovery was 93% of synthetic substance P added to tissue that was extracted.

Immunofluorescence

Tissue samples were formalin-fixed and 10μm frozen sections were cut. An indirect immunofluorescence method was used. Antibody 56 was used diluted 1 : 250 in phosphate buffered saline containing bovine serum albumin and 1% Triton X100. Evidence that staining was specific for substance P was provided by neutralisation experiments. There was 10% neutralisation with substance P, hepta-substance P and penta-substance P. Physalaemin and eledoisin reduced the staining by 90%. Other peptides did not reduce the intensity of the specific staining.

Results

Tissue Extraction

Highest concentrations of substance P were found in the hypothalamus, midbrain and brain stem of the rat brain, with high concentrations in the spinal cord (table I). After 8 hours, the substance P levels were unchanged except for an increased concentration in the striatum. After 24 hours there was an overall decrease in concentration, except in the midbrain where levels remained stable.

A sample of human spinal cord, obtained 18 hours after death, was cut longitudinally and the ventral and dorsal sections were assayed separately. The substance P concentrations of the ventral section was 8.6×10^{-13}moles/mg of protein and for the dorsal section the concentration was 1.3×10^{-12}moles/mg of protein.

Immunofluorescence

Specific staining for substance P occurred in the outer layer of the dorsal horn of the rat spinal cord (fig. 2). Specific staining was achieved up to 48 hours postmortem. The specific staining was mostly granular in appearance although fine fibres were seen at earlier autopsy times. Similar staining was seen in the dorsal horn of human spinal cord.

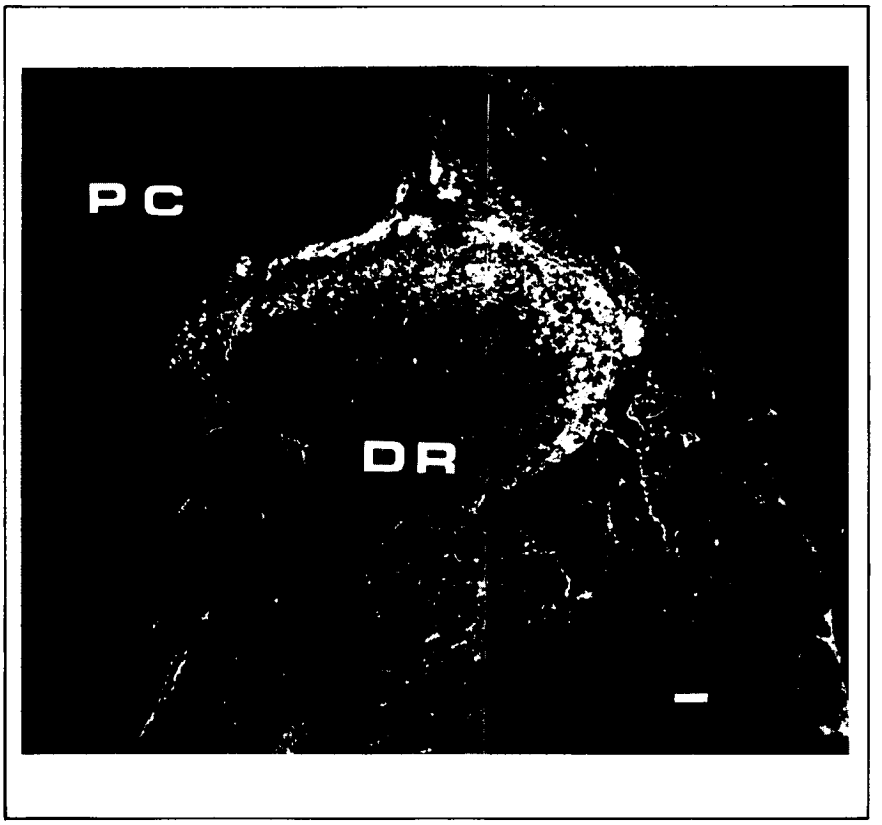

Fig. 2. Immunofluorescence photomicrograph. Substance P in the outer layers of the dorsal horn and dorso-lateral tract. Rat spinal cord, 10μm section. PC: posterior column; DR: dorsal horn. Calibration: 100μm.

Discussion

The concentration of substance P extracted from rat brain was similar to previous studies (Brownstein et al., 1976) and to concentrations found in human brain (Gale et al., 1978). Substance P levels remained stable, left in tissues at 4°C, up to a period of 8 hours. Substance P was still detected using both RIA and immunofluorescence 24 hours postmortem. The rate of degradation of substance P may be important when studying the distribution in autopsy samples of normal and diseased human tissue.

Substance P concentrations in the dorsal section of human spinal cord is approximately twice the amount found in the ventral section. Takahashi and Otsuka (1975) found similar proportions in cat spinal cord. However, Kanazawa and Jessell (1976) have reported the concentration in the dorsal section of rat spinal cord to be approximately 10 times the concentration found in the ventral section. Preliminary studies suggest a difference in the distribution of substance P in the ventral horn of rat and human spinal cord Further studies are needed to validate these observations using both RIA and immunohistochemical techniques.

Summary

A radioimmunoassay has been developed for measuring substance P-like immunoreactivity. Assay sensitivity was 0.7fmoles of substance P. Using the radioimmunoassay substance P-like immunoreactivity was detected in postmortem tissue samples from the central nervous system of rats and humans.

Immunofluorescence studies confirmed the localisation of substance P in the dorsal horn of the spinal cord.

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Optic Nerve Decompression in Benign Intracranial Hypertension

*C.J. Kilpatrick, D.V. Kaufman, J.E.K. Galbraith and J.O. King.**

Benign intracranial hypertension is a condition characterised by symptoms of raised intracranial pressure, papilloedema, an absence of focal neurological signs apart from a sixth nerve palsy, raised cerebrospinal fluid pressure with normal constituents and normal contrast radiology. It is usually a self-limiting condition without sequelae (Johnston and Paterson, 1974). Occasionally complications such as visual failure, endocrine disturbance and empty sella syndrome develop suggesting that this syndrome is not entirely benign (Smith, 1958; Foley and Posner, 1975; Barber and Garvan, 1980). The most sinister complication is visual failure after prolonged papilloedema. Smith (1958) in his series of 36 cases of benign intracranial hypertension reported visual impairment in 15%.

Various forms of medical treatment have been tried to protect the optic nerve from the effects of persistently raised intracranial pressure. Occasionally benign intracranial hypertension is refractory to the usual medical treatment and may require surgical intervention. Recently, decompression of the perioptic meninges has proved effective in the treatment of papilloedema (Davidson, 1969; Smith et al., 1969; Galbraith, 1973; Galbraith and Sullivan, 1973; Burde et al., 1974; Davies and Zilkha, 1976).

Optic nerve decompression was first described by de Wecker in 1872. He operated on 2 patients and noted the relief of papilloedema and symptoms of raised intracranial pressure. Power in the same year and Carter in 1889 reported their experience of optic nerve decompression. Thirty years later Müller reported 19 cases in which a rectangle of dura was excised from the optic nerve sheath (Müller, 1916; Müller, 1917). Hayreh in 1968 demonstrated experimentally in monkeys that eleva-

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tion of the intracranial CSF pressure played a significant role in the production of papilloedema. He showed that incision of the optic nerve sheath relieved the CSF pressure surrounding the optic nerve, with improvement in the state of the optic disc. Since this experimental work, optic nerve decompression has gained increasing popularity as a procedure to relieve papilloedema.

Methods

Case Selection

This is a preliminary report of 14 patients with benign intracranial hypertension who were treated with optic nerve decompression. Ten patients were female and 4 male and the ages ranged from 26 to 56 years. The indication for surgery in all patients was unrelieved papilloedema and impending visual failure as indicated by recurrent obscurations, deterioration in visual acuity or visual fields, despite medical treatment.

Preoperative Assessment

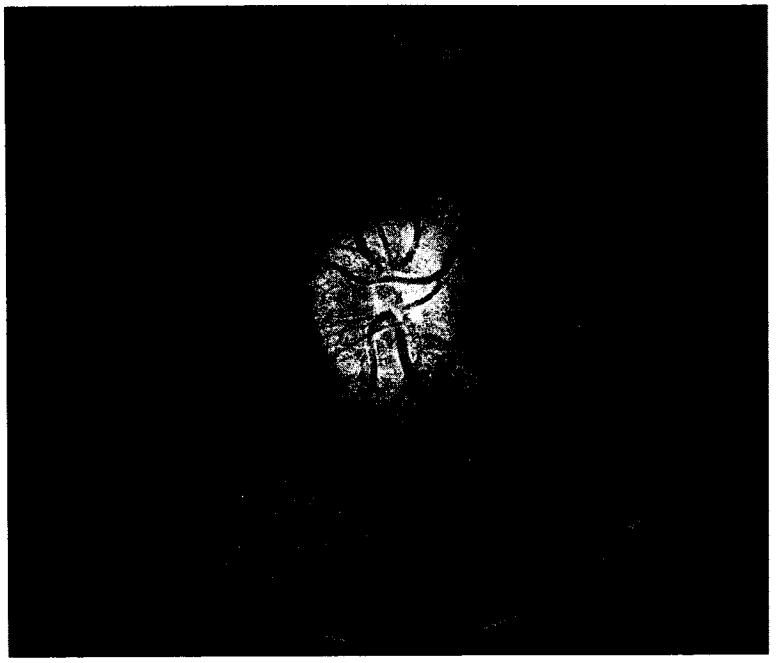
Preoperatively all patients had bilateral papilloedema and 11 patients complained of bilateral or unilateral visual obscurations. In the immediate preoperative period, only 6 patients had either headache or diplopia as symptoms of raised intracranial pressure. Six patients had evidence of visual failure with papilloedema and early optic atrophy. In 7 patients preoperative fluorescein angiograms were performed. In 1 patient intracranial pressure was monitored preoperatively, during surgery and for the first 24 hours after surgery.

Surgical Procedure

The operations were performed between 1970 and 1980 by one surgeon (JEKG). Eleven patients had bilateral optic nerve decompression and 3 patients had a unilateral procedure. The operation is performed from the medial side of the globe via a limbal conjunctival incision. Traction sutures are looped beneath the insertion of the superior and inferior recti. The insertion of the medial rectus is exposed and a marking suture inserted in the upper border of the muscle, which is then detached from the globe and allowed to retract into the orbit. A modified tracheal dilator is inserted medial to the globe and the blades moved apart, pushing the globe laterally. Firm traction upwards and laterally on the traction sutures allows the orbital fat to fall away from the optic nerve, which can then be seen in the depths of the incision. Short

Fig. 1. Right optic fundus showing moderate papilloedema.

Fig. 2. Left optic fundus showing marked papilloedema.



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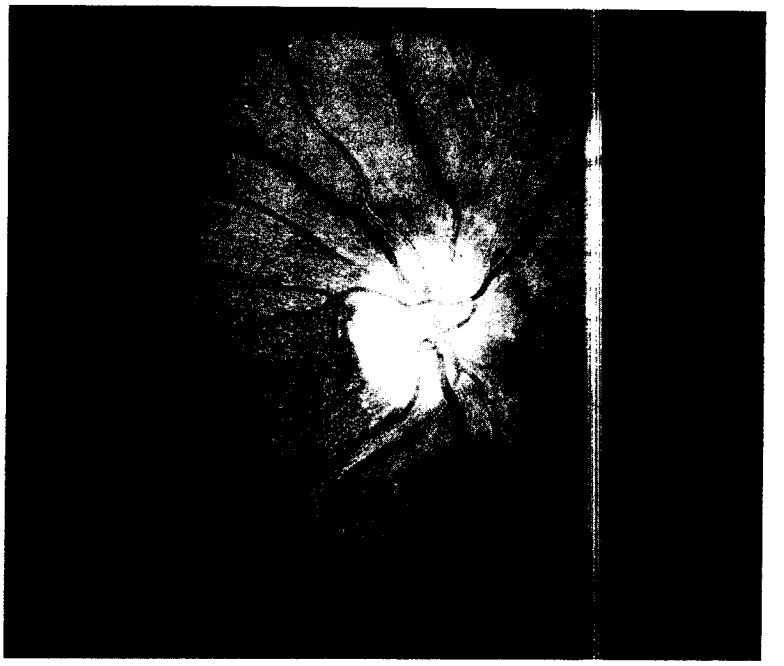

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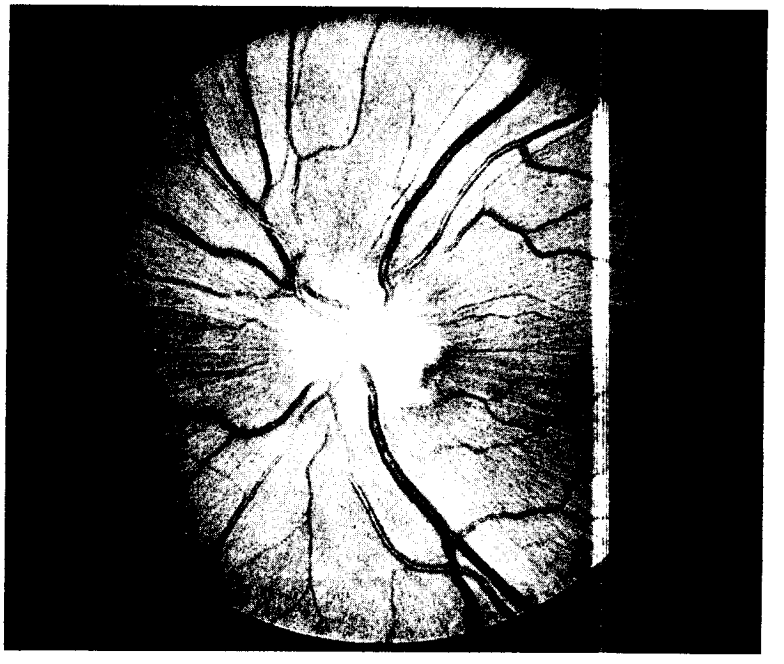

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ciliary vessels are pushed aside, then an incision is made in the dural and arachnoid sheath and a window is excised. Cerebrospinal fluid is usually seen to flow from the incision. The retractor is removed, the medial rectus reattached to the globe and the conjunctiva closed.

Results

Postoperative Assessment

In all patients bilateral papilloedema resolved within 6 weeks, including the 3 patients who had a unilateral procedure (figs. 1,2,3,4). Visual obscurations resolved postoperatively in all cases. In 1 of the 6 patients with visual failure, vision continued to deteriorate. The other 5 patients had no further deterioration or improvement in visual function after surgery. Postoperative fluorescein angiograms in 5 patients all showed resolution of papilloedema. CSF isotope scans were performed in 2 patients to try to demonstrate a leakage of fluid from the intracranial cavity into the orbit. Only 1 scan in fact demonstrated this finding. Symptoms of raised intracranial pressure resolved after surgery in 3 of 6 patients who had preoperative headache or diplopia. The intracranial pressure was monitored in 1 patient and showed elevation of the pressure preoperatively with no significant change during surgery and in the first 24 postoperative hours.

Complications

Complications were minimal and transient. Diplopia due to extra-ocular muscle imbalance was common during the immediate postoperative period but in all cases this resolved. A number of patients developed transient asymptomatic, eccentric pupils, probably secondary to trauma to the posterior ciliary nerves. One patient developed a transient third nerve palsy which was attributed to traction.

Follow-up Assessment

Symptoms of benign intracranial hypertension recurred in 3 patients. Two patients developed obscurations 6 months and 2 years respectively after surgery and each required a lumbo-peritoneal shunt and 1 patient developed headache which responded to medical treatment. The other 11 patients remained free of symptoms and signs of raised intracranial pressure during a follow-up period ranging from 10 years to 4 months.

Fig. 3. Right optic fundus showing resolved papilloedema 5 weeks after left optic nerve decompression.

Fig. 4. Left optic fundus showing resolving papilloedema, 5 weeks after left optic nerve decompression.

Discussion

Optic nerve decompression in the management of patients with benign intracranial hypertension is well described but its exact mode of action remains uncertain. The operation may protect the optic nerve by lowering the intracranial pressure as a result of a persistent CSF leak through the optic nerve sheath window, or by a local effect directly reducing the pressure within the subarachnoid space surrounding the optic nerve. Papilloedema and visual obscurations resolved in all cases and in 5 of 6 patients with visual failure, there was no further deterioration of visual function. These results confirm the local benefit of this procedure in protecting the optic nerve. In 3 of 6 patients, symptoms of raised intracranial pressure resolved after surgery. In 3 patients unilateral optic nerve decompression was performed and yet papilloedema resolved in both eyes. These observations support the hypothesis that in some patients, optic nerve decompression may lower the intracranial pressure. Davidson (1969) noted loss of symptoms of raised intracranial pressure in 5 patients. However, in his series, unilateral optic nerve decompression had no effect on the contralateral eye. Galbraith and Sullivan (1973) similarly reported loss of symptoms of raised intracranial pressure in 3 of 7 patients.

In 1 patient, intracranial pressure was monitored to directly assess the effect of optic nerve decompression. The baseline pressure was raised and remained so after opening both optic nerve dural sheaths. Hayreh (1968), operating on monkeys, noted a lowering of intracranial pressure in one animal after unilateral optic nerve decompression but commented that this was uncommon in the rest of the series. This would suggest an individual variation both in humans and in monkeys which may be related to the disparity in size between the optic nerve and the optic canal. Despite previous optic nerve decompression, symptoms of benign intracranial hypertension recurred in 3 patients. These findings suggest that in some patients, the procedure has no significant effect on the intracranial pressure. In the 11 patients who remained asymptomatic after optic nerve decompression, it is not possible to say whether the intracranial pressure was reduced indefinitely or until remission occurred, or whether the intracranial pressure remained elevated but produced no symptoms until the disease remitted spontaneously. No information is available as to how long the optic nerve sheath window remains open except that papilloedema recurred in 2 patients 6 months and 2 years respectively after surgery.

Davidson (1969) in his report of 5 patients with optic nerve decompression stated that patients with optic atrophy should be excluded from this operation since optic atrophy is irreversible. Six patients in this study had preoperative evidence of early optic atrophy and only 1 patient suffered further deterioration of visual function postoperatively. Sanders (1969), in his paper on the classification of papilloedema based on fluorescein angiographic appearances, commented on the signs of impending visual failure. He noted marked attenuation of retinal arteries without leakage of dye, and resolution of the vascular plexus on the disc surface in patients who went on to develop severe visual failure. In the patients who underwent fluorescein angiography, there was no correlation between the preoperative angiographic appearance of the disc and later visual deterioration. As 5 of our 6 cases with early optic atrophy showed no further deterioration after optic nerve decompression, surg-

ery should still be considered in this group. In future, fluorescein angiography on all cases may help to define further the patients unlikely to benefit from this procedure.

Optic nerve decompression has a place in the management of patients with benign intracranial hypertension who are resistant to medical treatment and therefore at risk of developing secondary optic atrophy and consequent visual failure. The procedure has a local effect by lowering the pressure within the subarachnoid space surrounding the optic nerve and in some patients there is also lowering of intracranial pressure.

Summary

Fourteen patients with benign intracranial hypertension who failed to respond to medical treatment, were treated with optic nerve decompression to prevent the sequelae of chronic unrelieved papilloedema. The mechanism by which optic nerve decompression protects the optic nerve is uncertain. These patients were reviewed to evaluate the efficacy of the procedure in the treatment of benign intracranial hypertension and to assess its mechanism of action. Preoperatively all patients had papilloedema, 11 patients had visual obscurations and 6 patients had evidence of visual failure. Postoperatively, visual obscurations and papilloedema resolved in all patients, and 5 of 6 patients had no further deterioration of visual function. Six patients had symptoms of raised intracranial pressure preoperatively and in 3 the symptoms resolved after surgery. Three patients had unilateral optic nerve decompression and papilloedema resolved in both eyes. In 1 patient intracranial pressure monitoring revealed raised pressure preoperatively with no significant change in the first 24 hours after surgery. We conclude that optic nerve decompression is effective in the treatment of benign intracranial hypertension, has its effect locally, and in some patients may lower the intracranial pressure.

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Familial Occurrence of Meningioma: A Case Report

*R. Pamphlett and R.A. Mackenzie**

There is as yet no consensus as to whether meningiomas can be inherited. There have been 4 previous reports of meningiomas occurring in families without evidence of neurofibromatosis (Gaist and Piazza, 1959; Wagman et al., 1960; Joynt and Perret, 1961; Sahar, 1965). Although it is possible that the occurrence of the tumour in these families was due to mere coincidence, hereditary factors may have played a part. To add to the body of information on the heritability of meningiomas, we report a family in which both father and daughter had meningiomas.

Case Report

Case 1

The proband (fig. 1) was a 75-year-old man who was admitted to hospital on 26 November 1980. He complained of progressively failing vision for 3 years, for which a diagnosis of glaucoma had been made. He had lost his sense of smell for 3 years, and had been noted by his family to have become increasingly short-tempered. Examination revealed bilateral anosmia, decreased visual acuity, and optic atrophy.

A computerised cerebral scan showed a large contrast-enhancing tumour arising from the olfactory groove (fig. 2a). Carotid angiography showed upward and backward displacement of the anterior cerebral arteries with a vascular blush on the floor of the anterior cranial fossa.

At operation a large tumour arising from the olfactory groove was removed. The histology was that of meningioma, showing a mixture of transitional and meningotheliomatous patterns (fig. 3a).

Case 2

The daughter of the proband (III,4 in fig. 1), a 27-year-old woman, was admitted to hospital on 13 January 1980. She complained of nonspecific headaches for 5 years. Examination revealed partial right-sided anosmia and optic disc pallor.

A computerised cerebral scan showed a contrast-enhancing tumour arising from the olfactory

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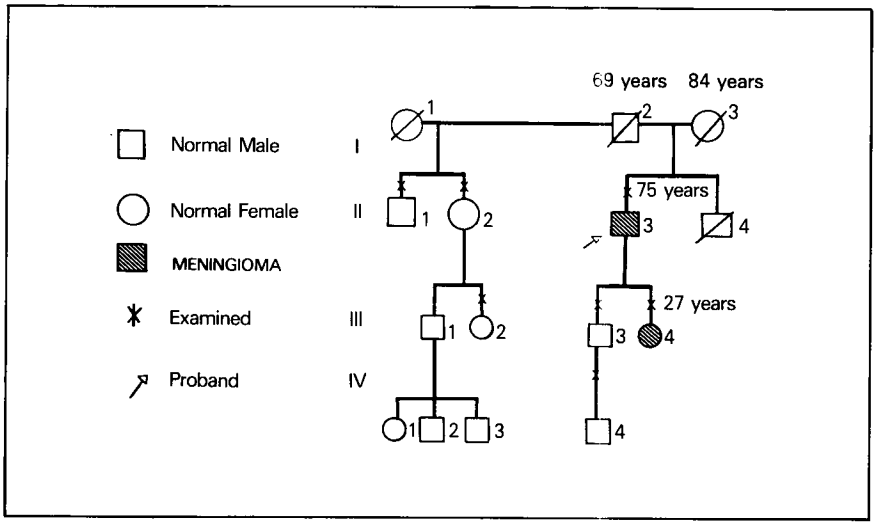

Fig. 1. Pedigree chart of the family.

groove (fig. 2b). Carotid angiography showed upward and backward displacement of the anterior cerebral arteries.

At operation a large tumour arising from the olfactory groove was removed. Histology was that of a meningioma, showing a mixture of transitional and meningotheliomatous patterns (fig. 3b).

Both father and daughter therefore have olfactory groove meningiomas of similar histological type. Neither they nor any other members of their family examined (fig. 1) had clinical evidence of neurofibromatosis.

Discussion

The Inheritance of Meningioma

To assess whether meningioma is inheritable, one must consider case reports, epidemiological evidence, and twin studies.

As the present report is only the fifth description of meningioma occurring in a family, it may be that this familial occurrence is due to mere coincidence. The incidence rates for meningioma per 100,000 per year are 0.49 for males and 0.70 for females (Schoenberg, 1978). Therefore the coincidence is great. An epidemiological study (Hauge and Harvald, 1960) examining the families of 155 patients with meningioma found no further cases of meningioma in these family members. Except for one pair of monozygotic twins each having meningioma (Sedzimir et al., 1973) twin studies have failed to show a genetic tendency to meningioma.

The case for the inheritance of meningioma is therefore far from conclusive.

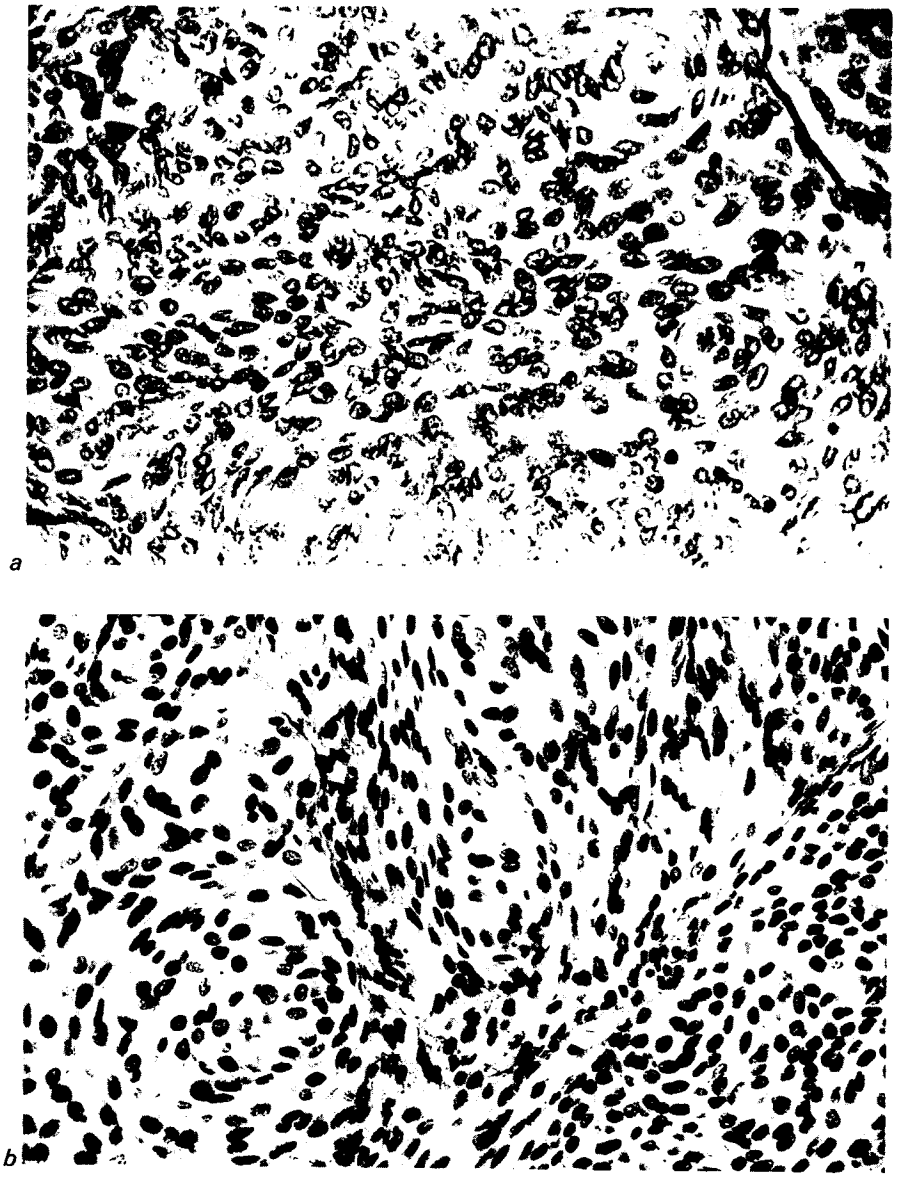

Fig. 3. Microscopic appearance of the tumour in (a) father and (b) daughter, in each case showing appearances of meningioma.

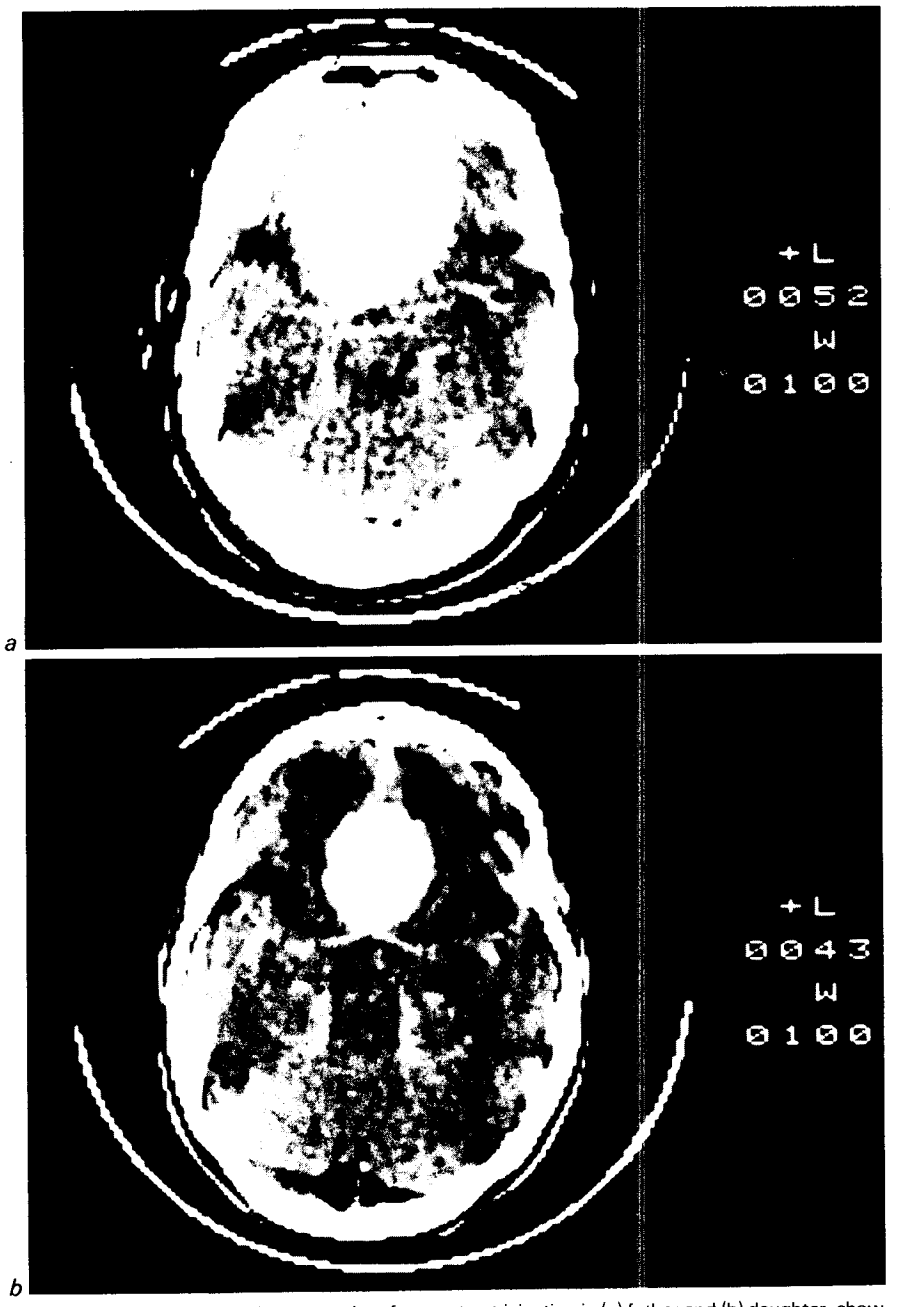

Fig. 2. Computerised tomography after contrast injection in (a) father and (b) daughter, showing in each case a contrast-enhancing lesion in the anterior cranial fossa.

Familial Meningioma and Neurofibromatosis

There is an increased incidence of meningioma in patients with neurofibromatosis of the central type (Rubinstein, 1972). Neither the 2 patients with meningioma here described nor any member of their family available for examination had clinical evidence of neurofibromatosis. However, a family has been described (Delleman et al., 1978) in which 4 members had meningioma without evidence of neurofibromatosis. Another member was found to have multiple cafe-au-lait spots, and yet another to have meningioma and bilateral acoustic neuromas. In this family it was suggested that all the cases of meningioma were due to unusual presentations of neurofibromatosis, and that this may be the situation in all cases of familial meningioma.

The antigenic activity of nerve-growth factor is raised in the serum of most patients with central neurofibromatosis (Fabricant et al., 1979). The measurement of nerve-growth factor in all patients with familial meningioma may therefore be useful in assessing whether they are formes fruste of neurofibromatosis.

The inheritance of meningioma remains an open question. All cases of meningioma in families should be reported, as this is one of the ways in which the issue may be settled.

Summary

A father and daughter were each found to have an olfactory groove meningioma. No members of the family were found to have neurofibromatosis. There have been 4 previous reports of meningiomas occurring in families, and the present report adds support to the hypothesis that meningioma can be a heredofamilial disorder.

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Senile Parkinsonism and Dopa Pharmacokinetics

G.A. Broe†, M.A. Evans, and E.J. Triggs**

Parkinsonism is essentially a disorder of aging with a low incidence below 60 years of age rising to over 2000 per 100,000, or 2% of the population, 70 years of age and over (Nobrega et al., 1967). However, modern drug therapy of Parkinson's disease including choice of drugs, modes of initiating therapy and maintenance doses have all been worked out in trials using a predominantly younger population (table I). From these trials high initiating doses of levodopa (0.5 to 1g), high increments of the same order and high maintenance doses (average 3 to 6g) are recommended without reference to age.

As many geriatricians are aware from clinical experience, the drug therapy of Parkinsonism in the elderly requires a major difference in approach from that advocated for younger age groups (Caird and Williamson, 1978; Anderson, 1976; Judge and Caird, 1978). Clinical trials carried out in older age groups confirm this (table II). Using this low dose regimen with low starting daily doses (100mg) and low increments (100mg), an equivalent therapeutic response is obtained in older subjects with similar short term and lower long term toxicity compared to the younger group (Vignalou and Beck, 1973).

This paper will first outline the clinical features of Parkinsonism in old age and secondly the therapy of senile Parkinsonism with particular reference to the pharmacokinetics of levodopa in the elderly.

Senile Parkinsonism — Clinical Features

Idiopathic Parkinson's disease itself is not a homogeneous entity either clinically or pathologically (table III).

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Table I. Average age and the average daily dose of levodopa used in early clinical trials

Reference	No. of subjects	Average age	Average dose/day (g)
Cotzias et al. (1969)	17	51	5.8
Godwin-Austen et al. (1969)	18	56	3 to 8
Klawans and Garvin (1969)	105	65[1]	2 to 6
Barbeau (1969)	86	60	4.8
Mones et al. (1970)	152	55[1]	3 to 4
Stellar et al. (1979)	91	60[1]	3 to 5
Peaston and Bianchine (1970)	22	65	3.0
Mawdsley (1970)	32	61	4 to 9

1 Estimated.

A clinico-pathological continuum exists between a younger group of patients having the classic disorder with relatively selective damage to the nigrostriatal pathway in the brain and an older group (70 + years) with a different clinical picture, an altered therapeutic response and more widespread pathological changes in the brain (Carlsson, 1978; Broe, 1979). Rigidity and bradykinesia are diagnostic clinical features common to both groups.

In the younger group the classic triad predominates with an asymmetrical onset and course. Orthostatic hypotension, posture and balance defect and dementia occur but are mild and late compared to the other clinical features. Pathological changes comprise selective neuronal loss largely confined to brain stem nuclei, particularly substantia nigra and locus caeruleus.

In the older age group (70 + years) tremor is minimal and frequently essential in type. Rigidity and bradykinesia tend to be bilateral and symmetrical from onset and the disorder of balance and posture is an early disabling clinical feature. Orthostatic hypotension is more marked and dementia is more common and more progressive. Their brains show more widespread neuronal loss and biochemical changes. However the major defect, as in the younger group, is loss of pigmented dopaminergic substantia nigra cells with degeneration of the nigrostriatal pathway.

Table II. Studies in older patients treated with levodopa

Reference	No. of subjects	Average age	Average dose/day (g)
Broe and Caird (1973)	16	76[1]	1.7
Grad et al. (1974)	15	76	1.9
Sutcliffe (1973)	50	70	1 to 2
Vignalou and Beck (1973)	122	70 to 90	2.4

1 Estimated.

Table III. Classification of Parkinson's disease

1.	Idiopathic Parkinson's disease
	(a) Classical paralysis agitans
	(b) Senile Parkinsonism
	(c) Striato-nigral degeneration
2.	Symptomatic Parkinson's disease
	(a) Drug-induced
	(b) Post-encephalitic
	(c) Manganese toxicity

Therapy of Senile Parkinsonism

With a small increment, low dose regimen of levodopa we have found, both in the 1973 trial (Broe and Caird, 1973) and in subsequent clinical usage, that elderly subjects achieve an equivalent therapeutic response of younger subjects treated with relatively high doses of levodopa. Nausea, vomiting and postural hypotension are rarely a clinical problem. The incidence of abnormal movements and mental changes is low provided anticholinergics are not used in conjunction with a low dose levodopa therapy (Broe and Caird, 1973; Vignalou and Beck, 1973).

Anticholinergic agents are in general contraindicated in elderly subjects. They interfere with mental function and produce a toxic confusional state with prolonged use (Caird and Williamson, 1978; Broe and Caird, 1973; Broe, in press).

The use of combined therapy with a peripheral decarboxylase inhibitor is of limited value in the elderly (Broe, in press). There is evidence that combined therapy increases the incidence of abnormal involuntary movements and neuropsychiatric sequelae presumably by chronically increasing striatal dopamine levels. A 30% incidence of chronic or long term deterioration has been noted in major studies after 5 years of high dose levodopa therapy. These long term changes are first, loss of levodopa benefit due to progression of the disease, secondly 'on-off' effect and thirdly a progressive dementia. These effects are largely due to progression of the underlying pathological process in the brain. However, 'on-off' effect appears to be more frequent with 'high-dose' levodopa therapy and combined therapy. There is, in contrast, a low frequency of 'on-off' effect in the elderly population treated with low dose levodopa (Broe, in press).

Pharmacokinetics of Levodopa

It has recently been shown that the lower levodopa dosage requirements of the elderly are in part due to an increased bioavailability of oral levodopa in old age and this is associated with age-related changes in gastrointestinal absorption and metabolism of levodopa.

Levodopa is rapidly absorbed from the gastrointestinal tract and peak plasma levels usually occur within 1/2 to 2 hours, although individual and dose-to-dose variability in absorption are marked (Wade et al., 1974).

Levodopa as an aromatic amino acid is absorbed primarily in the small bowel by an active transport mechanism (Wade et al., 1973). Levodopa decarboxylase has a high activity in the gastric mucosa and the major part of orally administered levodopa in younger subjects is metabolised to dopamine in the stomach and not presented to the small bowel for absorption (Riviera-Calimlim et al., 1970).

Evans et al. (1980) have shown in elderly subjects (aged 71 to 86 years) a 3-fold increase in levodopa absorption after oral administration of levodopa in comparison with a group of young controls. Both elderly Parkinsonian patients on a low dose regimen of levodopa and elderly controls without Parkinsonism showed increased plasma levodopa levels in terms of computed area under the plasma concentration-time curve (Evans et al., in press).

Gastric emptying rate was measured in elderly Parkinsonian subjects, in elderly controls and in young controls and a 3-fold delay in gastric emptying occurred in the elderly. Hence increased levodopa absorption and higher blood levels occurred despite a much prolonged gastric emptying rate (Evans et al., in press). All other parameters of levodopa absorption including peak plasma concentration, multiple plasma peaks and short plasma half-life of 1/2 to 1 hour showed no significant difference between the elderly and young controls suggesting that site and method of absorption were probably the same in both age groups.

It is postulated from these studies that elderly subjects 70 years and over have a low activity of dopa decarboxylase in the stomach resulting in a markedly reduced local metabolism of levodopa despite prolonged gastric emptying. This results in presentation of much higher amounts of unmetabolised levodopa to the small bowel for absorption by the same active transport process as in younger subjects. This 3-fold increase in absorption explains in part why the elderly require approximately one-third

Table IV. Clinical features of Parkinsonism in younger and older patients

Clinical feature	Classical idiopathic Parkinson's disease (40 to 65 years)	Senile Parkinsonism (70 + years)
Tremor	Diagnostic Resting in type	Uncommon Essential or senile in type
Rigidity	Diagnostic Asymmetrical	Diagnostic Symmetrical
Bradykinesia	Diagnostic Asymmetrical	Diagnostic Symmetrical
Posture and balance defect	Mild and late	Early and progressive
Autonomic defect	Mild	Moderate to severe
Dementia	Mild and late	Early and progressive
Progression	Variable; slow or rapid	Slow
Chronic levodopa response	'On-off' at 2 to 5 years common (20%)	'On-off' rare and late

the dose of oral levodopa that younger patients require for an equivalent therapeutic response (Broe and Caird, 1973; Grad et al., 1974; Sutcliffe, 1973; Vignalou and Beck, 1973).

Summary

Senile Parkinsonism can be clinically differentiated from idiopathic Parkinson's disease in younger age groups. It has a slower clinical course, an altered therapeutic response and a more widespread neuropathology.

The drug of choice for senile Parkinsonism is levodopa given in low starting daily doses of 100mg, with low increments of 100mg every 4 to 7 days and low maintenance doses of 0.5 to 2.5g daily. Increased absorption of a given dose of levodopa in the elderly explains in part the lower dosage requirements.

Combined therapy with a peripheral decarboxylase inhibitor is usually unnecessary in the elderly and carries a higher risk of neuropsychiatric toxicity. The use of a peripheral decarboxylase inhibitor should be reserved for those few elderly patients with significant gastrointestinal side effects and for those who respond poorly to levodopa alone.

Anticholinergic agents are in general contraindicated in the elderly, either used alone or in combination with levodopa.

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Assessment of Disability in Multiple Sclerosis A New Approach to Epidemiological Study

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Epidemiological surveys of multiple sclerosis (MS) include, among their objectives, the determination of disease-related disability. Disability in such surveys, and in clinical practice, is frequently assessed according to scales devised by Kurtzke (1961, 1965). The Kurtzke scales (KS) are based on assessment of the degree of deficit in 8 separate system categories (pyramidal, cerebellar, brain stem, sensory, sphincter, visual, mental and other), complemented by a score which reflects overall functional disability, the Disability Status Scale (DSS). These assessments are usually based on examination of the patient by a neurologist, and it is acknowledged that such detailed assessments add substantially to the costs and difficulty of conducting surveys in which disability status and disease progression are monitored (Kurtzke, 1977).

The aim of the present study was to determine whether the Kurtzke system and disability scales could be adapted into a questionnaire format to be administered by interview technique without the necessity for examination by an interviewer trained in clinical neurology. The results of using this questionnaire form of the Kurtzke scales (QKS) are compared here with the results obtained by conventional means in 36 patients with MS and 11 healthy volunteer controls.

Methods

The Kurtzke scales for systems and for disability status were written in questionnaire format (see Appendix).

A registered nurse (VRJ) without previous neurological experience personally interviewed 24 patients in whom the diagnosis of MS was firmly established. During

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Table I. Comparison of the results obtained for each of the 9 separate categories using QKS and SKS. Subject numbers indicate either identical scores or discrepancy between the scores obtained, using the 2 techniques

Category	Subject numbers		
	personal interview		telephone interview
	patients	controls	patients
1. Pyramidal function			
Identical rating	19	5	8
Variance between ratings	5	6	4
2. Cerebellar function			
Identical rating	16	11	4
Variance between ratings	8	0	8
3. Brain stem function			
Identical rating	11	8	5
Variance between ratings	13	3	7
4. Sensation			
Identical rating	11	9	5
Variance between ratings	13	2	7
5. Sphincter control			
Identical rating	19	11	7
Variance between ratings	5	0	5
6. Vision			
Identical rating	11	10	7
Variance between ratings	13	1	5
7. Mentation			
Identical rating	18	11	8
Variance between ratings	6	0	4
8. Other functions			
Identical rating	24	9	12
Variance between ratings	0	2	0
9. Disability scores			
Identical rating	23	6	12
Variance between ratings	1	5	0

these interviews a Questionnaire Kurtzke Scale (QKS) was completed for each patient. The nurse also completed QKS by telephone for a further 12 patients with MS. 11 healthy volunteers had QKS administered by the nurse at personal interviews.

All 47 subjects were then independently assessed by a doctor with neurological training (RGB). Kurtzke ratings (Kurtzke, 1965) using the standard format (SKS) were determined for each of these patients, all of whom were clinically examined.

The results of these assessments by both QKS and SKS were subjected to statistical analysis, using the sign test (Conover, 1971). This tested for any consistent differences (either higher or lower) between the ratings as determined by QKS and SKS in

Table II. Comparison of the individual scores for each of the 9 system categories, where a discrepancy existed between the results obtained by QKS and SKS

Category		Personal interview																Telephone interview							
		patients													controls								patients							
1. Pyramidal function	SKS	5	4	3	3	4									1	0	1	1	1	1			3	4	4	5				
	QKS	6	3	4	2	3									0	1	0	0	0	0			4	3	2	4				
2. Cerebellar function	SKS	3X	3X	1	1X	4X	1X	2X	2X	4X	0						—						2X	4X	1X	1X	2X	2X		
	QKS	4X	4X	2X	2X	3X	2X	3X	3X	3X	1							—						3X	5X	2X	3X	3X	3X		
3. Brain stem function	SKS	0	2	3	2	5	0	0	0	2	3	3	0	1	1	1	0						1	0	2	0	2	1	1	
	QKS	1	1	2	1	4	1	3	1	1	2	4	1	2	0	0	1						2	1	1	2	3	0	0	
4. Sensation	SKS	4	4	4	5	4	2	2	3	4	1	0	2	4	1	1							2	0	4	2	2	4	3	
	QKS	3	3	2	4	3	3	3	2	3	0	1	3	3	0	0							3	1	3	3	1	3	0	
5. Sphincter control	SKS	1	2	5	3	3											—						2	2	2	1	2			
	QKS	2	3	4	2	4											—						1	1	3	2	1			
6. Vision	SKS	2	3	4	2	4	1	2	2	3	4	1	1	1	0								1	1	2	2	1			
	QKS	3	2	2	3	3	4	1	3	2	3	0	2	3	1		—						2	2	3	1	3			
7. Mentation	SKS	2	1	0	1	0	2										—						1	1	1	0				
	QKS	3	2	1	2	2	3										—						2	2	0	1				
8. Other functions	SKS														1	0														
	QKS							—							0	1										—				
9. Disability score	SKS	8													1	0	1	1	0						—					
	QKS	7													0	1	0	0	1						—					

X is the indication, as defined by SKS, to denote that weakness has contributed substantially to the ataxia.

following the disability status in cases where the diagnosis of MS had already been established.

A widely employed method for establishing disability status in MS uses formats defined by Kurtzke (1965). This approach suggests the need for expert clinical evaluation which augments costs and places some limitation on the applicability of such measurements in large scale surveys as well as in clinical work. It was felt that if Kurtzke scales could be completed by people other than doctors with neurological training, these ratings would attract greater acceptance and might be more readily applied in following disability in MS as well as in some other chronic neurological disorders. The present study was designed to test the hypothesis that a simplified method of applying the Kurtzke scales, using questionnaire form (QKS), would provide a reliable and accurate alternative approach. The use of QKS allows the researcher to assess the progression of disability before the confirmation of the disagnosis of MS but the assessment only assumes relevance if that diagnosis has been confirmed.

The above results support this view and indicate that the QKS is a reliable alternative for epidemiological studies. The scores defining overall functional disability (Number 9, tables I, II, III) were identical for 41 of the 47 subjects. In only 1 patient was there a discrepancy between the rankings obtained by QKS and SKS and this was between a score of 7 and 8. The difference between these 2 scores is marginal (see Appendix) and both imply very significant disability. The remaining 5 subjects were all healthy control volunteers and the difference in scores was between 0 and 1 (table II). Both these scores indicate an absence of functional disability (see Appendix) and the discrepancy between QKS and SKS relates to minor signs. The score defining overall disability is the most important assessment when monitoring disease progression and the QKS has been shown to be a very reliable method for determining this score.

The terms 'minimal', 'mild', 'moderate' and 'marked' are provided in the SKS to indicate severity of disability. These terms are relative and subjective. What appears 'minimal' to one observer may well appear 'mild' to another. Thus minor variation between observers for the assessment of these system functions is to be expected using either SKS or QKS. Where a discrepancy did occur between the scores obtained by the 2 methods, the difference in scores was quite marginal (table II).

Completion of QKS in patients with markedly impaired mentation may prove more difficult. A similar situation exists with SKS as patient cooperation and understanding are important in the neurological examination. Demented patients were included among the subjects, 10 of whom were institutionalised. No major discrepancies occurred as a result of this. Both SKS and QKS were disadvantaged and assessments by attending staff and relatives were taken into account. Clearly, interview by telephone is impractical with such patients but, if help is obtained from a reliable observer, the QKS can still be completed by the interview technique.

Comparison of the results obtained by QKS and SKS showed no significant variation and fully validated the use of the interview technique by someone without specific neurological training to define patient disability status. Such use of questionnaire evaluations is cost effective, sparing in requirements of highly trained personnel and particularly suitable for continuing longitudinal survey work.

Table III. Comparison of results obtained using the QKS and SKS for the purpose of applying the sign test to determine the significance of variance

Group and interview technique	Sign	The 9 identified systems in Kurtzke ratings								
		1	2	3	4	5	6	7	8	9
Patients personal interview	0	19	16	11	11	19	20	10	23	23
	−	3	1	6	9	3	3	7	1	1
	+	2	7	7	4	2	1	7	0	0
	n[1]	5	8	13	13	5	4	14	1	1
Controls personal interview	0	5	11	8	9	11	10	11	9	6
	−	5	0	2	2	0	1	0	1	3
	+	1	0	1	0	0	0	0	1	2
	n[1]	6	0	3	2	0	1	0	2	5
Patients phone interview	0	8	4	5	5	7	7	8	12	12
	−	3	1	3	4	3	1	1	0	0
	+	1	7	4	3	2	4	3	0	0
	n[1]	4	8	7	7	5	5	4	0	0

n = the number of patients who had discrepancies between results obtained by QKS compared with SKS.

1 No score showed significant variation at the 1% level.

each of the 8 system categories and the overall Disability Status Scale (9 ranked scores in all for each subject both by questionnaire and formal examination).

In analysing the results, the 3 groups of subjects identified above (patients seen, patients questioned by telephone and healthy controls) were treated separately to determine significance of variance between QKS and SKS results in these groups.

Results

The results obtained using QKS and SKS for the 3 groups (patient personal interviews, patient telephone interviews and control group personal interviews) were compared (table I). Where discrepancy was found between the scores obtained by QKS and SKS the difference in rank of disability was marginal (table II). The 9 ranked scores were individually assessed for each of the 3 separate groups of subjects described above (table III). Using the sign test there was no significant difference at the 1% level ($p = 0.01$).

Discussion

When defining disability status for diseases it is necessary to confirm the diagnosis by conventional means. It is emphasised that the present study did not aim to diagnose MS but rather to develop a simple method for accurately determining and

Summary

The Kurtzke system and overall disability scales (KS) for multiple sclerosis were adapted to questionnaire form (QKS). A qualified nurse recorded Kurtzke ratings, by QKS, from 36 multiple sclerosis patients and 11 healthy controls. These scores were compared with ratings obtained by a doctor with neurological training using the conventional history/examination technique. The results obtained by these 2 methods were closely comparable. The use of a questionnaire appears to be a valid and accurate approach to the determination of disability in multiple sclerosis and may be of particular value in epidemiology and therapeutic trials in this condition.

Acknowledgements

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Appendix

Disability Scores

From the nine (9) lists below, please circle the single most appropriate score (number) from each which best describes the patient's disability.

PATIENT'S NAME: ..... DATE: .....

Score *Power of Arms and Legs (Pyramidal Function)*

0 Normal
1 Some weakness of any limb/s but no problem doing everyday things, e.g. walking, holding things.
2 Slightly worse than No. 1 and there is a slight problem doing everyday things.
3 Worse than No. 2 with mild to moderate difficulty using either both legs, OR using one side (e.g. right arm and right leg), OR complete loss of use of one limb.
4 Worse than No. 3 with marked loss of use of both legs or one side.
5 Worse than No. 4 with complete loss of use of both legs or one side OR difficulty using all four limbs.
6 Paralysis of all four limbs.

Score *Coordination (Cerebellar Function)*

0 Normal
1 Some incoordination (clumsiness) but not sufficient to cause any problem.
2 Mild incoordination causing slight problem, e.g. cannot do fine skills.
3 Worse than No. 2 with moderate incoordination of the body or limb.
4 Worse than No. 3 with severe incoordination of all limbs.
5 Worse than No. 4. Cannot do movements requiring coordination because of clumsiness.

(Place an X next to the numbers selected in this section if you feel that weakness has contributed to the problem).

Score *Function of Head and Neck (Brain Stem Function)*

0 Normal
1 No problems with function but have noted abnormal things involving the head (such as flickering eye, drooping face, funny sensation).
2 Worse than No. 1 with moderate flickering of the eyes or some other mild problems involving the function of the head.
3 Worse than No. 2 with severe flickering of the eyes OR marked double vision OR moderate problems involving the functions of the head.
4 Worse than No. 3 with marked problems pronouncing words or other marked problems involving the functions of the head.
5 Worse than No. 4. Cannot swallow or speak.

Score *Ability to Feel Things up to the Neck (Sensory Function)*

0 Normal
1 Decreased ability to feel something vibrating (e.g. a tuning fork) or some-one writing a number on one or two limbs.
2 Worse than No. 1 with decreased ability to feel something vibrating on 3 or 4 limbs OR a problem knowing in which direction the toes or fingers are moving — with eyes closed — (called 'position sense') in 1 or 2 limbs.
3 Worse than No. 2 with mild decrease in the ability to feel pain or touch OR no 'position sense' in 1 or 2 limbs.
4 Worse than No. 3 with moderate decrease in the ability to feel pain or touch for at least most of 1 limb OR severe problems with 'position sense' in 3 or 4 limbs.
5 Worse than No. 4 with complete loss of sensation in 1 limb OR moderate decrease in the ability to feel pain or touch for most of the body.
6 Loss of sensation up to the neck.

Score *Bowel and Bladder Function*

0 Normal
1 Mild problem with starting to pass water OR urgency (must go to toilet as soon as you feel the urge) OR problem emptying bowel or bladder.
2 Worse than No. 1 with moderate problem OR rare loss of control of bladder (wetting self).
3 Worse than No. 2 with frequent loss of control of bladder.
4 Worse than No. 3 needing urine catheter but bowel function all right.
5 Loss of bowel and bladder function.

Score *Ability to See Things Clearly (Vision)*

0 Normal
1 A possible blind area but vision with glasses (if worn) is normal.
2 The worse eye has a definite blind area and vision with glasses (if worn) is mildly decreased.
3 Worse than No. 2: Noticeable loss of part of the field of vision. Vision with glasses (if worn) moderately decreased.

4 Worse than No. 3: Severe loss of vision in one eye. Vision in good eye mildly to moderately decreased.
5 Worse than No. 4: Severe loss of vision in worst eye (Can only count fingers). Vision in good eye still useful.
6 Worse than No. 5: Severe loss of sight.

Score *Ability to Think Clearly (Mental Functions)*

0 Normal
1 Change in mood only (depression or feeling 'high').
2 Mild decrease in ability to think clearly.
3 Worse than No. 2 with moderate decrease in ability to think clearly.
4 Worse than No. 3 with marked decrease in ability to think clearly.
5 Cannot think clearly at all.

Score *Things not Related to Multiple Sclerosis (Other Functions)*

0 Nothing else wrong.
1 Something else wrong: Please state .....
.....

Score *Disability Scale*

0 All the groups above scored 0.
1 No real problems (No score above No. 1 in any of the above groups).
2 Mild problems (No score above No. 2 in any of the above groups).
3 Worse than No. 2 but fully able to get about though with some problem (No score above No. 3 in any of the above groups).
4 Worse than No. 3 but can get about and look after self for a 12 hour day (No score above No. 4 in any of the above groups).
5 Worse than No. 4. Could not work a full day without help OR could not walk more than several blocks without aids (No score above No. 5 in any of the above groups).
6 Worse than No. 5. Need aids (e.g. frame, cane, crutches, brace) to walk.
7 Worse than No. 6. Restricted to wheelchair but able to wheel chair and able to enter and leave chair alone.
8 Worse than No. 7. Restricted to bed but can use arms.
9 Worse than No. 8. Restricted to bed and fully dependent.

Abstract

Generalised Glycogenosis Type II in Cattle

*J. McC. Howell, P.R. Dorling, P. Di Marco and R.D. Cook**

A herd of cattle has been established in which calves are born with generalised glycogenosis type II. Ten affected animals have been born and in 9 of them their disease status, as indicated by a decreased acid α-glucosidase activity and excessive glycogen deposition in muscle, was detected on the day of birth. The tenth animal was found dead shortly after birth and the morphological changes of generalised glycogenosis were found in its tissues. Two clinical syndromes have been seen. Two animals died aged 3 and 5 months of age after showing acute respiratory distress. These animals showed signs of heart failure and had cardiomegaly. In the second group of animals, 5 calves grew well and were clinically normal until they were 9 months of age. At this time they failed to maintain weight gain, showed muscle weakness and were killed in a state of extreme weakness when they were aged between 12 and 16 months. Affected animals in both groups had abnormal ECG tracings and elevated levels of serum creatine kinase, lactate dehydrogenase and α-hydroxybutyric dehydrogenase. Excessive amounts of glycogen were deposited in voluntary, cardiac and smooth muscle. The cardiac and voluntary muscles showed a vacuolar myopathy (Howell et al., in press). Swelling, vacuolation and glycogen deposition were present in neurones in the central and autonomic nervous systems and retina, in glia and in Schwann cells and fibroblasts in peripheral nerves. The excess glycogen was both membrane-bound and free within the cytoplasm. Changes similar to those seen in axonal dystrophy were present and some nerve fibres in peripheral and central nervous systems showed Wallerian degeneration (Cook et al., in press). The tissues of these animals showed a lack of acid α-glucosidase (EC 3.2.1.3) activity (Howell et al., in press; Cook et al., in press). Evidence of enzymically inactive proteins that cross react with antibodies raised against acid α-glucosidase from the

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muscle of normal animals was not found (Dorling et al., in press). These findings indicate that syndromes equivalent to the infantile and childhood forms of human generalised glycogenosis type II have been found within this herd of cattle. The adult onset form of the disease has not yet been seen. The condition appears to be controlled by a recessive allele at a single autosomal locus (Howell et al., in press). Enzyme replacement studies have started in the 2 young calves. Muscle from affected and non-affected animals has been grown in tissue culture and the biochemistry and morphology of cultured muscle and muscle in the animal will be compared. Enzyme replacement therapy will be investigated in these cultures.

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Abstract

Computer Analysis of Peripheral Nerve Conduction Velocity Distribution

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Nerve conduction velocity (CV) is used as a physiological parameter of nerve function in laboratory and clinical studies. Available techniques usually allow only one CV parameter to be defined, that of the fastest fibres. Recent electro-physiological developments indicate that it may be feasible to define the range of CVs in a nerve by signal processing, after making certain assumptions. The compound action potential (CAP) recorded from nerve or muscle was considered to be generated by a basic ac-

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tion potential (AP), convolved with a time delay profile of AP arrival at the recording site. The delay profile is determined by the distribution of CVs in the nerve between the point of stimulation and recording. Given 2 CAPs obtained after stimulation of the nerve at different distances from a recording site, it was considered possible to estimate the basic AP shape, delay profile, and hence CV distribution of the nerve. Computations were performed digitally, and analysis was in the frequency domain based on the spectral content of the signals.

The validity of the approach and assumptions was first tested by computer simulation. CAPs with pre-determined AP shape and delay distributions were presented to the analysis program. In all cases the program accurately defined the AP and the delay profile. Recordings were next made from hindlimb nerves and muscles in pentobarbitone anaesthetised cats, some with intact nerves, and others more than 6 weeks after total hindlimb deafferentation. Sections of nerves were removed at the recording sites, electronmicrographs were montaged, and histograms of axonal diameters measured using a Leitz ASM image analyser. Because of the known relationship between axonal diameter and fibre conduction velocity, a comparison between computed CV distribution and fibre diameter histograms was made. The fit of these data for nerve and muscle recording indicated that the approach gave valid results under the biological recording conditions used. Recordings made from human muscle and nerve have yielded CV spectra which match the expected distribution of nerve fibre CVs. Considerably more work will need to be done before this approach can be fully assessed, but results so far indicate that it may have useful future application.

Abstract

Ovine Muscular Dystrophy: A Genetic Primary Myopathy of Sheep which Resembles Human Dystrophia Myotonica

*B.A. Kakulas, I.K. Passmore and R.B. Richards**

Ovine muscular dystrophy was first described by McGavin and Baynes in Queensland in 1969. The original observations were limited due to loss of the gene soon after its discovery. Therefore the early reports were confined to brief clinical and pathological descriptions of the disease.

A similar (perhaps identical) ovine muscular dystrophy was rediscovered in Western Australia in 1979 by Dent et al. Because there is no known connection be-

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tween the Queensland and Western Australia flocks, it is presumed that the current disease is the result of a new mutation.

In the affected Western Australia flock of 2500 sheep there are about 25 dystrophic animals giving an incidence rate of 1%. Males and females are equally affected. On this farm there are 50 breeding rams. Further data are required to prove autosomal dominance but this is the mode of inheritance compatible with present knowledge. Breeding experiments are in progress.

The disorder manifests clinically as unsteadiness of gait and progressive weakness, particularly of the hind limbs, from about 6 months of age onward. Sheep up to 5 years old show signs of the disorder but total paralysis is unusual. In hot weather, ruminal tympany or bloat is common and this is more severe in the worst affected animals. Cataracts have been found in some older sheep and testicular atrophy is present in some of the older rams but not in all of those known to be affected. Reproduction is possible in younger animals. In the advanced stages, respiratory distress develops and is the usual cause of death. There is no response to selenium or dietary treatment with vitamin E. Serum CPK levels are elevated to 600mU/L (normal 50-200mU/L).

Pathologically, in sheep which have died naturally, there is advanced atrophy and pallor of musculature particularly the limb girdle muscles and especially the vastus intermedius. Microscopically there is outfall of muscle fibres in the advanced disease and in the vastus intermedius this may be as high as 99% loss with fat and fibrous tissue replacing the absent muscle fibres. There is also polyfocal necrosis, incomplete regeneration and central nucleation. The muscle nuclei also tend to form rows, both at the periphery of the muscle fibres and in the centre. Histochemical Type I fibres are more affected. In many muscles and especially in the vastus intermedius, subsarcolemmal masses are abundant. Both these features are highly reminiscent of human dystrophia myotonica. Ringbinden are not seen. With the electron microscope the subsarcolemmal masses contain dilated endoplasmic reticulum as would be expected and there is myofibrillar atrophy. Dense lysosomal bodies are abundant.

The material presented is based on 65 biopsies from about 60 sheep and on 20 necropsies at different stages of the disease.

Although the condition is important in its own right as a true animal dystrophy with agricultural and biological relevance, this new ovine dystrophy promises to shed light on human dystrophia myotonica with which it shares many features. The myopathology is strikingly similar and dominant inheritance, cataracts and testicular atrophy are surprisingly close to the human disease. Therefore, the further study and experimental manipulation of the model disorder is potentially of great promise in the complete understanding and eventual solution of human dystrophia myotonica.

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Abstract

Saccadic Eye Movements: Quantitative Analysis of Kinematic Parameters in Normal Subjects and Patients with Neurological Disorders

G.W. Thickbroom, J.L. Black* and F.L. Mastaglia†*

A detailed study of saccadic eye movements in 20 normal subjects and in patients with neurological disorders has been carried out using electro-oculographic techniques and computer analysis of the velocity profiles.

Both target tracking and voluntary saccades were analysed for the normal subjects. Calculation of peak saccadic velocity and latency, maximum eye acceleration and deceleration, duration of saccade, skewness and generalised statistical measures of shape were calculated for saccades of 4, 8, 12, 16 and 20 degrees in abduction and adduction for left and right eyes separately. The data showed an increased velocity and a trend towards increased latency with increasing angle of eye movement. The duration was found to be greater and the peak velocity and acceleration were less for the abducting eye than for the adducting eye during refixation.

In addition to quantitative parameters of saccade shape, average saccade waveforms for target-following jumps were displayed for each eye in abduction and adduction and for each angle of saccade. Gaussian fits to the saccade profiles showed that for refixations of up to 20 degrees the saccades were closely symmetrical and gaussian in shape. In the case of large angle voluntary saccades of 45 degrees the saccades were asymmetrical and broadened.

A subset of the analysis has been incorporated into an existing test of saccadic eye motion in use in our clinical neurophysiology laboratory. Saccade shape parameters are provided for voluntary 45 degree saccades and for saccades in response to a target jump of 15 degrees. Preliminary results in patients with multiple sclerosis have shown increases in saccade duration and saccade asymmetry in some cases. In myasthenia gravis marked saccade asymmetries interpreted as being due to intrasaccadic fatigue have been found in some cases. By contrast saccade shape parameters have been normal in cases of motor neurone disease studied so far.

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Abstract

Plasma Exchange in Idiopathic Polyradiculoneuropathy

*R.F. Raper, J.P. Isbister and P.M. Williamson**

Plasma exchange was utilised in the management of 6 cases of acute Guillain-Barré syndrome and in 2 cases of chronic relapsing polyradiculoneuropathy. In each case 2 to 3L exchanges were performed 2 to 3 days apart. The mean time lapse between initial symptoms and first exchange in the 6 acute cases was 7.8 days with a range of 4 to 15, and the mean number of exchanges performed in this group was 3.8 with a range of 3 to 6. All of the 6 acute cases were bed-ridden at the height of their illness. Two were totally paralysed, requiring assisted ventilation.

Five of the 6 acute cases showed objective improvement within 4 days of their first exchange (range 1 to 4 days). All 5 had major functional improvement within 3 weeks; all were ambulant and were breathing spontaneously. Subsequent functional recovery in all 5 has been complete. The sixth case remains severely disabled after 6, 3L exchanges. No clinicopathological feature absolutely distinguishing this case from the others was identified, although serum concentrations of all immunoglobulins in this case were normal in contrast to the high concentration of IgM in the serum of the other patient with comparably severe disease.

Both cases of chronic relapsing polyradiculoneuropathy improved within a few days of plasma exchange on 2 separate occasions. Both were on concurrent oral immunosuppressive regimens. In 1 of the 2 cases, improvement after plasma exchange occurred without any change in oral immunosuppressive therapy. Both are currently maintained on oral immunosuppressive therapy, one with adjunctive second weekly plasma exchanges.

The rapid rate of recovery seen in the 5 cases of acute Guillain-Barré syndrome, and the time course of recovery after plasma exchange in the 2 cases of chronic relapsing polyradiculoneuropathy, coupled with the now extensive evidence supporting a role for humoral immune mechanisms in the pathogenesis of at least some cases of this group of disorders, are suggestive of a role for plasma exchange in the management of both acute monophasic and chronic relapsing polyradiculoneuropathy. The clear definition of the precise nature of this role awaits the results of controlled trials.

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Abstract

Treatment of Attacks of Cluster Headache with Oxygen Inhalation

*Michael Anthony**

The pain of cluster headache is due to vasodilatation of the cranial arteries. Vasoconstrictive agents (commonly ergot derivatives) rather than analgesic preparations may relieve the attack but they require time to produce their effects and frequently they are ineffective. However, oxygen inhalation can produce intracranial vasoconstriction within minutes and theoretically it would be a more effective method of treating an attack of cluster headache.

To test this hypothesis, 12 patients were investigated during a bout of cluster headache. Observations were made in each case during 2 separate headaches. *In 5 patients* the headaches occurred spontaneously; in the remining *7, they were induced* by the sublingual administration of 1 mg Trinitrin. During the first headache, patients took their usual oral medication (ergot derivatives or analgesic tablets); during the second headache, they inhaled oxygen through a CIG polymask at 8L/minute. The time required for the relief of headache on each occasion was noted and the results were compared.

Reduction in headache duration, when compared to the untreated attack, was noted by 8 out of the 12 patients when oral medication was used and by every patient when oxygen was inhaled. The mean duration of headache for the untreated attack, when oral medication was used and when oxygen was inhaled, was 103, 60 and 22 minutes, respectively. Only 1 patient obtained relief faster with ergot derivatives than with oxygen inhalation and all patients expressed preference for oxygen treatment.

It is suggested that oxygen inhalation is a simple, speedy and effective method of arresting an attack of cluster headache. It is further suggested that since raising PO_2 causes intracranial vasoconstriction, dilatation of the vessels in this arterial territory must play a greater role in the causation of the pain of the attack than has been considered to be the cause so far.

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Abstract

Post-viral Reflex Myoclonus

*A. Fisher, F.L. Mastaglia and W.M. Carroll**

Myoclonus may result from a variety of aetiological agents and may apparently arise as a result of disturbances at a number of levels in the central nervous system. However, the neuro-anatomical localisation in most cases remains imprecise. Recent electrophysiological and neuropharmacological investigations have defined a number of distinct types and have led to a greater awareness of the problems inherent in the classification of such cases.

Two patients with reflex myoclonus induced by peripheral stimulation and presumed to have arisen as a result of viral infection of the nervous system were studied in depth. In both cases involvement of the abdominal muscles was a feature and was the sole site of myoclonus in one case.

In both cases myoclonic jerks could be consistently evoked by electrical stimulation of mixed and sensory peripheral nerves and by muscle stretch, cutaneous tactile and cold stimuli, and by startle. The EMG bursts evoked by these stimuli were of long duration (approximately 100msec in one case and 350msec in the other) and occurred after a latency of 100 to 150msec, the latency of onset varying by up to 20msec in both cases. In the case in which the myoclonus involved proximal limb as well as abdominal muscles, there was a descending pattern of activation.

In both cases there was no electrocerebral correlate of the myoclonic jerks in the electroencephalogram, and cortical somatosensory evoked potentials were normal.

The clinical and electrophysiological findings distinguish these cases from other reported cases of reflex myoclonus of so-called 'cortical' or 'reticular' type. The site of origin of the myoclonus is uncertain but it is likely that a long polysynaptic suprasegmental reflex pathway is involved.

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Abstract

Recurrent Febrile Coma with Focal Cerebral Oedema: An Autosomal Dominant Disorder with Intermittent Hyperalaninaemia

*R.B. Fitzsimons and W.H. Wolfenden**

Case Report

A.B., a 22-year-old station clerk, presented lightly comatose to Sydney Hospital on the evening of 21.8.79. That morning he had noted left-sided parasthesie and weakness with difficulty speaking, and his conscious state then rapidly deteriorated. On admission he had left arm paresis, deviation of the eyes to the right and a high fever (39°C). Cerebral CT scan was initially considered to be normal. The CSF contained 1026 RBC/cmm, but was otherwise normal. Subsequent examinations revealed a mild CSF leucocytosis (up to 12 WBC/cmm). Screening tests for drug ingestion, infections and commonly recognised metabolic disorders were negative.

Carotid angiography, performed 1 week later after some clinical recovery, demonstrated an apparent space-occupying lesion in the right cerebral hemisphere, with marked displacement of the anterior cerebral vessels across the mid-line. Later that day the patient's conscious state rapidly deteriorated, in association with intense hyperthermia (41°C), and with hypoventilation. He suffered a respiratory arrest and required ventilator support. Repeat CT scan demonstrated intense oedema of the right cerebral hemisphere, with mid-line shift, but no 'structural' space-occupying lesion. He was treated with high-dose steroids, mannitol and antipyretics, and gradually recovered over several weeks. There were residual cerebellar signs, which have now cleared, and he remains well.

Previous Health

(i) On 25.3.76 he had been admitted comatose and hyperthermic to Sydney Hospital. After a gradual recovery he was found to have residual cerebellar ataxia and vocal cord paresis. No cause was found.

(ii) Severe migrainous headaches with left hemiparesis from childhood.

Family History

His father (D.B.) has a long history of periodic focal neurological disturbance associated with headache, and of episodes of fever and coma lasting several days. Carotid angiograms (1970) were reported to show a left hemisphere space-occupying lesion, and were followed by fever and coma. He now has cerebellar degeneration. D.B.'s father was also ataxic. One of A.B.'s siblings (P.B.) is mildly mentally retarded, and suffers from periodic headaches with focal numbness, weakness and prolonged 'sleepiness'. He has signs of cerebellar incoordination.

A.B. has intermittently elevated levels of blood alanine, a metabolite of pyruvate. The possibility that members of this family are affected by an abnormality of pyruvate dehydrogenase, an enzyme which is known to be abnormal in certain spino-cerebellar degenerations, is therefore being investigated. The cases resemble in many respects a previously reported patient with hyperalaninaemia (Lonsdale et al., 1969; Pediatrics *43*: 1025), who suffered from intermittent cerebellar ataxia, confusion, obtundation and very high fevers, apparently precipitated by minor injuries.

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Abstract

Plasmapheresis in Chronic Relapsing Polyneuropathy

*J.D. Pollard and J.G. McLeod**

Four patients with chronic relapsing polyneuropathy are described, whose treatment regimen included plasmapheresis. In each patient a series of 8 2L exchanges were given over a period of 10 days. In 1 patient the treatment was successful in 3 successive relapses and this patient has been maintained in excellent health for over 1 year by 1 2L exchange every 3 weeks. In 3 patients, however, there was no improvement after plasmapheresis.

In the successfully treated patient high levels of immune complexes have been demonstrated repeatedly. This patient has recovered with remarkable completeness from 10 severe attacks. Two sural nerve biopsies performed 9 years apart showed very little progressive nerve damage. In the other cases, despite a history of multiple relapses and remissions and/or very slow nerve conduction, nerve biopsy findings showed a progressive loss of myelinated fibres and prominent features of axonal degeneration. It is concluded that the diagnosis of chronic relapsing polyneuropathy, based upon clinical features and electrophysiological studies, may not indicate a single disease entity. The results in the successful case and in 5 other such cases in the literature suggest that plasmapheresis may prove a useful adjunct to treatment in cases of chronic relapsing polyneuropathy. However, criteria predictive of success have not been delineated but histological confirmation of primary demyelination and the occurrence of immunological abnormalities may be important.

Abstract

Plasmapheresis of Rabbits with Experimental Allergic Neuritis (EAN)

*J.H. Antony, J.D. Pollard and J.G. McLeod**

In 1955 an allergic neuritis was induced in rabbits by intradermal injection of heterologous or homologous nerve in Freund's adjuvant. Clinical and pathological similarities exist between this experimentally-induced disease and the naturally occurring acute idiopathic polyneuritis or Guillain-Barré syndrome (GBS) in humans.

A recent trend in the treatment of GBS has been the use of plasmapheresis or plasma exchange and, for this reason, it was considered that assessment of the effects of plasmapheresis on EAN in rabbits would be valuable.

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A total of 14 rabbits were injected with homogenised bovine peripheral nerve in complete Freund's adjuvant on day 0. At 1 and 2 weeks after injection, 6 of the rabbits were plasmapheresed by insertion of a silastic catheter into the central ear artery and removal of 1/6 to 1/4 of the blood volume. After centrifugation of the blood the serum was removed and the red cells were returned through a venous scalp vein needle. This procedure was repeated so that a total of 1/2 to 1/3 of the blood volume was removed on each occasion. A control group of 8 animals were untreated. All animals were examined twice weekly for evidence of limb weakness and were weighed. At 5 weeks electrophysiological studies were performed on animals of both groups then they were perfused and appropriate sections of peripheral nerve studied by light and electron microscopy.

At 5 weeks weight loss in the plasmapheresed group was 0.04 ± 0.29lb compared to −0.56 ± 0.70lb in the control group, a significant difference.

At 2 weeks only one plasmapheresed animal had possible weakness whereas 5 control animals displayed definite weakness and 3 had possible weakness. At 5 weeks 2 plasmapheresed animals were definitely weak with the other 4 having possible weakness. All of the controls at 5 weeks had definite and often severe weakness.

Neurophysiological studies performed at 5 weeks revealed no difference in latency or conduction velocity between the groups. However, there was a difference in the length of the action potential and the amplitude of the action potential, indicating that more dispersion occurred in the control group compared to the plasmapheresed group. Preliminary histological studies of L3-4 nerve roots and sciatic nerve suggest more widespread demyelination in the control group of animals.

Our study suggests that plasmapheresis has a beneficial effect on the course of EAN in rabbits.

Abstract

Clinical Features of Hereditary Motor and Sensory Neuropathy Types I and III in Childhood

*R.A. Ouvrier, J.G. McLeod, G. Wise, G. Morgan and T. Conchin**

Eleven cases of Dejerine Sottas disease (HMSN Type III) are compared with 7 cases of dominantly inherited hypertrophic Charcot Marie Tooth disease (HMSN Type I).

Of HMSN Type III cases 64% caused concern in the first year of life as opposed to 29% of HMSN I cases. The mean age of walking was 16 months in HMSN I and 28 months in HMSN III.

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Presenting features in both groups were hypotonia, delay in achieving motor milestones, frequent falls or poor running ability.

The relative frequency of physical abnormalities in HMSN I *vs.* HMSN III cases was as follows: facial weakness 29 *vs.* 63%; nystagmus 29 *vs.* 27%; proximal muscle weakness 14 *vs.* 91%; ataxia 43 *vs.* 100%; moderate to severe sensory loss 17 *vs.* 60%; pes cavus 57 *vs.* 73%; spinal deformity 14 *vs* 45%; clinical hypertrophy of nerves 28 *vs.* 82%. The overall degree of functional disability was similar in the two groups.

Nerve conduction velocities were markedly abnormal in HMSN III and moderately reduced in HMSN I. Mean spinal fluid protein was 48mg% in HMSN I and 99mg% in HMSN III.

The hypertrophic neuropathies of childhood are usually clinically distinctive but there is some overlap of phenotype expression.

Abstract

Embryonic and Fetal Myosins in Human Skeletal Muscle: The Presence of Fetal Myosins in Duchenne Muscular Dystrophy and Infantile Spinal Muscular Atrophy

*R.B. Fitzsimons and J.F.Y. Hoh**

Recently described electrophoretic techniques for separating myosin isoenzymes have been adapted for analysis of myosins from diseased and developing human skeletal muscle.

These methods clearly show that fetal/embryonic myosins differ from both fast and slow mature myosins. Fetal myosins are not normally detected beyond the first month of post-natal life, except in premature infants. They each have a high calcium-activated ATPase activity under alkaline conditions. This would account for the histochemical classification of fetal fibres as Type II, although physiological differences between adult fast-twitch muscle and fetal muscle are well recognised in lower animals. For instance, it is known that the contraction times and low physiological actin-activated myosin ATPase of developing muscle resemble the findings in slow-twitch muscle, although the histochemical profile and myosin light chain composition are more typical of fast-twitch muscle. Such apparent discrepancies are consistent with the existence of specifically fetal myosins, which differ from fast and slow

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mature myosins, and in which a high calcium-activated ATPase activity under alkaline conditions does not reflect a similarly high physiological actin-activated ATPase activity. These considerations are important when determining the relevance of histochemical studies to the physiological properties of neonatal muscle, especially in premature infants, e.g. ventilatory muscle in neonates with respiratory failure.

The presence of fetal myosins in Duchenne dystrophy probably reflects the associated marked muscle regeneration, whereas the large amounts of fetal myosin present in infantile spinal muscular atrophy is evidence that innervation is necessary for the normal cessation of fetal myosin synthesis.

Abstract

Disturbed Colour Naming and Alexia without Agraphia

*G.A. Nicholson and R. Joffe**

Disturbances of colour naming have been variously classified as disconnection syndromes, agnosias or aphasias.

A patient who presented with alexia without agraphia but with a disturbance matching the seen colour to the spoken name was studied. Computer-assisted tomography showed left occipital infarction with involvement of the splenium of the corpus callosum. The patient's responses to testing were recorded by colour videotape.

There was a right hemianopia, a mild fluent aphasia with some object naming difficulties. Colour naming was persistently impaired whereas colour selection on verbal request (matching the spoken name to the seen colour) was less affected. Colour matching was normal.

A similar case attributed to interhemispheric disconnection, was described by Geschwind and Fusillo, but their patient had both inability to match spoken colour names with seen colours and vice versa and could comprehend words spelled orally.

Although the patient described here had a corpus callosum lesion, the preservation of matching colour to the spoken word together with defective comprehension of spelled complex words suggests disordered verbal associations in the dominant hemisphere as the mechanism, rather than Dejerine's classical interhemispheric disconnection theory.

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Abstract

The Effects of some Stimulating and Recording Variables on the Components of the Visual Evoked Response

*C. Yiannikas and J.C. Walsh**

Studies of cerebral evoked potentials in man are developing rapidly and in several directions. In such an expanding field, it is useful to consider a number of factors which have been found to influence the validity and consistency of evoked potential data. The data presented in this paper describe the effects of pattern reversal stimulation using variable check sizes and diameter of stimulating field, and recording using varying low pass filters and electrode types, on the transient visual evoked potential.

Ten healthy subjects from 18 to 38 years of age with normal visual history and acuity were studied. The stimulus consisted of checks which subtended an angle of 27', 55' or 110' in a circular checkerboard pattern of 2°, 4°, 8°, 15° and 20° diameter. The latency of the P $\overline{100}$ was prolonged on central 2° and 4° stimulation using 55' and 110' checks when compared to full field stimulation. The amplitude of the major positive component varied with the diameter of the stimulating field, with up to 50% of the normal response arising from the first 4°, and was maximal with checks subtending an angle of 27', particularly in the first 4° of stimulation. The amplitude and latency of the N $\overline{70}$ and N $\overline{135}$ components were affected by both check size and the diameter of the stimulating field.

A further 20 subjects were studied using a pattern reversal stimulus with a chequerboard of 20° diameter and check units subtending an angle of 55'. The transient evoked potentials were recorded using a varying low pass filter of 80Hz, 800Hz, 1.6KHz and 3.2KHz and recording simultaneously with silver-chloride electrodes and stainless steel needle electrodes. It was found that below 800Hz there was a distortion in the time relationship of the evoked potential components resulting in a phase shift which led to a significant prolongation of the P $\overline{100}$ latency. The amplitude of the major positive component was not significantly affected. The duration of the P $\overline{100}$ peak was significantly prolonged making accurate estimation of the latency of the P $\overline{100}$ difficult. There was no significant difference in the P $\overline{100}$ latency between the needle and the silver silver chloride recording techniques. The amplitude of the major positive component was marginally reduced in the evoked response recorded with the stainless steel needle electrode.

In view of the variability demonstrated in these studies it is suggested that some standardisation of check size, size of stimulus field and band pass is necessary.

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Abstract

Evoked Responses in Multiple Sclerosis: An Electrophysiological Follow-up Study

*J.C. Walsh, R. Garrick, J. Cameron and J.G. McLeod**

Visuàl, spinal, somatosensory and brain stem auditory evoked potentials were performed on 56 patients with definite multiple sclerosis at the beginning and end of a 2 1/2 year follow-up period. At the initial examination one or both visual evoked potentials were abnormal in all but 9 patients and 5 of these had abnormalities of either spinal or somatosensory evoked responses; that is, one or more abnormal results were obtained from 91% of patients.

At the final examination the visual evoked potentials had become abnormal in 5 of the 9 patients and in 4 of those with normal visual evoked potentials the spinal or somatosensory evoked potentials had become abnormal in 3; one or more abnormal result was obtained from 98% of patients. There was a significant increase in latency of the components of the evoked responses over the period and improvement in the evoked responses was rare. The deterioration of these electrophysiological measurements paralleled the clinical deterioration over the 2 1/2 years of follow-up study.

Abstract

Somatosensory Evoked Potentials in Guillain-Barré Syndrome and Chronic Relapsing Polyneuropathy

C.E. Storey and N.M.F. Murray†

Somatosensory evoked potentials (SEP) to median nerve stimulation at the wrist were recorded in 12 patients with Guillain-Barré syndrome, including one with the Miller Fisher variant and in 5 patients with chronic relapsing polyneuropathy.

Averaged responses were obtained from surface electrodes on Erb's Point, the cervical spine (C2 and C7) and the hand area of the contralateral parietal region, using a common midfrontal reference. The amplitude and latency of the 3 major negative waves, N9, generated in the medial cord of the brachial plexus, N13, probably originating in grey matter of the cervical cord and brain stem, and the cortical compo-

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nent N20 were measured, N9, N13 and the N9 to N13 interval, a measure of conduction time between brachial plexus and cervical cord were correlated with arm length.

Findings were correlated with conventional nerve conduction studies (NCS) and electromyography. SEP were abnormal in 13 patients (76 %). The majority showed prolongation of both N9 latency and N9 to N13 interval, with varying emphasis on peripheral nerve and roots. In 2 patients abnormalities were confined to the plexus-cervical cord segment and in one other slowing was entirely peripheral. There was no abnormality of central conduction between cervical cord and cortex. Sensory NCS were normal in 1 patient with abnormal SEP. Studies of motor conduction, which included F-wave measurements, showed a parallel distribution of abnormalities, but reliable F-wave identification was difficult when slowing was pronounced. Three patients had normal SEP and NCS but severe widespread denervation on electromyography.

Pathological changes may be confined to the nerve roots in Guillain-Barré syndrome, especially early in the course of the disease, when up to 20 % of patients have normal NCS. F-wave studies can reveal slowing of proximal motor conduction in the absence of peripheral changes and SEP provide complementary information on sensory conduction.

Abstract

Increased Sensitivity of Electrodiagnosis in Carpal Tunnel Syndrome

*R. Hjorth and C. Kilpatrick**

In the electrodiagnosis of carpal tunnel syndrome (CTS) the traditional tests measure the motor and sensory latencies for median nerve conduction across the wrist. These traditional tests diagnose most cases of CTS but electromyographers are aware that there are some cases where the traditional tests are normal but subsequent events, such as relief of symptoms by surgical decompression, or the finding of abnormalities on repeat testing at a later date, confirm that the patient had a true CTS.

It would be desirable to increase the sensitivity of electrodiagnosis so as to diagnose the cases at present missed by the traditional testing. With this aim, a set of normal control values was collected measuring the traditional latencies but with additional emphasis on 3 aspects which have been claimed to increase sensitivity:

1. Conversion of sensory latencies to conduction velocities.
2. Comparison of ulnar and median values for latencies and velocities.
3. Comparison of median and radial thumb-to-wrist sensory potentials.

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Normal values are reported and the diagnostic yield of the tests, individually and in combination, reported for a consecutive series of 70 cases of CTS.

Defining CTS as being a suggestive clinical picture plus demonstrated abnormality in at least one measure of median conduction across the wrist, the diagnostic yield in the 70 cases was as follows:

Electrodiagnostic measurement	% abnormal in 70 consecutive cases of CTS
A. Traditional	
Motor latency from wrist	47
Sensory latency index to wrist	56
B. Sensory conduction velocity (CV)	
Index to wrist	66
C. Comparative: median *vs* ulnar	
Comparing motor latencies	51
Comparing sensory latencies	69
Comparing sensory CV	69
D. Comparative: median *vs* radial	
Comparing latencies	87
Comparing CV	84

The study of thumb-to-wrist conduction in radial and median nerves is a particularly valuable test.

Abstract

Blink Reflexes to Sudden Falls

*G.M. Halmagyi and M.A. Gresty**

Normal volunteers and patients without semi-circular canal function lying comfortably on a specially constructed couch were unexpectedly released into a brief, safe free fall, while the EMG activity of the orbicularis oculi was recorded. All subjects and patients showed a burst of EMG activity starting 30 to 40msec after release. If either supraorbital nerve was electrically stimulated for up to 200msec before release the EMG response was abolished. Also no blink reflex could be elicited by supraor-

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bital nerve stimulation for about 300msec after release. It seems that the blink reflex to free fall is a startle reflex evoked by stimulation of the utricle. This technique might be developed into a practical test of human utricular function.

Abstract

Observations on the Clinical Presentation of Perineural Spread of Cutaneous Basal and Squamous Cell Carcinomas into the Trigeminal and Other Cranial Nerves

*J.G.L. Morris and R. Joffe**

Three patients are presented in whom a trigeminal neuropathy resulted from perineural spread of basal or squamous cell carcinoma arising in the skin of the face. In all 3 patients other cranial nerves eventually became involved. The evolution of symptoms and signs in each case can be explained on the basis of a lesion initially affecting superficial branches of the trigeminal or facial nerves and later spreading centrally. The finding of selective involvement of a terminal branch of the trigeminal or facial nerves should lead to a consideration of this diagnosis. Confirmation can be made by performing a biopsy of the peripheral branch affected. The clinical features of this disease are contrasted with those of other recognised causes of trigeminal and facial nerve lesions.

Abstract

Hyperglycinaemia: Effect of Strychnine Therapy in a Neonate

P.G. Procopis†

A newborn girl presented on day 2 with the sudden onset of hypotonia, failure to suck and marked lethargy. A diagnosis of primary hyperglycinaemia was made on the basis of markedly elevated glycine levels in the blood, urine and cerebrospinal fluid in the absence of ketosis or organic aciduria.

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As glycine is an inhibitory transmitter in the central nervous system especially in the spinal cord, other investigators have treated a small number of these children with strychnine which acts as an excitatory transmitter. Although one child with a tardive form of the disorder has been reported as doing well, other treated children have fared poorly.

The present patient was treated with oral strychnine in increasing doses from the tenth day of life. Muscle tone and ability to suck improved. At the age of 6 weeks, the strychnine was stopped. However, she again became hypotonic and had to be tube fed. Strychnine was restarted and her muscle tone and sucking ability again improved. Despite the undoubted improvement with strychnine treatment, the child nevertheless appears severely mentally retarded and epileptic. The EEG remains severely abnormal and shows changes typical of the disease.

In this child, strychnine therapy had a beneficial effect on muscle tone and sucking, but no discernible effect on intellectual function.

In Memoriam — Leonard Bell Cox, 1894-1976

Felix qui potuit rerum cognoscere causas
— Virgil. Georgics II, 458

Four years have passed since Leonard Cox, eminent Victorian, first President of the Australian Association of Neurologists, died suddenly in his eighty-second year. It is fitting that we should commemorate his life and his notable contributions to our discipline.

Born in Prahran, the son of the Reverend Edward Cox, Leonard was educated at Wesley College and the University of Melbourne, graduating in 1916. Thereafter, after a brief residency at the Melbourne Hospital, he joined the AIF as Captain in the Army Medical Corps. Having achieved the MRCP (Edinburgh) in 1919 he returned to Melbourne as Beaney Scholar in Pathology and during the tenure of this appointment gained his Doctorate of Medicine. He then began the difficult task of practising as a general physician with which he combined activity as a part-time anaesthetist, as was the custom of the day. At this time, Cox recalled, he again made contact with John Fullerton Mackeddie, the brilliant and colourful Honorary Physician to the Alfred Hospital. After a period of locum tenens for Mackeddie while he was abroad, Cox joined him in practice, and there learned much of the more technical aspects of neurology from the mercurial chief; this included pneumo-encephalography, lipiodol myelography and alcohol injection of the trigeminal ganglion.

was greatly delighted by the subsequent invitation to head a medical delegation to China in 1956. This visit was recalled with enthusiasm by Professor Y.K. Feng.

In 1948, in consultation with others, Leonard Cox helped establish the National Gallery Society of Victoria. He became President of this body 4 years later and served as Chairman of both the National Gallery and Cultural Centre Committee and Trustees of the Gallery. During this era the new Gallery was built, and he published an historical study of the growth and development of the Gallery under the title 'The National Gallery of Victoria 1961-1968'. For his services to the Gallery, Cox was awarded the CMG in 1968.

This bare recitation of the activities of a life-time convey only vaguely the personality of the man, intensely self-disciplined, an original thinker and basically retiring by nature. His interests in book-collecting, in the propagation of rhododendrons and camellias were known to few but his intimate friends. He retired to live in his cottage in the hills at Olinda in 1962, descending only to Gallery Society meetings in Melbourne. In his time at Olinda he helped establish the National Rhododendron Garden near his house, and assisted in the collection of rare species for it.

The pleasure Leonard Cox achieved from his life was shared with his wife, the former Nancy Trumble, and their daughter Barbara of whom he was quietly very proud.

A. Fisher.

Throughout this time and after his appointment to the staff of the Alfred Hospital in 1934, Cox worked additionally at the Baker Institute of Research which had been founded by the impetus of Mackeddie. There the seeds of his earlier training in neuropathology came to fruition with the production of his important paper 'The Cytology of the Glioma Group with special reference to the Inclusion of Cells derived from the Invaded Tissue'. This was the first practical simplification of the original Bailey-Cushing classification of gliomas, and was based on a sound experimental approach. Cox submitted this paper originally to the editor of 'Brain', but Gordon Holmes rejected it, allegedly because the paper was too long. It was published with alacrity by the American Journal of Pathology in its entirety and was widely quoted until superseded by more modern studies. Certainly this paper and other successors in the field of neuropathology written by Cox established this science firmly in Australia. He was Honorary Lecturer in Neuropathology at Melbourne University until 1951.

The Alfred Hospital had always been receptive to what were termed deprecatingly 'subspecialists' and within a year or so of appointment Cox founded the Neurology Department and persuaded his brother-in-law Hugh Trumble towards neurosurgery. Thereafter the two worked in collaboration, with the diagnostic acumen of Cox providing ample opportunities for the outstanding technical skills of Trumble. Arising from this combined effort were the important observations made by Cox on the effects of tumours on the hypothalamus and brain stem, in particular pathological sleep. Russell and Bradley have already pointed out how this work preceded similar studies by Magoun 10 years later. In similar vein, Cox's paper on brain stem haemorrhage as a significant complication of intracranial tumour, published in 1938, antedated the resurrection of this entity described by Duret in the last century, by the Boston school of neuropathology. In 1946 in conjunction with Jean Tolhurst, Cox published his monograph on human torulosis which is still regarded as a classic work.

In an age of didactic teaching Cox was outstanding, and his lecture notes given at the beginning of his course in neurology were sought eagerly by those outside his hospital. At the bedside he was the classic exemplar of the intuitive neurologist. Not for him were the extended and sometimes wearisome examinations conducted with solemnity by some exponents. From the history, he would seize the essentials and apply the appropriate test situations for proof, thereby reaching the clinical diagnosis with maximum efficiency. He was rarely wrong.

For many years the idea of an Association or Society of Neurologists had been in the mind of Cox and after prolonged discussions with Graeme Robertson and Sydney Sunderland the Australian Association of Neurologists was inaugurated in 1950 and Cox was elected President, a position he retained until 1962. The outline of those early years has been given by John Game and reported in the Proceedings of the Association, Volume 12, 1975. We owe the strength and stability of the Association to the prescience and resourcefulness of all the founders, led by Cox.

From his early years Leonard Cox had been interested in Chinese art and in pursuit of this he learned the calligraphy and became deeply immersed in the history of the Chinese culture. His personal collection of Chinese ceramics was widely admired and formed the basis for a series of semipublic illustrated lectures on Chinese art. He

The list of references must be arranged alphabetically by first author's name (and initials if more than one author of the same name) or by second or third etc authors if more than one author of same name and initials. If the sequence of the authors' names and initials is identical, the references should be arranged chronologically by year of publication. Samples of references are listed below. *Note:* titles of journals are *not* to be abbreviated. Supply inclusive pagination for all articles.

Journals: Carruthers, R.K.; Giles, G.R.; Clark, C.G. and Colligher, J.C.: Conservative surgery for bleeding peptic ulcer. British Medical Journal 1: 80-82 (1967).

Book: Keen, H.: Minimal diabetes and arterial disease: Prevalence and the effect of treatment; in Cammerini-Davalos and Cole (Eds) Early Diabetes, p.437-445 (Academic Press, New York 1970).

Supplement: Keen, H.; Jarrett, R.J.; Chlouverakis, C. and Boyns, D.R.: The effect of treatment of moderate hyperglycemia on the incidence of arterial disease. Postgraduate Medical Journal 11(Suppl.): 960-966 (1968).

Tables: Type double spaced on a separate sheet, number with Roman numerals (I, II etc) and provide a legend for each. Tables should be comprehensible without reference to the text. Data given in tables should in general not be duplicated in the text or figures. Any necessary descriptions should appear as numbered footnotes at the bottom of the table.

Illustrations: Illustrations are referred to in the text by Arabic numerals (1, 2 etc). Legends for illustrations should be typed on a separate sheet, numbered correspondingly and should make the illustration understandable independently of the text. If no specific mention of it is made in the text the approximate position of each illustration should be marked in the margin.

For line drawings, good-quality glossy prints or black ink drawings are requested. Symbols, abbreviations and spelling should be consistent with the text. **Figures should be professionally drawn and photographed, if possible.**

Lettering and symbols on figures should be clear and large enough (16 point sans serif type is preferable) to be easily readable after 50% size-reduction. When possible submission of figures already reduced to conform to the column or page-size requirements of the journal will facilitate publication. In already reduced form, column width should not exceed 6.3cm and full page-size should not exceed 13.9cm × 17.5cm.

The author's name, the figure number and top of the figure must be indicated (lightly) on the back of each figure.

If illustrations from previous articles or books are to be used in papers submitted, the written permission of author(s) and publisher must accompany each illustration.

Abbreviations and Symbols: Use recognised abbreviations or SI symbols for units. The first time an uncommon abbreviation appears, it should be preceded by the full name for which it stands.

Drug Names: Generic names should always be used, but if not available, brand names which take an initial capital and single quotes ('Name') can be used. In original articles, the maker of the study drug must be given.

Instructions to Authors

Authors are requested to read carefully and comply with the following:

Manuscript Preparation: Articles will be published in English. Submit two copies of the complete manuscript, including text pages, references, tables, legends, footnotes and figures. Only typed copy, doubled spaced on one side of preferably A4 (206mm × 294mm) typewriter paper, and with liberal margins is acceptable.

Subdivision of Articles: Manuscript should be prepared and paginated in the following manner:

1) Title page
2) Summary
3) Text pages
   - Introduction
   - Methods
   - Results
   - Discussion
4) Acknowledgements
5) List of references
6) Tables
7) Figures and captions
8) Footnotes

Title Page: There should be a separate title page with title, authors and institutions where the work was done, indicating city and country, and a condensed running title of not more than 50 letters including spaces.

The name and address of author to whom reprint requests should be addressed should appear separately as the second page.

Summary: The third page should contain a summary. The summary should not exceed 150 words. It should be factual not descriptive, and should present the reason for the study, the main findings (give specific data if possible), and the principal conclusions.

House Style: Papers reporting clinical studies or experimental work lend themselves to the sectional heading style of presentation and review articles also can be improved by a more limited use of this approach.

Method: Description of the experimental method should be succinct, but of sufficient detail to allow the experiment to be repeated by others.

Results and Discussion: Conclusions and theoretical considerations must not appear in the results section, nor is a recapitulation of the results acceptable for the discussion section. Where relevant, a concise statement of the implications of the experimental results, particularly to the clinical use of drug(s), should appear as a separate section.

References: In the text, reference to published work is cited by author (alphabetically) and year — viz (Brown, 1968, 1969; Brown and Smith, 1967; Brown et al., 1969).

Subject Index