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Abstracts

The Graeme Robertson Memorial Lecture, 1979

Dr Darab K. Dastur, M.D., D.Sc. (Bombay), F.A.M.S., F.R.C. Path. (London), Professor of Neuropathology at the Neuropathology Unit, Postgraduate Research Laboratories, Grant Medical College and J.J. Group of Hospitals, Gate No. 12, Bombay-400 08, India, was invited to give the Graeme Robertson Memorial Lecture for 1979, at the Annual Scientific Meeting of the Australian Association of Neurologists held in May 1979, in Brisbane, Australia.

Dr Dastur chose for his lecture the topic 'Aspects of Neuropathology in India'. Two of the aspects he considered are presented in the first two papers in this volume.

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I. Aspects of Cuprogenic Disorder in Wilson's Disease in India

D.K. Dastur and D.K. Manghani†*

Details of the clinical, familial and biochemical features of Wilson's disease in India, studied by us jointly with Dr N.H. Wadia, have been reported earlier (Dastur et al., 1968; Manghani and Dastur, 1968; Dastur et al., 1969). A comprehensive account of the 'inherited cuprogenic disorder' of liver, brain, kidney and cornea which Wilson's disease represents, has been published more recently (Dastur and Manghani, 1977). In the present communication a brief resume of some of the salient findings will be presented, with emphasis on the disturbed copper metabolism characteristic of the disease. These observations are based on an intensive study of patients from 1959 to 1967. A brief account will then be given of our limited findings in a large number of patients suspected of having Wilson's disease during the period 1970 to 1978.

1. 1959 to 1967

Subjects Studied

No racial or geographic predilection was found for Wilson's disease. Because Bombay is on the West coast of India, the largest number of patients naturally came from Western India, but in the 9-year period we had patients from Northern,

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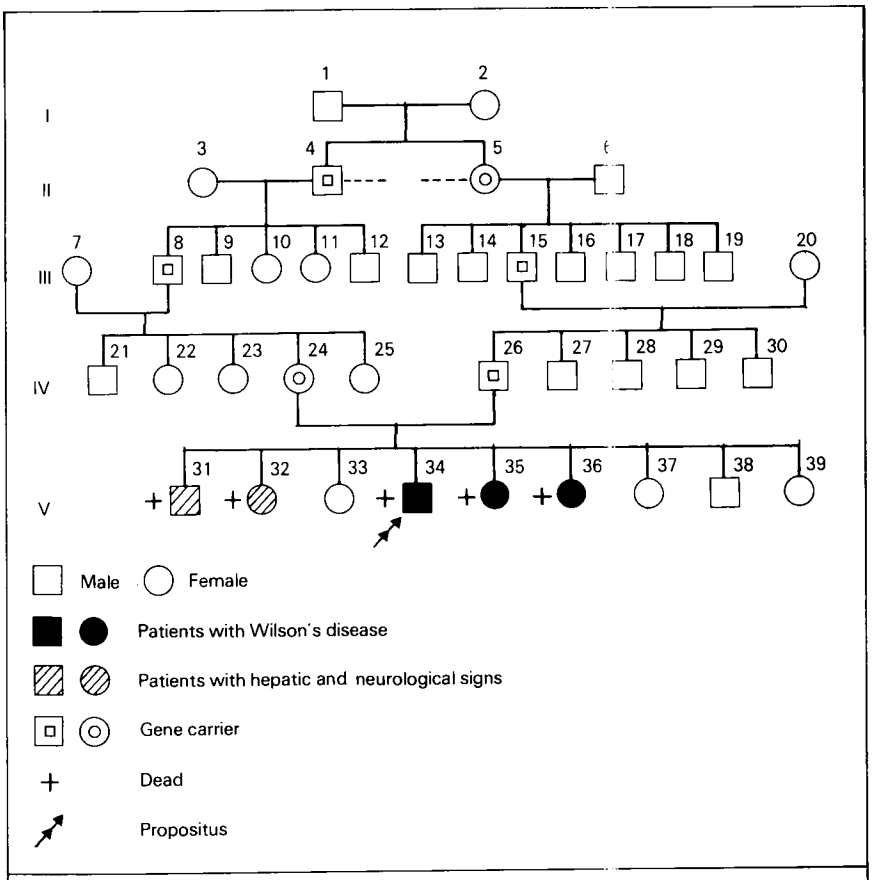
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Male
Female
Patients with Wilson's disease
Patients with hepatic and neurological signs
Gene carrier
Dead
Propositus

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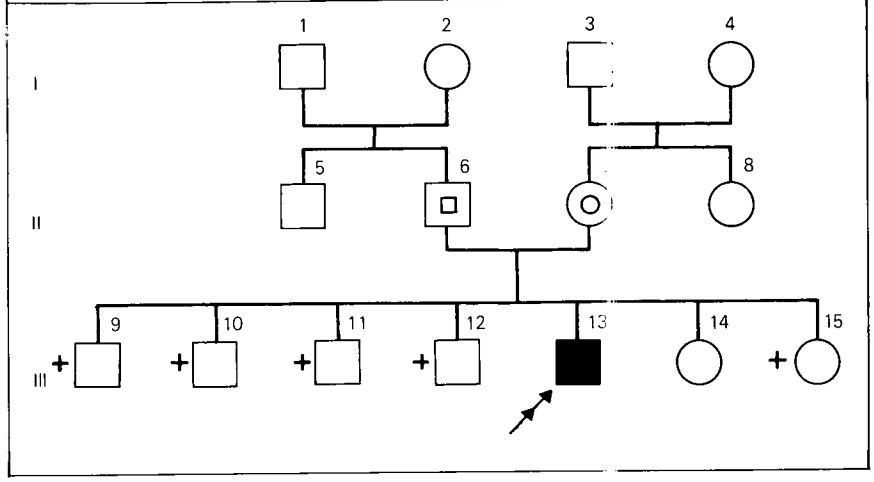
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Southern and Central India as well. While the majority of patients were Hindus — both Brahmins and non-Brahmins — there were also Muslims and 1 Parsi patient in our group of 25 proven cases. In all, 105 subjects from 16 families, comprising 25 patients and 80 non-affected siblings, were investigated in terms of the cuprogenic disorder.

Results

The consanguinity rate was 25%, lower than expected considering the fact that Wilson's disease is a classical autosomal recessively inherited disorder. The Mendelian law of such inheritance, with a ratio of 1 to 3 for affected to unaffected siblings, appeared to apply (with 25 of 105 subjects showing the disease). 2 typical family pedigrees are illustrated in figures 1 and 2. In the F.H.P. family (fig. 1) 5 of 9 siblings were affected, while in the M.K.S. family (fig. 2) only 1 of 7 siblings was affected. The first family was Muslim from Rajasthan, the second family was Hindu. Patients in both families had the predominantly neurological form of the disease, but the propositus of the first family died of massive haematemesis consequent to hepatic cirrhosis.

As the mean age of the patients was only about 14 years, a common neurological sign was failing performance at school, along with involuntary movements, with or without rigidity.

Disease Type

In the 25 patients, the predominating signs were neurological in 14, hepatic in 3 and 'osseomuscular' in 8.

Almost all patients had an enlarged liver, and 8 had clinical and radiological evidence of rickets, or osteoporosis with bony deformities. The latter group also showed proximal muscle weakness; this is referred to as the osseomuscular type of Wilson's disease. This aspect was further expanded in our later papers (Dastur et al., 1969; Dastur and Manghani, 1977). These patients had a slightly later age of onset and a longer duration of the disease, but identical disturbance of copper parameters, except for a lesser elevation of direct-reacting serum copper (expressed as a percentage of total copper) compared to the other patients. They also had Kayser-Fleischer (K-F) rings in the cornea, on gross examination and slit lamp microscopy. Nevertheless, a slightly milder form of the overall disease was manifest in these 8 patients: there were

Fig. 1. Pedigree of the F.H.P. family, showing 5 generations (I-V).

Fig 2. Pedigree of the M.K.S. family. See figure 1 for key.

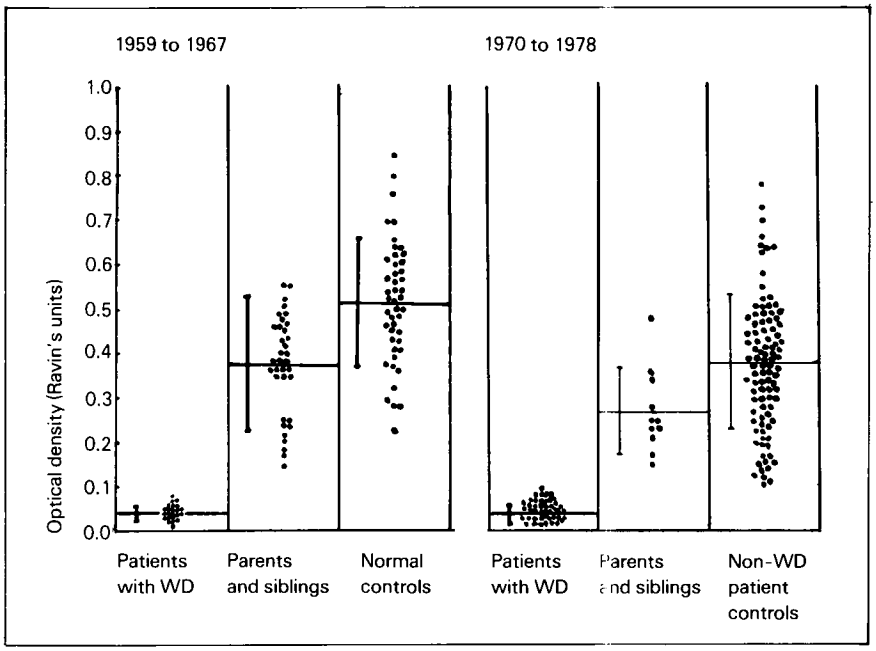


Fig. 3. Serum copper oxidase levels in patients with Wilson's disease (WD) and control groups.

no deaths over a 7-year period of observation, compared to death in 1 of 3 patients with the predominantly hepatic form of the disease and in 5 of 14 with the predominantly neurological form.

Copper Metabolism

The parameters of copper metabolism investigated were serum copper oxidase representing caeruloplasmin; total, direct-reacting and indirect-reacting serum copper levels; 24-hour urinary copper excretion; urinary calcium and phosphate excretion in some of the patients, and semi-quantitative assessment of urinary amino acids. These investigations were also carried out in the parent-sibling group, and in normal control subjects. The serum copper oxidase level was found to be markedly lower in every patient and significantly lower for the patient groups (0.040 ± 0.017 Ravin's units) compared to the sibling groups (0.369 ± 0.153 Ravin's units). In the latter it was significantly lower than in the normal control group (0.508 ± 0.139 Ravin's units). Individual values are given in the scattergram (fig. 3). While the literature indicates that 5 % of patients with Wilson's disease may not have depressed copper oxidase, we did not have any such patients.

The next most diagnostically helpful parameter of disturbed copper metabolism was the direct-reacting serum copper. This represents the free copper which either gets deposited in tissues or excreted in the urine. The moiety (diethyldithiocarbamate-bound copper) was invariably raised. Moreover, this value, expressed as a percentage of total copper, (which itself may or may not be elevated), was a better indication of pathological alteration, as discussed in our review (Dastur and Manghani, 1977) and illustrated for a few cases (fig. 4).

The renal tubular reabsorption defect characteristic of Wilson's disease was evidenced by massive generalised amino aciduria (on 2-directional paper chromatograms) in all patients, in the absence of increased circulating levels of amino acids. In the patients with the osseomuscular form of the disease there was, in addition glycosuria and proteinuria, suggesting a picture similar to that of the Toni-Fanconi syndrome.

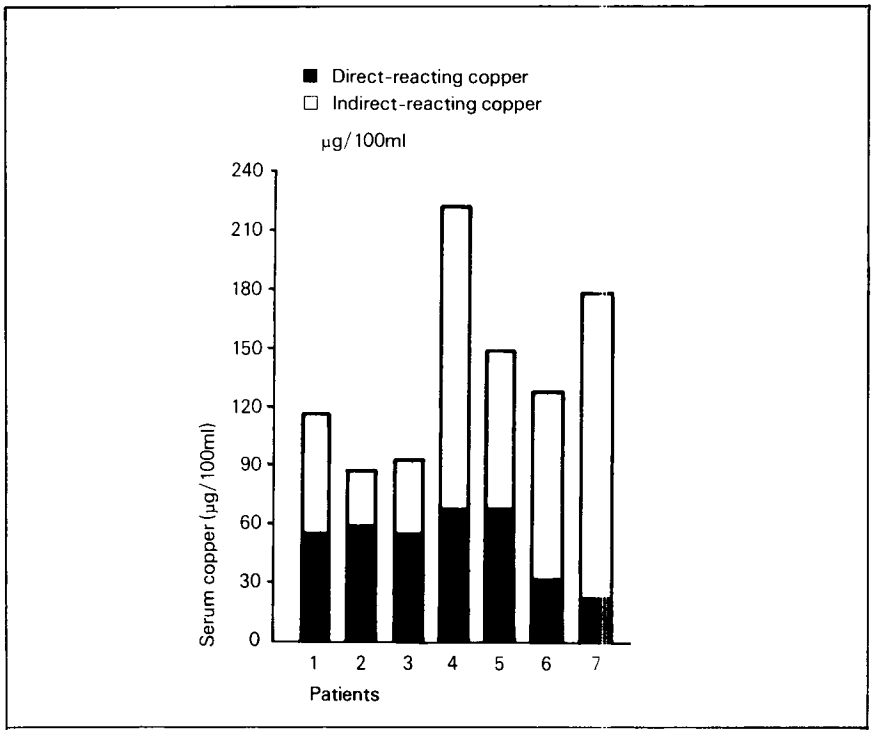
Discussion

The chain of pathogenetic events suspected from our investigation confirmed that the primary event as suggested originally by Scheinberg and Gitlin (1952), is a severe deficiency (or rarely absence) of the copper-binding protein caeruloplasmin, representing the genetically determined defect of Wilson's disease. This, probably along with increased absorption of copper from the gut, leads to high circulating levels of free copper (direct-reacting) which, in turn, is excreted in the urine and at the same time gets deposited in certain tissues where it exerts deleterious effects. In the brain, the cerebral cortex as well as the basal ganglia and, rarely, other regions, show degenerative changes and glial cell reaction, which are responsible for the complex neurological pictures. In the liver, characteristic postnecrotic cirrhosis with glycogen degeneration of nuclei results. Wilson's disease emerges as a typical inherited cuprogenic disorder of liver, brain, kidney and cornea.

2. 1970 to 1978

Subjects Studied

During the 9-year period from 1970 to 1978, 145 subjects were investigated: 44 with Wilson's disease proven by low serum copper oxidase levels; 11 parents or siblings of patients, and 90 patients in whom Wilson's disease was suspected (because of neurological and/or hepatic signs) but with normal serum copper oxidase levels. The mean serum copper oxidase level in the patient group was 0.041 ± 0.020 (Ravin's units), with a range of 0.015 to 0.095, which is comparable to our earlier findings in part 1 of the present paper.


Direct-reacting copper
Indirect-reacting copper
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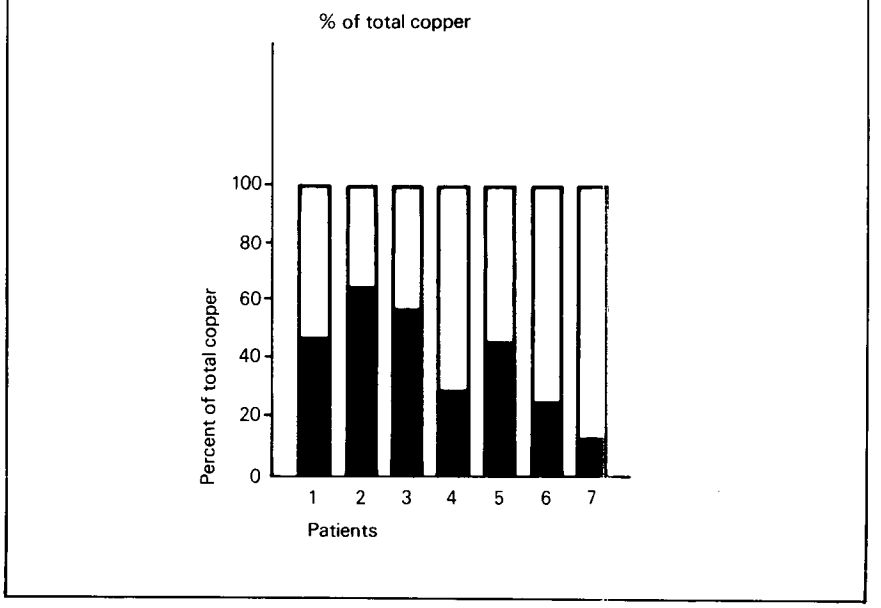
4a


% of total copper
100
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40
20
0
Percent of total copper
1 2 3 4 5 6 7
Patients

4b

Results

It is of interest that, as with the study of the earlier decade, the mean age was quite low (12.3 years) when the patients first came to hospital. The mean age of the patients with predominantly hepatic forms of Wilson's disease was slightly lower than that of the whole group (9.0 years), a feature we noticed earlier (Dastur et al., 1968).

Disease Type

Case histories were available in 38 of the 44 patients with Wilson's disease. In all of them neurological changes were present. However, in only 22 were the signs predominantly neurological throughout the course of the illness. In 7 patients the disease was predominantly hepatic. In another 7 the disease was either predominantly osseomuscular in nature or there was a history of rickets and weakness for many years prior to onset of neurological symptoms. 2 patients (siblings) were asymptomatic when the low serum copper oxidase was detected. It is important to note that a much smaller proportion of patients (7 out of 44) presented with the osseomuscular type of disease, compared to the higher proportion (8 out of 25) in our earlier study (Dastur et al., 1969). Even in some of these 7 patients there might have been merely a coincidental presence of rickets, which is quite common in the malnourished population of our country.

28 of the 34 patients where this information was available had clear K-F rings even on naked eye examination; 2 had doubtful K-F rings, and 4 had none on gross examination.

Copper Metabolism

The mean serum copper oxidase level for the small group of 11 siblings or parents of patients was 0.258 ± 0.09 (Ravin's units), which was statistically significantly higher ($p < 0.001$) than the mean value in patients. As in the earlier study (Manghani and Dastur, 1968), in 90 patients with neurological or hepatic disorder but not Wilson's disease, the mean serum copper oxidase level was 0.366 ± 0.15 (Ravin's units). This is significantly higher than the value in the parent-sibling group. Thus copper oxidase estimation might detect heterozygotes of Wilson's disease. It was noted that this mean value (0.366) in the patient control group was lower than

Fig. 4. Direct-reacting serum copper expressed (a) in μg per 100ml and (b) as a percentage of total copper in 7 patients with Wilson's disease.

the mean value in the normal control group of our earlier study, which was 0.508 ± 0.139 (Ravin's units) [Dastur and Manghani, 1977].

In 15 of the patients and in 11 of the patient controls of the second study, direct-reacting serum copper was also estimated, this also being an important and reliable parameter of Wilson's disease. The mean level in the patients was 60.10μg% and in the controls 12.74μg%. These different values were highly significant, and were comparable to the levels obtained in an earlier study (Manghani and Dastur, 1968).

Summary

A brief account is given of some aspects of Wilson's disease in India, studied during the periods 1959 to 1967 and 1970 to 1978, with emphasis on disordered parameters of copper metabolism. Among the latter, serum copper oxidase (representing caeruloplasmin) was found to be the most constant laboratory evidence of Wilson's disease. It was drastically lowered in all patients in both periods (25 and 44 patients respectively), when compared to its level in the parents and siblings of the patients, in other neurological patients and in normal subjects serving as controls. The other constantly involved parameter was direct-reacting serum copper which was highly significantly elevated in the patients compared to the other groups. Most of the patients presented with a predominantly neurological form of the disease, smaller groups presenting with predominantly osseomuscular or hepatic forms. The mean age of patients in both periods was approximately 13 years.

Acknowledgements

Grateful acknowledgement is due to Dr N.H. Wadia, for clinical collaboration in the first study; to Dr B.S. Singhal, Dr P.M. Udani, Dr B.D. Patel, Dr M.M. Wagle, of the J.J Group of Hospitals; to Dr E.P. Bharucha, Emeritus Professor of Neurology, K.E.M. Hospital, Bombay, for providing clinical material and to Mr R.S. Palekar for carrying out the laboratory estimations during the years 1970 to 1973.

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II. Pathology and Pathogenesis of Chronic Myelopathy in Atlanto-axial Dislocation, with Operative or Postoperative Haematomyelia or other Cord Complications

*D.K. Dastur**

The first part of the title of this paper describes an uncommon form of myelopathy, the pathology of which had not been studied until the account of Dastur et al. (1965). The combination of conditions described in the full title is so rare that there has been no report on it before or since (Dastur et al., 1965). There are two brief reports on the pathology in a single case of cord compression at Cl level by a fractured detached odontoid process (Elliott and Sachs, 1912; Alexander et al., 1953). The clinical and radiological features of atlanto-axial dislocation were first described from Bombay (Wadia, 1960; Bharucha and Dastur, 1964), and further details on a larger group were given by Wadia (1967). 6 cases were fully described with clinico-pathological correlations (Dastur et al., 1965).

A total of 11 cases of such myelopathy complicated by acute haematomyelia during surgical decompression or other fatal postoperative catastrophes were studied from 1958 to 1968. The salient features of the pathological changes and the dual pathogenesis of this condition in the 11 patients are here presented.

Group 1. Cases 1 to 6 (1958-1964)

Cases 1 to 6 were male patients who presented with motor (mostly corticospinal) and, to a lesser extent, sensory (mostly posterior column) signs and symptoms of high

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Table I. Main features of the craniovertebral anomaly and the CNS in the 6 male patients who made up Group 1: subgroup (a) comprises cases 1 and 5, aged 40 and 9 years; subgroup (b) comprises cases 2, 3, 4 and 6, aged 20, 30, 16 and 19 years respectively

Features	Subgroup (a)		Subgroup (b)
Odontoid process	Detached		Attached to axis
Trauma	No history		Minor injury in 3 cases
Associated anomalies	Nil		Present (see text)
Dislocation	Reducible and intermittent		Irreducible and constant
Compressing bones and fibrous bands	Arch of atlas and upper edge of body of axis		Tip of odontoid process
Site of cord compression	Lower (C2 segment)		Higher (C1 and medulla in 3 cases)
Nature of compression	Intermittent; in flexion only		Constant (movements limited by spasms)
Ligaments at autopsy	Better defined and intact		Ill-defined with transverse ligament unclear in 3, not looked for in Case 3
Operative haematomyelia or postoperative catastrophe	Nil (Case 1; pyogenic meningitis), small (Case 5)		Large in all
Level of above	C1 to C2 segment		Medullospinal
Cord oedema	Less		More
Brain oedema	Nil		Present (severe in 2)
Degeneration in spinal cord	Case 1: no surgical catastrophe, and therefore no haematomyelia; death due to purulent meningitis; severe and sharply defined lateral column degeneration from C3 down to lumbar cord. Anterior horn cell degeneration more in dorsal cord than in cervical	Case 5: surgical haematomyelia, paracentral in the compressed cord at C1-C2, with glial-vascular reaction; severe border zone sponginess, most in lateral columns	Generally haemorrhagic necrosis at site of maximum compression: the lower end of medulla and C1-C2 segment of cord. Case 6: haemorrhage up to mid-medulla. In most cases severe degeneration of lateral columns and mild of posterior columns. Varying degrees of border zone oedema and anterior horn cell loss

cervical cord compression. This had been progressive, or had partially improved and had then become stationary, over a period of several months. Radiological examination revealed atlanto-axial dislocation and one or more bony anomalies in this region. Surgical decompression of the medullospinal junction was carried out in all 6 patients. Haematomyelia was precipitated during the operation in 5 cases, and terminated fatally within 1 day in 2 cases, within 5 days in 2, and within 48 days in 1 case. In the sixth patient (Case 1) acute postoperative lepto-meningitis led to death.

Autopsy confirmed the radiological findings and revealed in 3 cases ligamentous changes between and around the first 2 vertebrae. In the above 5 cases recent paracentral haemorrhages or posthaemorrhagic necrosis were detected at and just above the site of compression. Histological examination revealed acute space-occupying haematomyelia and tissue destruction or subacute posthaemorrhagic vasculo-fibroglial proliferative reaction, both being maximal in the grey horns, especially anterior. The acute and subacute changes also appeared to include severe circumferential oedema of the upper cervical cord and the lower end of the medulla, particularly of the lateral white columns. These changes masked the more chronic changes in the white matter resulting from preoperative bony compression of that region. However, long standing partial or total degeneration of the pyramidal tracts at the site and in lower cervical and dorsal cord segments was observed in all the cases. Ascending degeneration of the posterior columns was less readily detectable. Anterior horn cell damage noticed at sites far below those of compression or haemorrhage could be related to the clinical finding of wasting of the upper limbs. On the whole there was fair clinico-pathological correlation. The histological changes were more evident in extent and severity than the clinical.

Additional information on the 6 cases is shown in table I, modified from an earlier paper (Dastur et al., 1965). The primary distinguishing feature of the 2 subgroups in table I was the nature of the odontoid process — whether it was attached to the axis or detached, since this was a critical part of the craniovertebral anomaly.

Discussion

The quadriplegia or quadriparesis, accompanied by severe sensory loss up to the level of the clavicles, was probably produced by damage to the lateral and posterior columns of the spinal cord at a level between the lower end of the medulla and C2 segment of the cord. At times the gross operative haematomyelia or postoperative inflammatory and glial cell reaction extended to lower cervical levels also (as in Case 6). Some of the neuropathological features are illustrated in figures 1 to 5.

The nature and mechanism of the suddenly produced haematomyelia merit consideration. The essentially paracentral or central location of these haemorrhages placed them in the territory of the sulcal branches of the anterior spinal artery. Since the main vessels were invariably unaffected, it was the smaller intraparenchymal

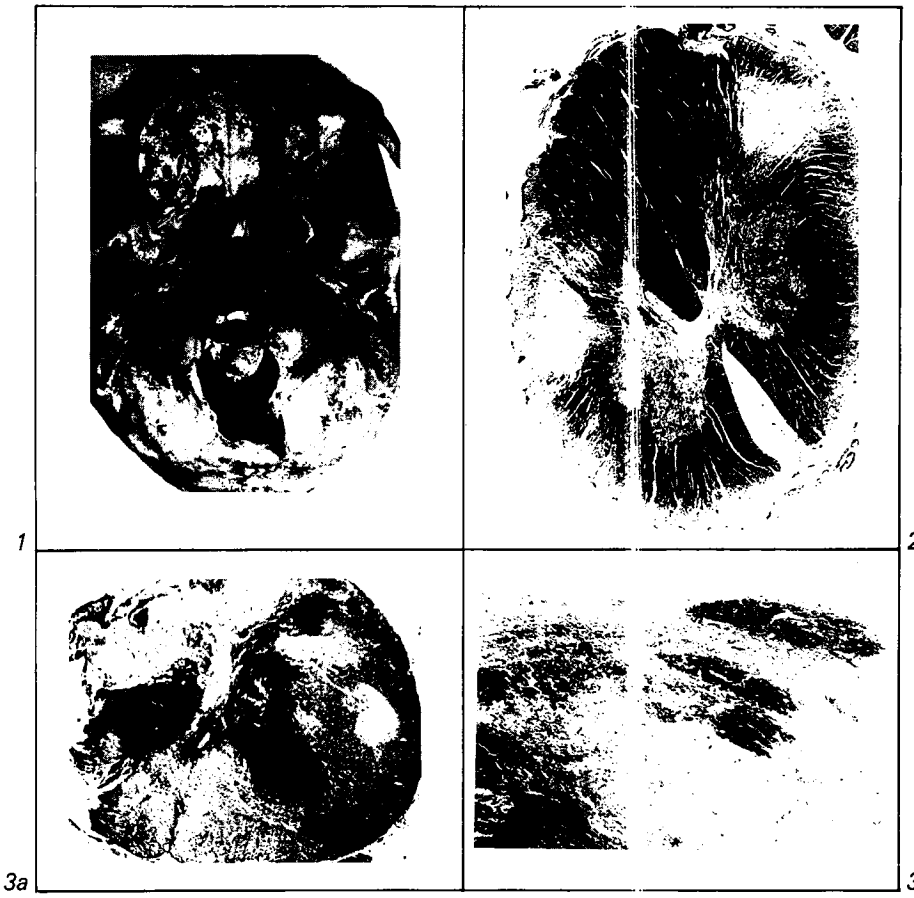

Fig. 1. Case 1. Base of skull, showing the upper separated third of the odontoid in situ between the occipital condyles, rotated backwards to show attachment by the alar ligaments and the pseudojoint surface produced by it at the anterior margin of the foramen magnum (the posterior margin of which was removed at operation).

Fig. 2. Case 1. Cross section of the spinal cord at the lower cervical level showing demyelination of both lateral columns. The posterior columns are well myelinated at this level. Border zone rarefaction is seen around the entire anterolateral sector of the cord (Heidenhain's iron haematoxylin stain for myelin x 14).

Fig. 3. Case 3. (a) Cross section of the upper cervical cord at the level of recent operative haematomyelia. Note bilateral 'spectacle' haemorrhages in the paracentral regions. The haemorrhage on the right extends into the posterior horns. Also note the haemorrhages destroying the greater part of both anterior horns (Weil-Weight stain for myelin x 9) (b) Closer view of illustration 3a showing tongues of haemorrhage in the right posterior horn, and including the border of the right paracentral haemorrhage in the lower left corner. Note pallor of myelin in the inner part of right lateral column (Weil-Weight stain for myelin × 40).

branches that bled. Moreover, it may be surmised that these arteries must have been compressed severely enough preoperatively for them to rupture when the full head of blood pressure was suddenly released into them by surgical removal of the compressing agent, often the posterior arch of the atlas or the odontoid, or a dense fibrous knuckle in the posterior dura mater. The mechanism of the haemorrhage destroyed greater parts of the anterior grey horns, the proximal portion of the posterior horns and posterior columns, the crossing spinothalamic fibres, and extended into the inner parts of the lateral columns. At times the haemorrhage reached up to the tips of posterior horns, as in Case 4. Being an acute space-occupying lesion, the haemorrhage produced surrounding oedema, especially in the lateral border zones.

Group 2. Cases 7 to 11 (1964-1968)

The 5 cases referred for pathological examination during this period had, with one exception (Case 10), atlanto-axial dislocation with an attached odontoid process. The 4 patients with the attached odontoid varied in age (from 27 months to 45 years), in the anatomical features of the craniovertebral anomaly, and in the other non-osseous anomalies. These 5 cases are presented in table II. Neurofibromatosis was present in Case 8 and a small syrinx in one posterior horn in Case 9. In Case 8 the combined presence of atlanto-axial dislocation and a large dumb-bell-shaped neurofibroma at C1 to C2 nerve roots was responsible for the pressure atrophy of the cord.

The neurological features of quadriplegia, with extensor plantar responses and deep sensory impairment up to the clavicles, were also present in the patients of this group. Sudden respiratory arrest at the time of removal of the compressing tissue (bony or fibrous) during neurosurgery was noticed in 3 of these 5 cases (8, 10, 11), with survival of about 5 to 6 weeks in the 2 adults (Cases 10 and 11) but immediate death in the child (Case 8). In the patients with the longer survival there was a cellular and vascular reaction around the accumulated blood which persisted longest in the deepest parts of the posterior horns. However, of the 2 patients from this later period in whom such a surgical catastrophe did not take place, there was death from laryngeal oedema and airway obstruction in Case 7, and unremitting paralytic ileus in Case 9. It may be noted that in these 2 patients sudden release of pressure was not effected at the operation, which took the form of anterior bone grafting in Case 7 and skull traction in Case 9.

Discussion

The lateral columns, specifically the crossed pyramidal tracts, in the chronically compressed spinal cord, have a greater vulnerability than the other peripherally

Table II. Main features of the craniovertebral anomaly and the CNS in Group 2

Feature	Case 7	Case 9	Case 10	Case 11	Case 8
Age	39yrs	36yrs	25yrs	45yrs	27m
Sex	M	M	M	F	F
Odontoid process	Short and attached	Short and attached	Detached	Attached, short and tilted	Attached
Trauma	Fracture right graft from first operation 3yrs previously, no trauma	Nil	Nil	Nil	Nil
Associated anomalies	Occipitalised atlas, twisted facets of atlas and axis. C2-C3 fused	Klippel-Feil syndrome, atlas fused to occiput. C2-3 and C4-5 fused; spina bifida	Nil	Fusion of body of axis to anterior arch of atlas	Atlanto-axial dislocation with congenital neuro-fibromatosis. Megacephaly, cervico-kyphosis. Defective posterior arch of atlas. Facial and occipital neurofibromas
Dislocation	Fixed	Fixed	? reducible	Fixed and forward (spinal canal behind dens, extremely narrow)	Constant and gross
Compressing bones and fibrous bands	Short odontoid and large dural knuckle below it	Rudimentary odontoid, and dural band below it	Posterior arch of atlas	Posterior arch of atlas and odontoid	Odontoid and schwannoma at C2

Site of cord compression	Maximum C2 (cord only 4mm A-P); but generally from C1-C3	Lower medulla, by dens in foramen magnum; C1 by dural band; C2-C3 slightly	C2 segment	Lower medulla and C1	C2-C3
Nature of compression	Constant (movements limited by bony anomalies and surgical grafts)	Constant	Mainly in flexion	Constant and severe	Constant
Ligaments at autopsy	Ill-defined and thin transverse ligament	Not ascertained	?	1) Narrow but tough transverse ligament 2) Fan-like ligament from dens to anterior arch of atlas	?
Operative haematomyelia or postoperative catastrophe	Nil. 1st operation 3 years previously; posterior spinal fusion, later fibrous thickening of dura; 2nd operation (this admission): anterior bone grafting, postoperative laryngeal oedema, obstructive dyspnoea and death	Surgery: traction only. Severe postoperative paralytic ileus and distension, and bladder paralysis	Immediate. Postoperative quadriplegia and respiratory arrest; survived hypoxia for 6 weeks, (in artificial respirator)	Respiratory arrest on elevation and removal of posterior arch of atlas; survived for 5 weeks in artificial respirator	Respiratory arrest, cardiac arrest and death on the 'table'
Level of above	—	—	C2 segment	Medullospinal	C1-C2
Cord oedema	Moderate	Moderate	Moderate	More, circumferential	Mild, border zone

Table II. (continued)

Feature	Case 7	Case 9	Case 10	Case 11	Case 8
Brain oedema	Moderate	Moderate, white matter	Brain stem oedema	Severe	Severe oedema, cerebrum cortex more than white matter
Degeneration in spinal cord	Lateral and posterior columns	Total lateral column and partial (circumferential) posterior column C3 > C6; syrinx in posterior horn, C6 > C3; anterior horn cell degeneration	Crossed and uncrossed pyramidal tracts, gliosis in posterior horns and columns; ? posthaemorrhagic	Resolving haemorrhages C1-C2 with fibroblast, astrocytic reactions in centre of cord; dorsal cord fairly preserved	? posthaemorrhagic gliosis and vascularisation, in posterior columns at C2 and C3-C4

placed ascending or descending tracts. The greater proportion (nearly 90%) of the myelinated pyramidal fibres in most mammals are small delta fibres, under 4μm (Patton and Amassian, 1960). It is also known that delta fibres of the nerves are most affected by anoxia (Gelfan and Tarlov, 1953). As suggested by Dastur et al. (1965) anoxia could well have played a major role in the production of demyelination of the descending corticospinal tracts, as was seen in at least 3 of the patients (Cases 4, 7 and 10). The myelin loss can be well shown in appropriately stained thick paraffin sections, but is more dramatically revealed in the Marchi preparations on frozen sections. Only in Case 7 was regeneration clearly evidenced, in the form of skeins and whorls of proliferated Schwann cells in an extremely atrophic part of the upper cervical cord and at the site of total degeneration of the posterior half of the cord (fig. 8). The appearance with cell stains was almost reminiscent of a schwannoma.

It is also interesting to consider the effects of anoxia on anterior horn cells of the compressed upper cervical cord and of the lower cervical and upper dorsal cord. This was responsible for the cases where wasting of the hand muscles occurred clinically in 12 of the 28 patients in Wadia's series (1967). Sometimes the motor neurones of the upper dorsal cord were lost more than those of the cervical cord, suggesting the 'last-field' theory of blood supply to the cord, whereby this area (about D2-D4 segments) suffers anoxia most because the branches of both the anterior spinal artery and the abdominal aorta terminate in the region, with a reduced blood flow. A similar situation may develop in cervical spondylosis (Wilkinson, 1960).

While posterior column changes were second only to those of the lateral columns, even in the larger material of Wadia (1967) cutaneous sensibility was seldom involved. It was the loss of vibration sense, often up to the clavicles, which was the main feature, and this was appropriately borne out by the frequent detection of posterior column degeneration in our autopsy material.

Implications for Treatment

After the necropsy findings on these first few cases, the neurosurgeons in Bombay naturally gave up attempts at open reduction of the atlanto-axial dislocation. The main surgical procedures tried out so far include posterior decompression with fusion, with or without laminectomy, and anterolateral fusion. In reviewing the results of surgery in 71 patients over a 15-year period, Sinh (1976) favoured the latter procedure (carried out in 26 patients). He stressed the value of skull traction for reduction of dislocation, prior to surgery for fixing the vertebrae. Using Greenberg's radiological classification of atlanto-axial dislocation (1968), Sinh found more 'fixed' dislocations in patients with occipitalised atlas without abnormality of the odontoid, and more 'reducible' dislocations in patients with a well developed odontoid which had not fused with the body of the axis. However, the prognosis after surgery was found to be directly related to the preoperative neurological condition of the patient. Where surgical catastrophes were avoided, postoperative deaths were said to be due

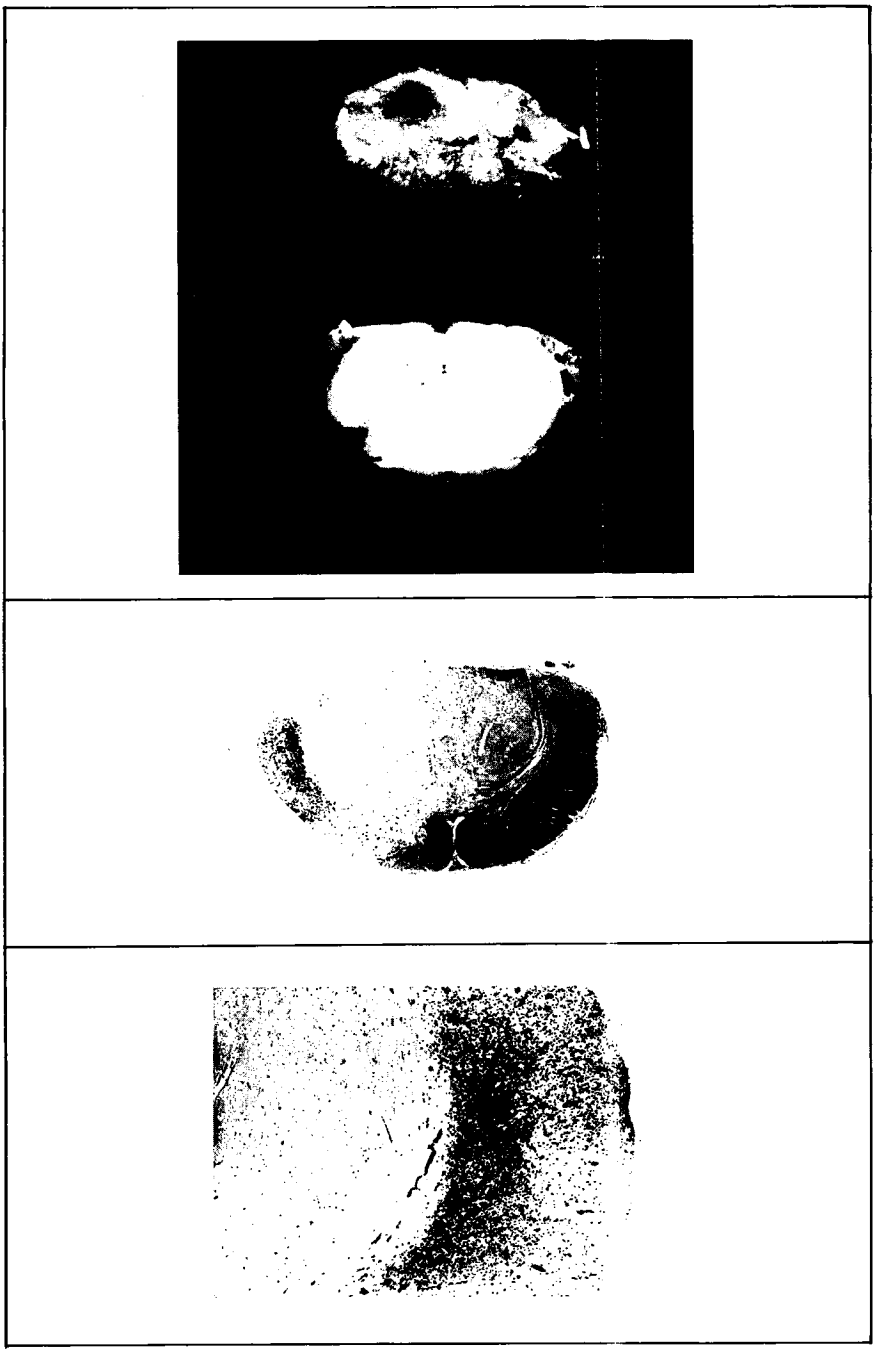

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Fig. 5. Case 6. Successive cross sections through the medulla oblongata and spinal cord in a patient admitted to hospital with established quadriparesis and wasting of the muscles of the left hand. At operation the odontoid process was found pushed up beyond the foramen magnum, compressing the lower third of the medulla. 1-3. Lower third of the medulla showing haemorrhages in the midline and towards the right. Note the marked narrowing of the left half of the medulla where the odontoid was pressing into it. 4. The medullospinal junction. 5 and 6. The totally crushed and almost destroyed first cervical segment. 7. Second cervical segment: small bilateral haemorrhages. 8. Lowest limit of haemorrhage on the narrower left side in this section through C3. 9. Grossly normal fourth cervical segment of the cord. However, this section (and still lower levels) showed degenerated anterior horn cells. At necropsy the odontoid was seen to be small but surrounded by a mass of tough fibrous and ligamentous tissue. This tissue extended backwards from the anterior border of the foramen magnum and occipitalised atlas, becoming adherent to the odontoid and pushing it backwards, thereby producing severe compression of the lower end of the medulla and the upper end of the cord.

to respiratory infection consequent to poor respiratory capacity (resulting from weakness of the diaphragmatic and intercostal muscles).

Summary

Pathological features are described, and clinico-pathological correlations are made, in 11 patients presenting the unusual combination of chronic compressive

Fig. 4. Case 5. (a) The upper cross section is of the C2 level of spinal cord just below site of maximum compression, showing a large haemorrhage in the right anterior horn region and a smaller one in the left paracentral region. The lower section is about 3 segments below the upper. (b) Marchi preparation of a level between the above 2 sections, showing myelin breakdown products in the lateral columns (Marchi stain x 8). (c) Closer view showing granular myelin breakdown products in the lateral column (Marchi stain x 27).

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6b

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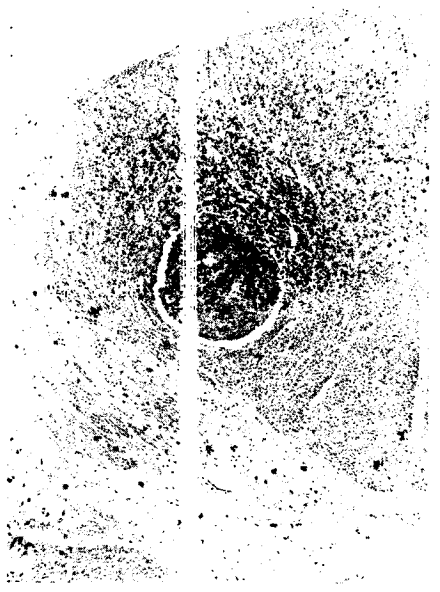

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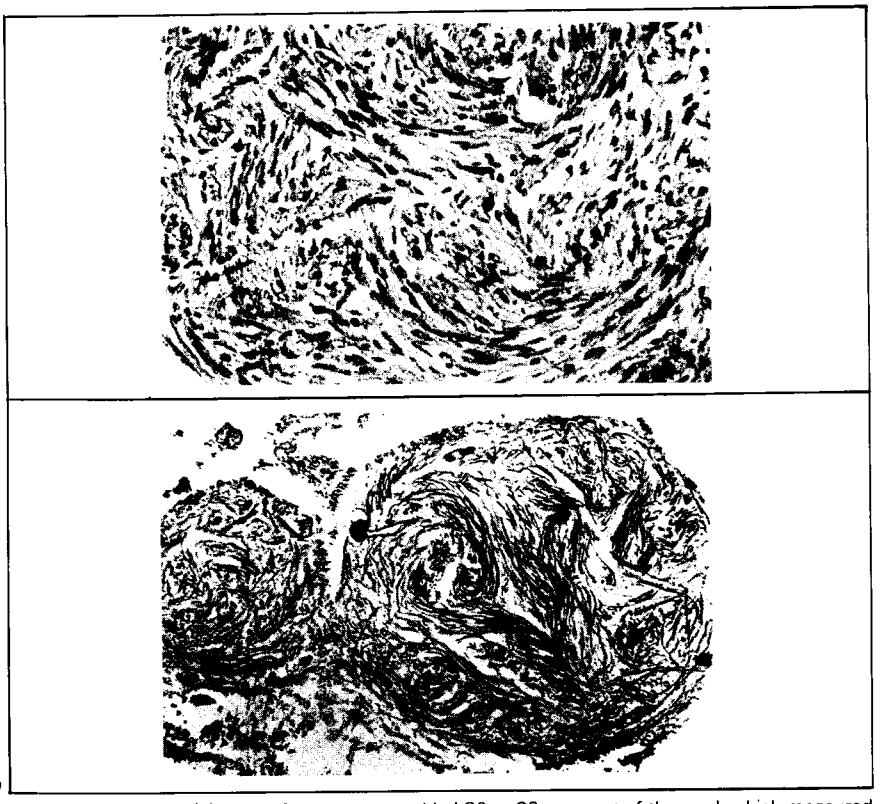

Fig. 8. Case 7. (a) Level of the most atrophied C2 to C3 segment of the cord, which measured only 4mm in the anteroposterior direction. There are dense skeins of elongated Schwann cells arranged in interlacing bundles in the severely degenerated posterior part of the cord (haematoxylin and eosin × 250). (b) The bundles contain thin smooth axis cylinders, representing a regenerative effort at the site of maximum degeneration (Holmes' Silver stain × 100).

Fig. 6. Case 7. (a) Postmortem skiagram of craniovertebral junction. Note fused and malformed C2 to C3 vertebrae with asymmetrical articular facets and the short odontoid a little to the left of the midline. (b) Dissected specimen of the vertebral part of the bony anomaly showing the hump of the odontoid process (a little to the left of the midline), with its 2 alar ligaments pulled up by forceps. The anterior surface of the posterior longitudinal ligament is seen extending from below the dens as a broad smooth band. Note the twisted articular facets of the axis, the right facet (R) pointing forwards more than upwards, while only the edge of the left facet (arrow) is seen as it is pointing directly upwards. (c) The dissected specimen of the cerebellum, the medulla oblongata and the upper cervical cord from behind, after cutting open the dura mater, including the dense knuckle (D). Note maximum narrowing of the cord at about C2 level (arrow).

Fig. 7. Case 7. Marchi preparation, including one posterior column and part of one posterior horn, showing a necrotic zone (x 27).

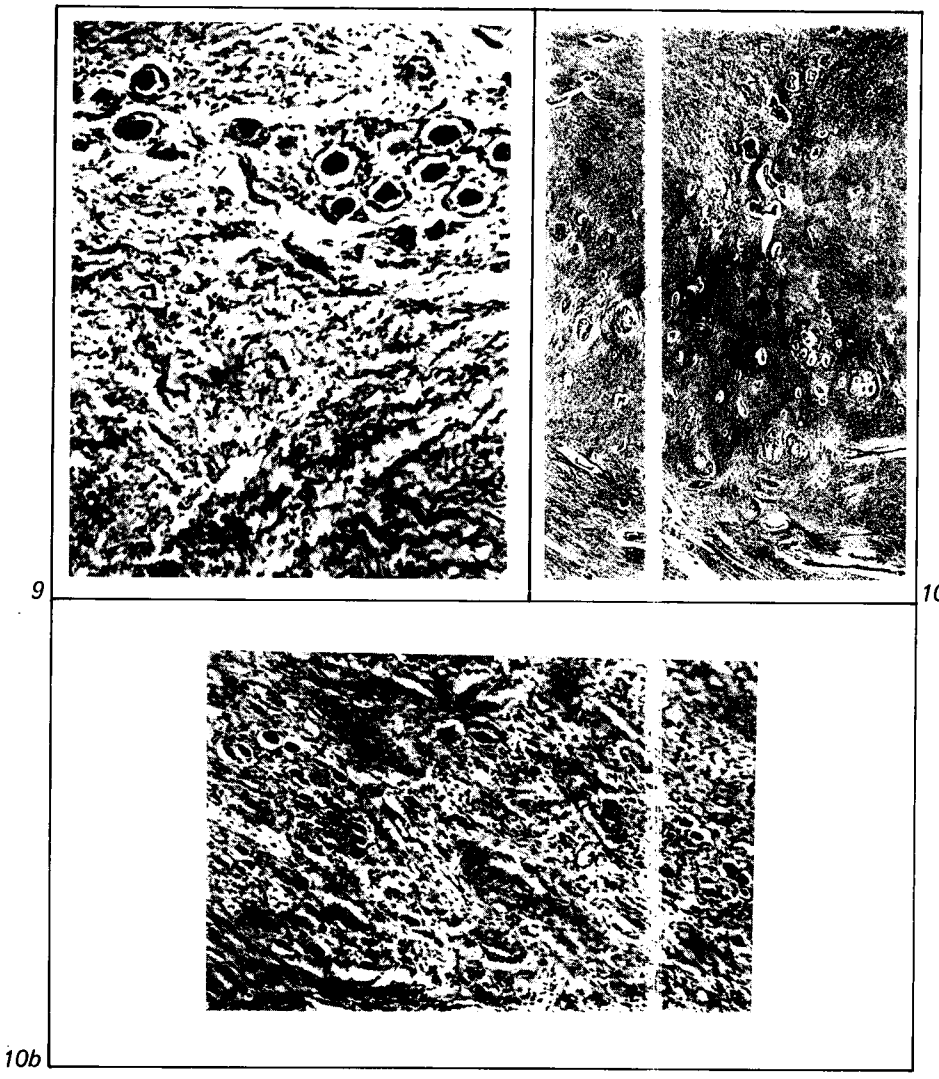

Fig. 9. Case 8. A 27-month-old child with congenital neurofibromatosis, including a large neurofibroma pressing on the cord, arising from the nerve roots of C1 and C2 (haematoxylin and eosin × 100).

Fig. 10. Case 8. Section of the spinal cord at the C2 to C3 level just below the site of maximum compression by the schwannoma and the atlanto-axial dislocation.

a) A slightly gliosed but still vascularised region in the deeper part of the 2 posterior columns, possibly representing healing in an area of necrosis (PTAH x 40). b) Glial cell proliferation amidst the remaining shrunken anterior horn cells on one side of the same segment (haematoxylin and eosin x 100).

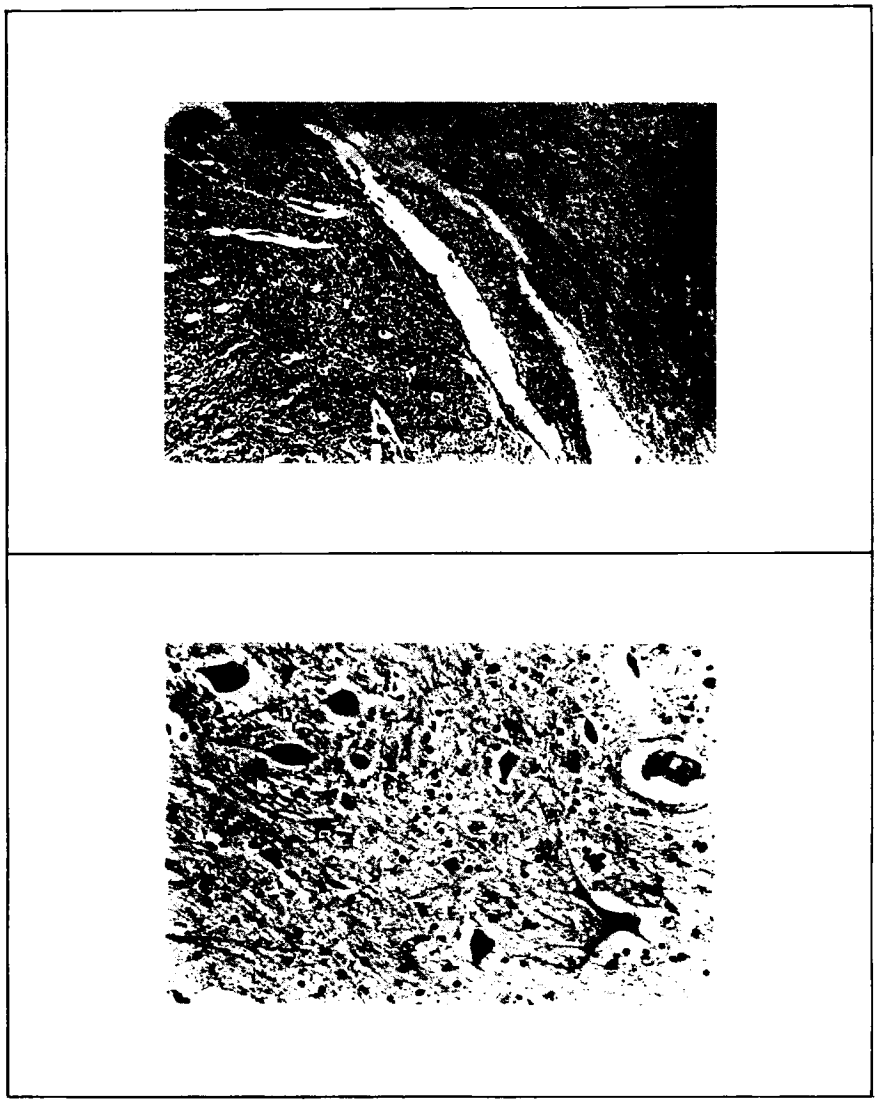

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Fig. 11. Case 9. The necropsy specimen in this case confirmed pressure by the odontoid involving the lower medulla and the C1 cord segment. The posterolateral portion of the spinal cord at about C3 level is shown, with the pale demyelinated lateral column on one side, the better myelinated posterior column on the other and the posterior horn region in the centre. Note the thin gliotic band of tissue in a cavity representing the posterior horn region (Kluver-Barrera x 40).

Fig. 12. Case 9. Lower cervical cord segment showing part of one anterior horn. Note the general depletion of anterior horn cells and the shrinkage and chromatolysis of the remainder (haematoxylin and eosin x 250).

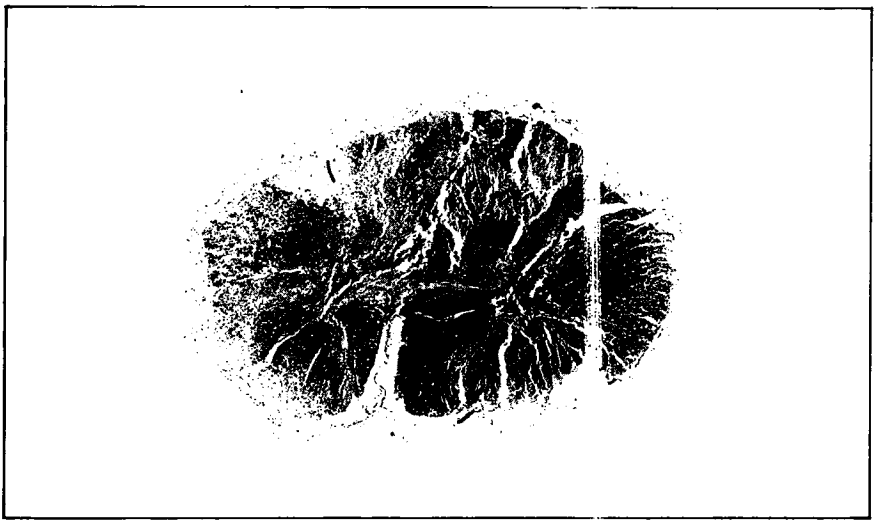

Fig. 13. Case 10. This patient had a detached type of odontoid, and more weakness and spasticity on one side than on the other. The upper level of the cervical spinal cord is shown (Marchi stain × 12). Crossed and uncrossed pyramidal fibres are degenerated.

myelopathy of the upper cervical cord due to congenital atlanto-axial dislocation, and sudden haematomyelia and respiratory arrest developing at open surgery for release of pressure on the medullospinal tissues, or as a postoperative catastrophe.

Necropsy and histological examination confirmed that the neuropathological substrate of intermittent or progressive quadriplegia and sensory changes (mainly deep sensory loss) was degeneration of the lateral and posterior columns. Loss of anterior horn cells of the lower cervical and upper dorsal cord led to weakness of hand and arm muscles. Acute paracentral haemorrhages occurring at the C1 to C2 or medullospinal level, in the territory of distribution of the sulcal branches of the spinal artery (due to sudden release of pressure at operation) were responsible for postoperative paralysis and sensory loss below C2 segment.

In terms of the bony anomaly (dissected at necropsy), the cases fell into 2 subgroups:

a) The majority with the odontoid attached to the body of the axis, but short and ill developed, at times accompanied by other bony anomalies and a poorly formed transverse ligament. This tended to produce a fixed type of dislocation with a higher level (medullospinal) and more severe compression of the CNS.

b) Fewer cases with a well formed but detached odontoid, producing a less severe myelopathy at a lower level (C1-C2), and generally more readily reducible on extension.

Acknowledgements

Grateful acknowledgement is due to the clinicians who referred the cases, notably Dr N.H. Wadia, Honorary Professor of Neurology, and Drs G. Sinh, H.M. Dastur and S.N. Bhagwati, Honorary Professors of Neurosurgery; and to Dr J.N. Sidhwa, Honorary Professor of Radiology, in Bombay. Special thanks are due to Dr Marion Smith of the MRC Research Unit at the Institute of Neurology, Queens Square, London, for the Marchi preparations of the spinal cord. It is a pleasure to thank Dr S.K. Pandya, Professor of Neurosurgery, for his excellent case notes when he was Registrar. Acknowledgement is due to Mr V. Talwadkar, Mr V.P. Kate, and Miss N. Patkar for the histologic technical assistance, and to Mr N. Solanki for photographic assistance.

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Thoracic Outlet Syndrome Secondary to Childhood Poliomyelitis

*N.W. Knuckey and S.S. Gubbay**

The syndrome of neurovascular compression was first described by Wellshire (1860) in patients with cervical ribs. However, Ochsner et al. (1935) described the syndrome in patients without cervical ribs and coined the term 'scalenus anticus syndrome'. Since this time many authors have implicated different aetiological factors, including sagging shoulders (Ochsner et al., 1935; Bertelsen, 1969), costoclavicular space compression (Falconer et al., 1943) and hyperabduction (Wright, 1945). It was not until 1958 that Rob and Standeven suggested the term 'thoracic outlet syndrome' to encompass all these aetiological factors. The following 2 case reports are of patients with thoracic outlet syndrome which appears to be secondary to inadequate support of the shoulder girdle, resulting from muscle weakness caused by childhood poliomyelitis. This association has not been recorded previously.

Case Reports

Case 1

A 26-year-old housewife was troubled by aching in the right upper limb and thoracic spinal area for 18 months, numbness in the right little finger for 6 months and weakness of the right hand for 3 months. Occasionally the right arm was discoloured and colder than the left. She had suffered from severe acute anterior poliomyelitis which had affected her right shoulder girdle and other muscles at the age of 6 months.

Physical examination revealed mild underdevelopment and wasting of the whole of the right upper limb and shoulder girdle, but mostly of the intrinsic muscles of the right hand. The right upper limb was

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hypotonic and hyporeflexic. She had mild impairment of pinprick and vibration sensation in the right little finger. There was tenderness and a systolic bruit in the right supraclavicular fossa.

Cervical and chest radiographs showed no evidence of cervical ribs. The electromyogram showed evidence of widespread, chronic partial denervation in the right upper limb but the ulnar nerve motor and sensory conduction estimations were normal. In January 1977, anterior scalenotomy was performed, from which she had an excellent sustained result, including disappearance of the systolic bruit.

Case 2

A 32-year-old Malaysian housewife had severe acute poliomyelitis at 3 years of age. For 5 years she had numbness in the medial 2 digits of the left hand eased by lying on her left side in bed. More recently there had been left neck and scapular pain.

General examination revealed an accentuated cervical lordosis together with an obvious thoracic kyphoscoliosis presumably due to old poliomyelitis. There was moderate bilateral sternomastoid and left shoulder girdle muscle weakness, and some winging of the right scapula. There was depression of the left triceps jerk, but sensation was normal. She was tender in the left supraclavicular fossa but there was no local bruit or vascular change in the arm.

Radiographs revealed bilateral cervical ribs and depression of the left shoulder girdle. Electromyography exhibited widespread, chronic partial denervation in the left upper limb muscles, but left ulnar nerve motor and sensory conduction was normal.

Scalenus anterior tendonotomy was performed in November 1975 when it was noted that the scalenus anterior was atrophied. She had a good sustained result. 3 months later when she developed numbness in the right hand a right scalenotomy was performed. At this second operation atrophic sternomastoid and scalenus anterior muscles were also noted. A good sustained result from this operation was obtained.

Discussion

The neurovascular bundle passes from the neck to the upper arm via a cervico-axillary canal which consists of a number of fibro-osseus triangles, the first and most important being the interscalenus triangle. Normally the neurovascular bundle passes free of compression through this triangle, over the first rib between the scalenus anterior and medius. Anatomical alterations may result in compression and increased angulation of the brachial plexus.

Factors other than cervical ribs would also appear to be of importance in neurovascular compression, since not all patients with thoracic outlet syndrome have cervical ribs and not all cervical ribs produce symptoms (Bertelsen, 1969). Jones (1910) showed how the postfixed brachial plexus resulted in increased angulation of the plexus over the first rib. Todd (1912) discussed how in the development of the shoulder girdle, it descends from its high position in childhood to a much lower position in adults. Excessive descent of the shoulders, as with poor muscular support, defective posture or lifting heavy weights, may result in increased compression of the brachial plexus over the first rib. Adson and Coffey (1927) discussed the anatomical importance of the scalenus anterior in the aetiology of the thoracic outlet syndrome. Firstly the scalenus anterior may be important in preventing anterior sliding of the brachial plexus to a lower, less angulated position on the first rib during shoulder

girdle descent, and secondly scalenus anterior hypertrophy may subsequently compress the neurovascular bundle.

Thus it can be appreciated that the aetiology of the thoracic outlet syndrome is multifactorial. The inter-relationships of the factors are shown in figure 1.

In these 2 patients with old poliomyelitis, subsequent depression of the shoulder girdle because of poor muscular support apparently produced brachial plexus compression in the intrascalenus triangle. In addition, the second patient had cervical ribs, which stresses the interaction of many factors in producing the thoracic outlet syndrome. The increased angulation of the brachial plexus contributed to the traumatic brachial neuritis, with subsequent arm pain and paraesthesia. Successful treatment was due to the forward sliding of the neurovascular bundle to a lower position on the first rib following scalenotomy, reducing stress on the brachial plexus.

Summary

2 women with acute anterior poliomyelitis affecting the upper limb girdles in early childhood later developed thoracic outlet syndromes, 1 of them bilaterally. It is thought that the poliomyelitis was a contributory factor in each case by allowing undue descent of the shoulder girdles, although cervical ribs were also present in the second case. This association had not been recorded previously. Both patients obtained

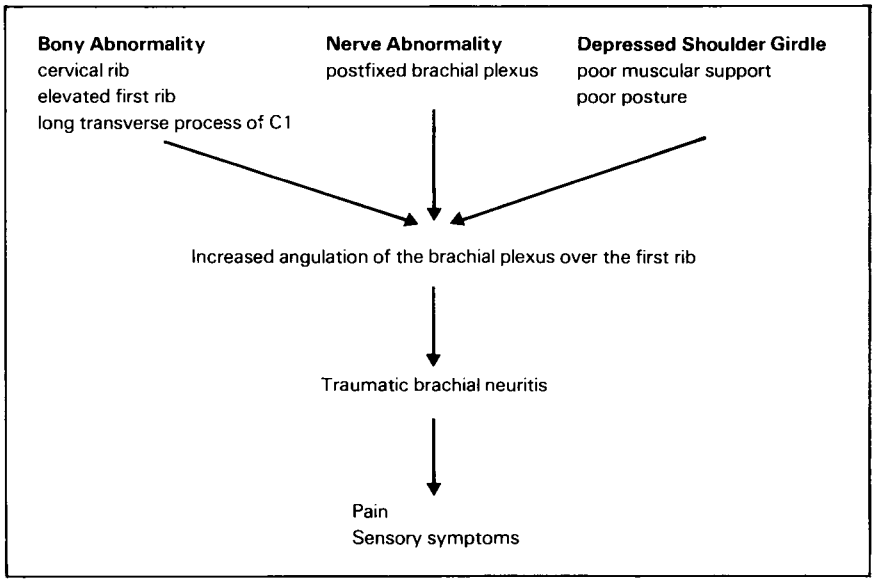

Fig. 1. Aetiological factors in thoracic outlet syndrome.

substantial relief from anterior scalenotomy, indicating that previous involvement of the shoulder girdle by poliomyelitis does not negate the efficacy of this operative procedure.

Acknowledgement

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A Retrospective Study of Carotid Endarterectomy

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

The problem of when to recommend a patient for carotid endarterectomy is not new. It can be a difficult decision and many neurologists and physicians adopt a conservative approach, particularly since the suggestion that simple drugs such as aspirin may be effective in preventing stroke in patients with transient ischaemic attacks. Recent studies provide conflicting evidence as to the efficacy of aspirin in stroke prevention (Fields et al., 1977; Canadian Co-operative Study Group, 1978).

Estimates vary as to the percentage of patients with transient ischaemic attacks who subsequently develop a completed stroke but it is probably at least one-third (Acheson and Hutchinson, 1964; 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 the carotid stenosis, removal of the stenotic lesion could be expected to reduce substantially the risk of future stroke.

The available evidence (Fields et al., 1970) supports the view that, in patients in whom transient ischaemic attacks are likely to be originating from carotid stenosis, endarterectomy reduces the incidence of subsequent 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 the prognosis (Bauer et al., 1969). The expertise of the vascular surgeon undoubtedly influences the outcome, and mortality and morbidity figures associated with carotid endarterectomy vary widely in different centres.

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Table I. Age range of 72 patients who underwent carotid endarterectomy

Age (yrs)	No. of operations
41-50	2
51-60	29
61-70	42
71-80	11
81-90	1

It therefore seemed important to determine our local mortality and morbidity figures for this operation. Because of our impression that many patients with transient ischaemic attacks are treated conservatively we were also interested to know the method of selection of patients for this operation, in particular the indications for the operation, the referral source and the neurological condition of the patients undergoing the procedure.

The records of all public patients submitted to carotid endarterectomy during a 5-year period in the vascular unit at the Princess Alexandra Hospital have been studied retrospectively. At present a similar study is in progress reviewing the records of all public patients submitted to the operation at the Royal Brisbane Hospital during the same period. The ultimate benefit of the procedure in reducing the incidence of stroke cannot be established on the basis of a retrospective study such as this. Therefore no systematic attempt was made to determine the long term result of the procedure.

Methods

Records were studied of all the public patients submitted to carotid endarterectomy at Princess Alexandra Hospital during the 5-year period from 1 July 1973 to 30 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 complete search of the operating theatre books in which all operations performed during the relevant period were noted. The records of 2 patients could not be found. 1 of these was operated on in February 1978 and the surgeon who performed the operation could recall the case. Apparently the operation was performed without mishap and there were no major complications afterwards. The second case was operated on in 1973 and unfortunately no record of the case could be found.

Table II. Number of carotid endarterectomies performed in each 6-month period from 1973 to 1978

6-Month period	No. of operations
July-December 1973	10
January-June 1974	5
July-December 1974	2
January-June 1975	5
July-December 1975	7
January-June 1976	9
July-December 1976	10
January-June 1977	8
July-December 1977	18
January-June 1978	11

Each carotid endarterectomy was performed by 1 of 4 vascular surgeons. In all cases endarterectomy was performed at the bifurcation of the common carotid artery and an atheromatous stenotic lesion — sometimes with associated thrombus — was removed from this region in either internal or common carotid arteries or both.

Results

85 operations were performed on 72 patients. 13 of the patients had bilateral procedures. There were 60 operations performed on males and 25 on females.

In 32 cases the right side was operated on and in 27 the left. Of the 13 bilateral procedures the right side was operated on first in 7. The age range of patients was 49 to 81 years (table I) with most patients being 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 could not be found. Thus the information contained in tables III to VII and in the figures refers to the study of 83 operations on 70 patients.

Table III shows the referral source of the patient. In a number of cases the patient was being seen by the vascular surgeon for another condition when the carotid problem arose. These cases have been grouped in the category of 'vascular surgeon referral'. The remainder of the 11 cases in this category were referred to the hospital from the vascular surgeon's private rooms. 'Other' cases were referred by a cardiac surgeon, a neurosurgeon and the superintendent of a country hospital.

Table III. Source of referral of patients for surgery

Referral source	No. of operations
General practitioner	16
Physician	27
Neurologist	20
Vascular surgeon	11
Ophthalmologist	5
Others	4

Table IV. Major indication for carotid endarterectomy

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

The most frequent indication for surgery was transient ischaemic attacks (table IV), followed closely by incomplete carotid stroke, where the neurological deficit lasted more than 24 hours, and amaurosis fugax. In the 2 cases of completed carotid stroke, endarterectomy was performed within hours after the episode. In 19% of operations the major indication was ischaemia in vertebrobasilar territory. In 13% of operations there were no cerebral ischaemic symptoms. Where a significant stenosis was found on the asymptomatic side at angiography, this was operated on after the symptomatic side had been dealt with, in 6 cases. An asymptomatic carotid stenosis was operated on in 3 cases prior to another vascular procedure — carotico-subclavian bypass graft in 2 and a vascular procedure in the legs in 1 case.

Figure 1 shows how long the indication was present before surgery. (Cases where the carotid stenosis was asymptomatic are naturally not included.) Figure 2

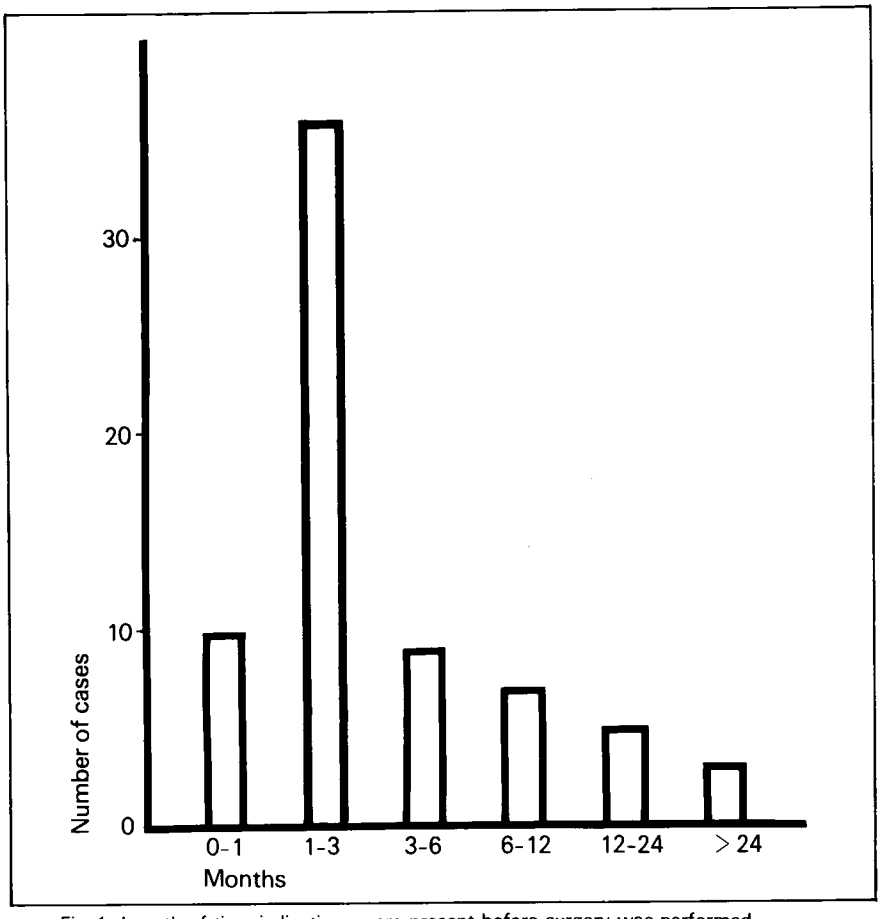

Fig. 1. Length of time indications were present before surgery was performed.

shows the delay from the time of first referral to the hospital to the time of surgery. (Again asymptomatic cases are not included.) More than two-thirds of operations were performed later than 2 weeks after the time of referral. 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. We were not able to tell how many patients developed a completed stroke during their wait for surgery.

Table V shows the neurological status of the patient immediately before surgery.

Of 83 operations, a Javid shunt was used in 49. This allowed circulation through the internal carotid artery from the common carotid artery while the endarterectomy

was being performed. As a general rule, if the 'stump pressure' (i.e. the pressure in the distal stump of the internal carotid artery with common, internal and external carotid arteries clamped) was less than 40mm Hg, then a shunt was used. Sometimes the shunt was not used because of other technical factors (e.g. where exposure was difficult with a high carotid bifurcation). A dacron patch graft was used in only 2 cases and the artery was wrapped in dacron in 1 case.

The complications resulting from the operation are shown in table VI. 1 death occurred in 83 operations. This patient died on the second postoperative day. He was regarded as a poor anaesthetic risk because of diabetes mellitus and chest problems. In addition, he was paraplegic from poliomyelitis at the age of 9 years. He had a severe scoliosis with hip and knee flexion contractures. The indication for operation was a carotid transient ischaemic attack, but the cause of death was not clear from the

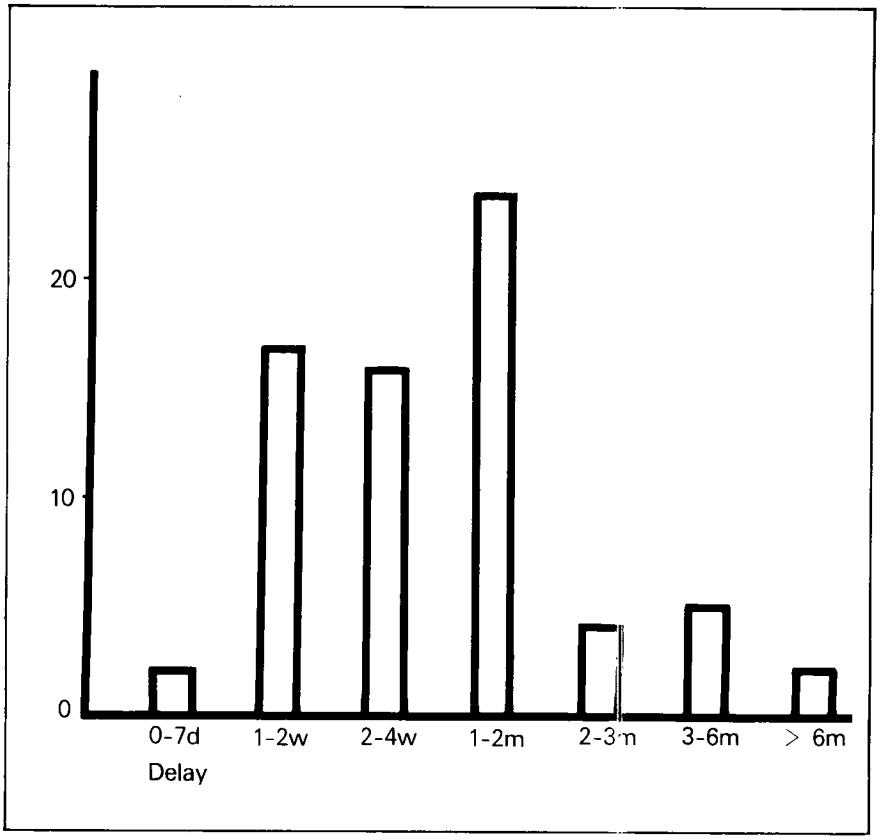

Fig. 2. Delay in days (d) weeks (w) and months (m) from first referral to hospital until endarterectomy was performed.

Table V. Neurological deficit immediately before surgery

Neurological status	No. of operations (%)
No deficit	62 (75)
Minor deficit (mild dysphasia, mild limb weakness)	10 (12)
Moderate deficit (monoparesis, hemiparesis, confusion, mental impairment)	7 (8)
Major deficit (hemiplegia ± aphasia)	2 (2.5)
Uncertain	2 (2.5)

Table VI. Complications resulting from carotid endarterectomy

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

Table VII. Duration of postoperative follow-up periods

Length of follow-up	No. of operations
0-6 months	16
6-12 months	19
1-2 years	20
over 2 years	27

records. The day before death he was noted to have difficulty coughing up sputum. Autopsy revealed pneumonia. There were no problems at the endarterectomy site and the brain was not examined.

There were 3 completed strokes resulting from 83 operations. 2 of these patients were operated on for incomplete carotid stroke, the other for vertebrobasilar insufficiency. 1 of these 3 patients had a mild neurological deficit immediately before surgery. The other 2 had no deficit. 6 cases had minor deficits after surgery (e.g. some weakness of the hand or a worsening of dysphasia) and in 73 cases there was no deficit. Thus in 95% of operations there were no major postoperative neurological problems.

Other complications included a wound haematoma needing to be drained in 4 cases. 1 patient developed cardiac failure following abrupt withdrawal of clonidine preoperatively. Another developed a possible myocardial infarct 4 days after operation. One patient suffered a haemorrhage from a chronic gastric ulcer 2 weeks after operation.

Following angiography before operation there was 1 completed stroke. This patient was operated on some hours afterwards. There was also 1 incomplete stroke following angiography.

The follow-up period varied from 2 weeks to 5.5 years, with a mean of 19.6 months (table VII). Most patients were followed for more than 12 months. There were 24 episodes of further relevant ischaemic attacks, but in 58 cases there were no further episodes during the period of follow-up.

We attempted to decide whether the carotid stenosis could have caused the symptoms that the patients experienced. Admittedly this is a subjective opinion formed from a study of the records of radiological and operative findings, and from whether the patients' symptoms persisted after operation. 71 operations were considered. In the remaining cases there were no symptoms referrable to the carotid stenosis and the operation was performed for an asymptomatic stenosis demonstrated radiologically. We concluded that the carotid stenosis was likely to have caused the symptoms in 51 instances, was unlikely to have caused those of 11 and in 9 cases the relationship was uncertain.

Discussion

It has been stated that the combined surgical mortality and morbidity rates ideally should be reduced to 1 to 2% (Hass, 1972). Therefore the figures presented in this study of 1 death and 3.6% completed stroke rate are not ideal but are acceptable considering the significant reduction in future stroke rate that could be expected.

The question of whether endarterectomy should be performed for asymptomatic bruit has not yet been decided (Fields, 1978; Thompson et al., 1978). Under these circumstances there is a need for careful neurological assessment preoperatively to

determine whether it is likely that the patient's symptoms are related to the carotid stenosis. It seemed unlikely in a number of patients in this series that the carotid stenosis was causing the symptoms, although this is difficult to evaluate because vertebrobasilar symptoms can occur in relation to a carotid stenosis. Closer communication between neurologist and vascular surgeon is therefore desirable in this regard so that a better selection of patients for operation can be achieved.

Another important feature of this study is the delay from the time of initial referral to the time of the operation. Marshall (1964) showed that many of the major strokes in carotid territory occurred within a month of the first transient ischaemic attack. Therefore if an operation is indicated, it should be performed with some urgency. The delays that have been shown make it seem likely that some patients may have developed a completed stroke while waiting for surgery, a situation which would not be evident in this study. Many of the delays are easily overcome. For example, a physician may order a single side carotid angiogram without recognising the importance of having both sides studied. Consultation with the vascular surgeon or neurologist beforehand should prevent this.

It is considered that the mortality and morbidity figures for this operation at Princess Alexandra Hospital are sufficiently low to encourage physicians to refer more cases, particularly those who have transient ischaemic attacks in carotid territory and who have no neurological deficit. It is these patients who have most to benefit.

Summary

85 carotid endarterectomies were performed by the vascular unit at the Princess Alexandra Public Hospital between 1 July 1973 and 30 June 1978. The case histories of the patients undergoing the procedure were studied and the immediate mortality and morbidity associated with the procedure during the period were determined. 1 patient died following the procedure and 3.6 % of operations resulted in a completed stroke. The indication for the operation, the referral source and the neurological condition of the patient undergoing the procedure were categorised in an attempt to determine the factors governing the selection of patients for this procedure. Excluding asymptomatic lesions, more than two-thirds of the operations were performed later than 2 weeks after the time of first referral to the hospital. Half the operations were performed after a delay of more than 1 month.

Acknowledgement

We are grateful to the surgeons of the vascular unit at the Princess Alexandra Hospital for permission to study their cases and also for the help which they have given us.

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The Stroke Syndrome of Long Intraluminal Clot with Incomplete Vessel Obstruction

*G.A. Donnan and P.F. Bladin**

Vascular headache as an accompaniment of transient ischaemic attack and stroke is well recognised, and this was the premonitory symptom in the 3 cases described here. In each case carotidynia or cervical tenderness was a marked clinical feature. The pathological change demonstrated was one of a long clot anchored to an area of atheromatous subintimal haemorrhage, and in spite of the length of the clots there was incomplete vessel obstruction shown angiographically. The recurrent nature of the clinical events may suggest that when complete carotid artery occlusion is prefaced by repeated transient ischaemic attacks, a pathological stage of long intraluminal clot with incomplete vessel obstruction may occur before complete occlusion.

Case Reports

Case 1

A 56-year-old right-handed man had an episode of left motor and sensory paresis of the left arm while nailing his paling fence. This lasted for a period of 10 minutes and was associated with an episode of right amaurosis fugax for a similar length of time. The next day, he noted a sudden onset of dull right cervical pain in the region of the carotid artery and radiating to his right ear. The pain lasted for much of that day and persisted until 7 days later when a further episode of left arm paresis occurred and the cervical pain worsened. After admission to hospital, he experienced recurrent episodes of paralysis of the left limbs and lower part of the face in spite of intravenous infusion of heparin. His history included hypertension for the preceding 6 months, and femoral reconstructive surgery which had been undertaken in 1966 and 1978.

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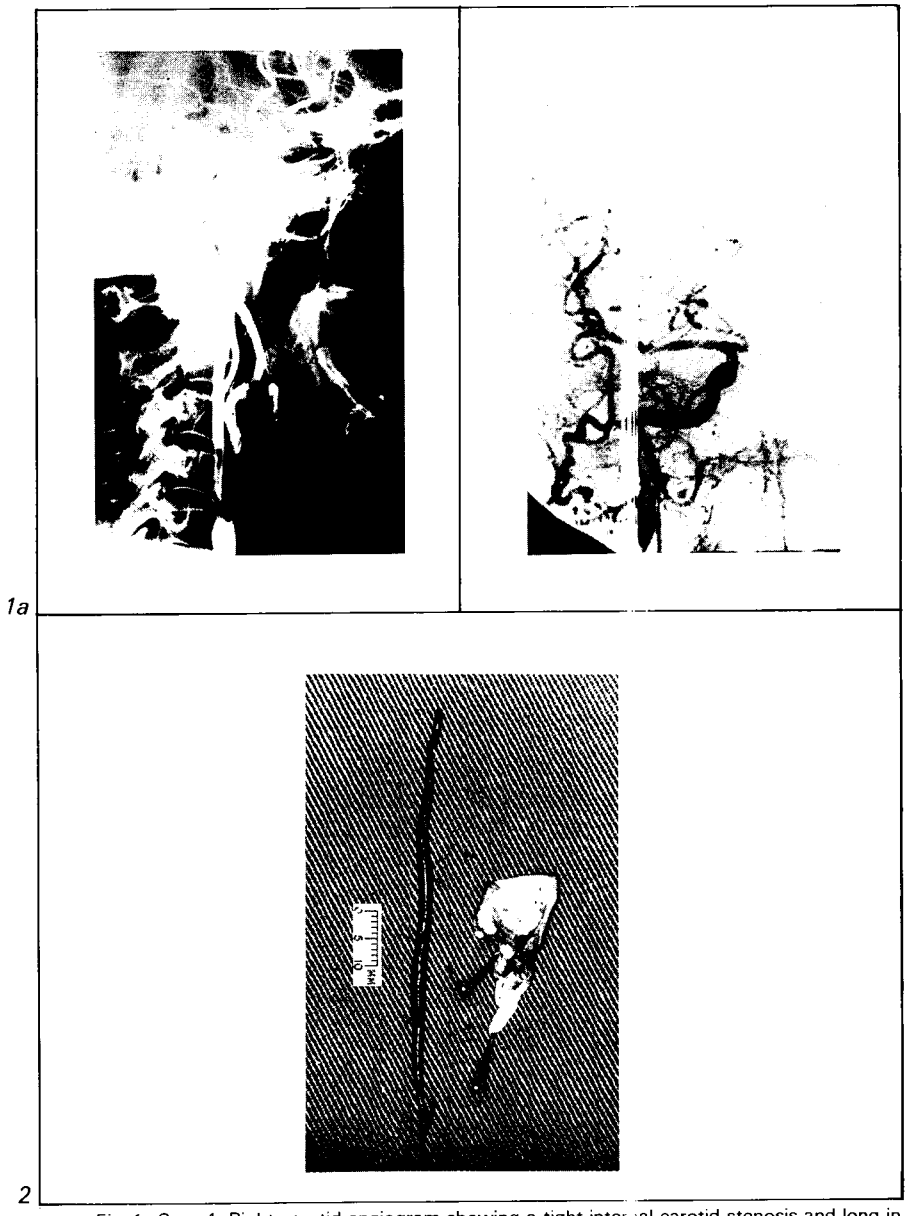

Fig. 1. Case 1. Right carotid angiogram showing a tight internal carotid stenosis and long intraluminal clot (a) with incomplete vessel obstruction to the level of the carotid syphon (b).

Fig. 2. Case 1. Pathological specimen of long intraluminal clot after surgical removal with adjacent internal carotid atheroma and sub-intimal haemorrhage.

Examination revealed mild hypertension (170/100mm Hg) and a radial pulse rate of 75/min with regular rhythm. He was markedly neglectful of his left side with normal visual fields, a marked left parietal drift and a mild paresis of the left limbs and lower face. The left plantar response was extensor and the deep reflexes were brisk and equal. There were no carotid bruits, but marked tenderness was present over the right carotid artery.

Immediate carotid angiography revealed a tight stenosis of the right internal carotid origin with a long intracarotid thrombus extending up to the level of the carotid syphon (fig. 1). Good cross filling of the right middle cerebral artery from the left circulation and a mild stenosis of the left internal carotid artery were found on left carotid angiography.

Immediate exploration of the right internal carotid confirmed the presence of a tight stenosis caused by an area of subintimal haemorrhage. Attached to this was a 10cm length of thrombus which was easily removed (fig. 2). An operative angiogram revealed subsequent vessel patency.

Postoperative recovery was excellent, with increased clarity of thought, although neuropsychological testing demonstrated severe right hemisphere dysfunction in spite of a normal CAT scan. An ECG showed nonspecific ischaemic changes. The lipid profile and ESR were within normal limits.

Case 2

A 52-year-old seaman with a history of hypertension for the preceding 6 months was disturbed by the sudden onset at 11 am of right facial pain extending from above the eyebrow to the lower jaw and into

Fig. 3. Case 2. Right carotid angiogram. Loose thrombus can be seen outlined above the area of internal carotid stenosis.

the right ear. Concurrently an episode of right amaurosis fugax lasting for 2 minutes occurred. The next morning he awoke to find that he had developed a mild paresis and numbness of the left upper limb. This progressed over the next 3 hours to result in paralysis of the left upper limb and partial weakness in the left lower limb causing him to limp. There was no facial involvement.

Examination 12 hours later showed the paresis to be improved, so that he was able to lift his left upper limb against gravity. There was also left visual and sensory neglect. There was marked tenderness over the region of the right carotid artery but no bruits were heard. The blood pressure was 130/90mm Hg and the radial pulse was 70/min with regular rhythm. 4 hours later his left arm again became paralysed.

Immediate angiography revealed an almost complete occlusion of the right internal carotid artery with evidence of a long intraluminal clot extending to the level of the carotid syphon (fig. 3). There was no filling of the middle cerebral artery. The left carotid system was normal.

Exploration of the right internal carotid artery revealed a tight stenosis at its origin due to subintimal haemorrhage. An 18cm thrombosis attached to this was easily extracted. Postoperative recovery was good except for some transient increase in left lower limb weakness, which improved within 24 hours. Within 1 month, the patient was able to walk with a limp, but his right upper limb remained paresed. CAT scan showed a right cortical infarct in the parieto-temporal region while the EEG showed some increase in slow activity over the right temporal regions. The lipid profile, ESR and ECG were within normal limits.

Case 3

A 33-year-old man with a history of excessive alcohol intake had been suffering from nonspecific frontal headaches and right anterior cervical pain for 3 weeks. On the day of admission the headache became localised to the right retro-orbital region with extension to the right ear and upper neck. This was associated with the onset of nausea, vomiting and vertigo, with ataxia to the right on standing.

After the patient was admitted to hospital, examination revealed signs of a right lateral medullary syndrome: nystagmus to the right, loss of right facial sensation, diminished right corneal reflex, and crossed thermo-analgesic loss to the left side of the body. There was marked cerebellar incoordination of right upper and lower limbs. The reflexes were equal and brisk, and both plantar responses were flexor. No bruits were audible. The blood pressure was 130/90mm Hg and the radial pulse 70/min with regular rhythm. 24 hours later weakness developed in the left leg and the left plantar response became extensor.

Vertebral angiography performed on the same day revealed an almost complete occlusion of the right vertebral artery with a long clot extending from the origin of the vessel up to the origin of the right posterior inferior cerebellar artery (fig. 4). Urgent right vertebral artery exploration was performed and a tight vertebral stenosis at the vertebral origin due to an area of subintimal haemorrhage was revealed. An attached 18cm thrombus was easily removed. The subsequent course was uneventful although some right-sided headache persisted in the week subsequent to the operation. 1 month after this event, there was evidence of only mild ataxia to the right and considerable diminution of the signs of the lateral medullary syndrome.

Discussion

Carotidynia was originally described by Fay in 1927. Since then sporadic reports have linked this syndrome with migraine (Hilger, 1949; Davies, 1961). Other conditions such as localised arteritis (Pearse and Hinshaw, 1956) or fibrosis of carotid sheath (Campbell and Evans, 1953) should also be considered. Cervical neck pain is also a feature of spontaneous dissection of carotid and vertebral arteries (Bladin, 1974), as is complete occlusion of the internal carotid artery. Theories which have been proposed to explain the presence of headache or cervical pain in complete occlu-

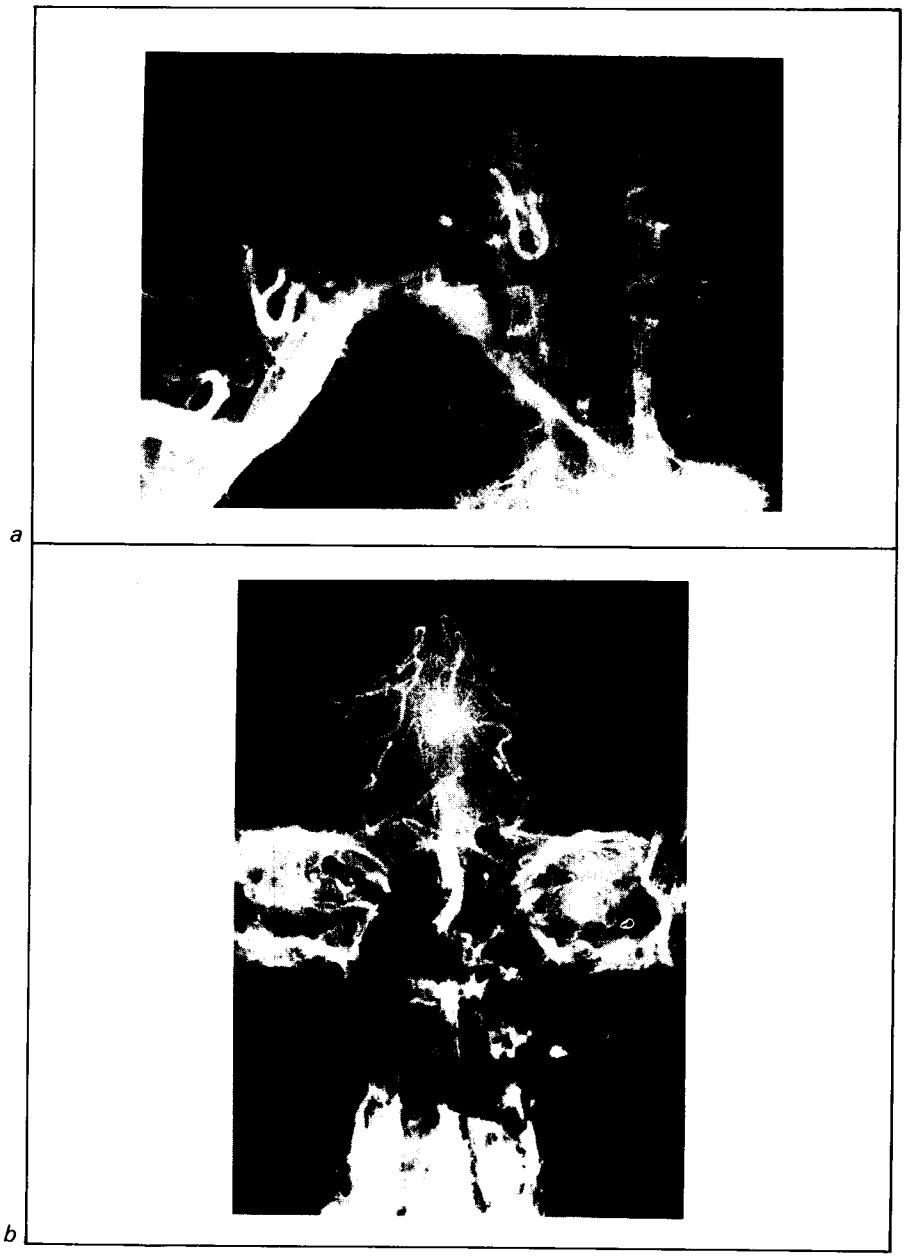

Fig. 4. Case 3. Right vertebral angiogram. Insinuation of dye around the lower regions of the long intraluminal clot can be seen (a). Upper region of clot ends near the origin of the right posterior inferior cerebellar artery (b).

sion of the carotid artery were recently reviewed (Fisher, 1968) and involved localised inflammation of the wall of the pain-sensitive carotid artery, localised dilation of collateral channels, or the direct effect of tissue ischaemia. From the original work of Fay (1932) it is known that stimulation of certain areas around the carotid bifurcation may produce referred headache. It is also known that endarterectomy in the region of the carotid sinus may result in headache. Hence local vascular trauma induced by subintimal haemorrhage in our cases may similarly have produced carotid tenderness and headache. Other likely mechanisms are the release of local vasoactive substances acting both locally at the site of partial arterial obstruction and distally to produce ipsilateral headache, as well as distention of the pain-sensitive carotid sheath secondary to the partial obstruction of blood flow.

The recurrence of clinical events in our cases may have resulted from an intermittent valve-like effect of the long clot. The possibility that this intervening pathological phase occurs in many cases of carotid occlusion must be considered. Repeated embolisation from the distal end of the long clot as an aetiological factor cannot be excluded, although this was not seen angiographically by demonstration of occlusion of distant intracerebral vessels.

The pathophysiology of the clot formation may have involved a sudden uplifting of a 'raft' of atheroma by an episode of subintimal haemorrhage. This may have acted as an anchor point as the clot propagated. The clot may then have grown to its ultimate length of 10 to 20cm rather than breaking off to produce an embolus. We feel that further recognition of this interesting stroke syndrome may help to establish its clinical features and pathophysiological basis.

Summary

A stroke syndrome is described in 3 patients where long intraluminal clot formation with incomplete vessel obstruction was seen angiographically. The vessels involved in 2 cases were carotid arteries and in the third a vertebral artery. This intervening phase of long clot formation may be a feature of many cases of complete vessel occlusion. The common features of the syndrome were vessel tenderness (carotidynia in 2 cases, and vertebral artery tenderness in the third), vascular headache, the presence of subintimal haemorrhage as an anchor point for the clot, and the recurrence of clinical events. Surgical removal of these clots was successfully undertaken in each case at the acute stage.

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Mr John Royle and Mr Andrew Roberts successfully operated on these patients.

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Neuromyotonia in the Spinal Form of Charcot-Marie-Tooth Disease

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The term neuromyotonia has been applied to delay in muscular relaxation after voluntary contraction, when this phenomenon results from disorder of peripheral nerve rather than muscle membrane. Other features of neural hyperexcitability seen in association with neuromyotonia are muscular fibrillation, fasciculation and myokymia (the asynchronous contraction of a number of motor units giving rise to undulation of the muscle belly). In contrast to true myotonia, neuromyotonia is abolished by the systemic or local administration of curare.

Neuromyotonia has been described in patients with peripheral neuropathy, heredofamilial and sporadic, as well as in others who were not considered to have a peripheral neuropathy in spite of the fact that distal weakness and absent tendon jerks were recorded in many of the case reports. The literature has been reviewed by Welch et al. (1972) and Lance et al. (1979).

Among the descriptions of patients with neuromyotonia in conjunction with peripheral neuropathy, the distribution of wasting and weakness resembled that of Charcot-Marie-Tooth disease in 7 patients: 2 brothers reported by Grund in 1911 and 1938 [summarised in English by Claes (1966)], 2 unrelated patients described by Gamstorp and Wohlfart (1959), 1 patient reported by Wettstein et al. (1977), and 2 siblings investigated by the present authors (Lance et al., 1979).

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We have recently encountered another family in which 8 members of 3 generations (denoted I, II and III) have distal wasting and weakness resembling that of Charcot-Marie-Tooth disease. One member (III.4 in figure 1) had been reported by McLeod and Prineas (1971) as an example of the spinal form of Charcot-Marie-Tooth disease or 'distal type of chronic spinal atrophy'. He subsequently developed pseudomyotonia and myokymia which led him to seek further advice. Examination of this patient and his relatives inspired the present report concerning evidence of neuronal hyperexcitability in this familial neuropathy.

Case Reports

The family tree is shown in figure 1.

Case 1.5

Between the ages of 20 and 30 years, this man was noted to be walking with heavy steps. When he was in his 30's, his forearms and legs became very thin so that he needed a walking stick to assist him. He was confined to a wheelchair for the last 16 years of life, eventually being unable to turn the pages of a book or drink a glass of water before his death at the age of 62 years.

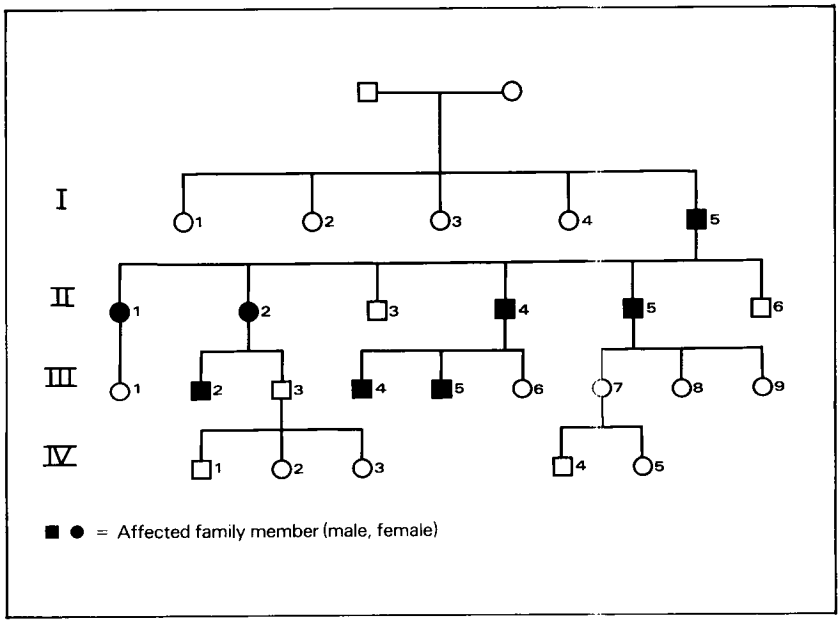

Fig. 1. Pedigree of family with the spinal form of Charcot-Marie-Tooth disease affecting 3 generations (I, II, III).

Case II.1

This woman, aged 73 years, had been unable to rise from a low chair since she was 40 years old. She had found progressive difficulty in climbing stairs and was eventually unable to walk more than a block without her legs 'feeling like jelly'. In her 50's, she became aware of twitching in her thighs and calves following exertion, and cramps in these muscles at night. She had not experienced sensory or bladder disturbance. In her 40's she had developed rheumatoid arthritis affecting her hands.

On examination it was found she had deformity of the fingers with ulnar deviation caused by rheumatoid arthritis, which confused assessment of the slight wasting and weakness observed in the small muscles of her hands. Wasting was not apparent in her lower limbs because of obesity but there was weakness of hip flexors more than extensors, knee flexors more than extensors, with severe weakness of dorsiflexors and plantar-flexors of the ankles. The knee jerks were reduced to a flicker and ankle jerks were absent. Plantar responses were flexor. There was no pes cavus. After contraction of the quadriceps and thigh adductors, myokymia was seen in these muscles for some minutes. She stated that her muscular cramps were followed by the same type of muscular twitching.

Case II.2

This was a woman aged 70 years. She could recall that cramps in the muscles of her calves, thighs and hands began to trouble her when she was about 20 years old. From this time she developed an odd jerky gait similar to her father's. For the previous 6 years she had noticed muscular twitching and found that the muscles of her hand went into spasm when she was engaged in fine movements such as sewing, so that the fingers of her right hand twisted over one another, forcing her to pull them apart with her other hand. At other times she had no difficulty in relaxing her grasp. She had suffered from rheumatoid arthritis in her hands since the age of 50.

Examination revealed that she had swelling and deformity of her hands without weakness of the small muscles. There was wasting of the distal third of her thighs and of the legs. The distribution of weakness was the same as that of her sister (Case II.1). After she contracted her thigh muscles, coarse undulating movements of the quadriceps muscles continued for several minutes after she attempted to relax. Her ankle jerks were absent and plantar responses flexor. Pes cavus was not present and there was no sensory loss. Percussion myotonia could not be demonstrated.

Case II.4

This man developed weakness of the legs with frequent cramps in the calves and feet at the age of 35 years. His gait was peculiar — 'like his father'. He was examined by McLeod and Prineas (1971) when he was 55 years old and found to have wasting of the muscles of the calf and of the anterior tibial compartment. Tendon reflexes were absent in the lower limbs. There was no sensory loss or pes cavus. He died of a cardiac arrest at the age of 62 years.

Case II.5

The twin brother of Case II.4, this man was examined at the age of 63 years. He had been a good sportsman in his youth and did not limp until he was 40 years old. Between the ages of 40 and 50 years he had become subject to night cramps and twitching in the calves. Muscular twitching had also been noticed in his forearms over the previous 10 years. If he plantar-flexed his foot firmly at any time, he experienced a painful cramp in the calf.

On examination it was found that he had slight wasting of the first dorsal interosseus muscles and severe wasting below the knees. Fasciculations and myokymia were seen in the quadriceps, hamstrings and calf muscles. His ankle jerks were absent. There was no sensory loss and the appearance of the feet was normal. 2 of his children (III.7, 8) and grandchildren (IV.4, 5) were examined and found to be completely normal.

Case III.2

This man, aged 41 years, was known to have had weakness and cramps of the legs since the age of 30, but had not been examined. He walked flat-footed and was unable to mount a horse without assistance, but was still very active.

Case III.4

This was a man aged 32 years, who was an athlete at school. At the age of 16, he noticed that he ran more on his heels than his toes and, by the time he was 20 years old, he gave up football because he could not run fast enough. Over the next 2 years, weakness of his legs progressed and then remained stationary for about 8 years before his power again deteriorated over a period of 2 years. His grasp was impaired, particularly in cold weather. For the previous year his condition appeared to have stabilised once again.

Since the age of 28, he had noticed that his biceps and hand muscles 'went into a spasm' after voluntary contraction. As this involuntary contraction subsided, he observed twitching of the muscles in his upper arms and at the base of his thumbs. The tendency to spasm or cramp of these muscles was worse in cold weather.

Examination showed that he had slight wasting of the small muscles of the hands and gross wasting of the legs and distal thirds of the thighs. His feet were of normal appearance. There was slight weakness of biceps, triceps and finger abductors, with severe weakness of the thenar muscles. Hip flexors were weaker than extensors and both extensors and flexors of the knees were moderately affected while there was no discernible contraction in the dorsiflexors and plantar-flexors of the ankle. The knee jerks were reduced to a flicker. The ankle jerks and plantar responses were absent. No sensory loss could be detected. After voluntary contraction of biceps and triceps muscles ceased, an involuntary contraction continued for 10 to 30 seconds, accompanied by myokymia and fasciculations. No after-contraction was observed in the quadriceps muscles although fasciculations were conspicuous. There was no percussion myotonia, Chvostek's sign or Trousseau's sign.

Case III.5

A man, aged 31 years, first noticed weakness of the calves and cramps in the hamstring muscles when he was 26 years old. On examination, the bulk of the quadriceps muscles was seen to be well preserved but myokymia and fasciculations were observed intermittently in these muscles, becoming continuous after voluntary contraction. Muscle bulk was lost on both sides below the knees. There was weakness of the dorsiflexors of both ankles, more on the right side, and of the plantar-flexors, more on the left side. Ankle jerks were reduced to a flicker. There was no sensory loss. The feet assumed the position of partial pes cavus with a high arch and extension of the proximal phalanx of the great toe.

Investigations

Electromyography, nerve conduction studies and sural nerve biopsy were undertaken in patient III.4 in 1969 before neuromyotonia was apparent, and again in 1978 when after-contraction and muscle fasciculations had been present for 4 years. The EMG results may be summarised by stating that signs of denervation were present on both occasions. During the 1978 examination, fasciculation potentials were present at rest in all muscles, increased after voluntary contraction, and occasional fibrillations and positive sharp waves were also noted. After maximal contraction of the biceps with the elbow flexed, motor units discharged spontaneously at 30 to 50 Hz while the muscle was visibly contracting, subsiding over 20 to 30 seconds into sporadic fasciculations as the muscle relaxed.

Motor and sensory conduction studies were normal in 1969, as was sensory conduction in 1978. There was slight impairment of motor conduction in the more recent study, the conduction velocity of the posterior tibial nerve being reduced to 36.6m/sec (normal >40m/sec) with a terminal latency of 7.6msec (normal <6.2msec). The findings were those of a purely motor neuropathy, consistent with a chronic spinal atrophy, with evidence of neural hyperexcitability (neuromyotonia).

Sural nerve biopsies in 1969 and 1978 showed no abnormality on light microscopy, including the examination of teased fibres. Electron microscopy in 1978 showed a slight increase in collagen pockets which was not present in the 1969 biopsy. This change is one which appears with age (Ochoa and Mair, 1969) and was not considered to be abnormal.

Electromyography of Cases II.2, II.5 and III.5 showed the changes of chronic partial denervation with spontaneous fibrillations and fasciculations (sometimes multiple, associated with myokymia) without evidence of peripheral nerve involvement. Conduction velocities and amplitudes in the sural, posterior tibial and median nerves were normal.

Response to Therapy

In patient III.4, muscular spasm (pseudomyotonia) was completely abolished by the oral administration of carbamazepine 200mg twice daily.

Discussion

Of the 5 patients with the spinal form of Charcot-Marie-Tooth disease who were examined, 3 had fasciculations and post-contraction myokymia, and 2 (Cases II.2 and III.4) had, in addition, pseudomyotonia. Table I shows the age at onset of manifestations in the 8 patients.

In 2 papers, published 27 years apart in 1911 and 1938, Grund described 2 brothers with painful cramps in the hands and calves, delay in relaxation of the grasp and wasting of the hands (Claes, 1966). Although the patients had sensory disturbance and tendon reflexes were absent, suggesting a peripheral neuropathy, Grund considered that the condition was a variant of dystrophia myotonica. Gamstorp and Wohlfart (1959) reported 3 patients with neuromyotonia, 2 of whom had the distribution of wasting associated with Charcot-Marie-Tooth disease. The first of these noticed muscular stiffness and myokymia at the age of 12 years and the second patient had bilateral footdrop by the age of 5 years, and found difficulty in relaxing his grasp later during childhood. The father of the second patient suffered from 'excavated feet and deformed toes' and had thin legs but no myotonia. The condition ceased to progress at the ages of 27 years and 10 years respectively. Muscle biopsies showed nonspecific atrophic changes; nerve conduction studies were not reported. The

Table I. Approximate age at onset of manifestations in a family with the spinal form of Charcot-Marie-Tooth disease

Case no.	Age (yrs)	Age at onset (yrs)			
		weakness	cramps	myokymia	pseudo-myotonia
I.5	62[1]	20	—	—	—
II.1	73	40	50	50	none
II.2	70	20	20	64	64
II.4	62[1]	35	35	—	—
II.5	63	40	45	45	none
III.2	41	30	30	—	—
III.4	32	16	28	28	28
III.5	31	26	26	26	none

1 Age at death.

present authors described 2 siblings of 25 and 29 years of age with a neuropathy indistinguishable clinically from Charcot-Marie-Tooth disease, in whom neuromyotonia became apparent at the ages of 12 and 13 years respectively. Sural nerve biopsy revealed changes of axonal degeneration involving myelinated and unmyelinated fibres while microneuronographic recordings showed that sensory as well as motor fibres were hyperexcitable (Lance et al., 1979). The association of neuromyotonia with an hereditary neuropathy without the features of Charcot-Marie-Tooth disease has been recorded by Sigwald et al. (1966) and Avanzini et al. (1969). Cases II.2 and III.4 thus appear to be the eighth and ninth patients described in whom pseudomyotonia has been a manifestation of Charcot-Marie-Tooth disease, although the fact that 4 such patients in 2 families have been seen by the present authors suggests that the association may be more common than previously supposed. The occurence of fasciculations and myokymia in other members of the present family suggests that neural hyperexictability short of pseudomyotonia may be even more common. Dyck (1975) has remarked that muscle cramps are a common feature of the hypertrophic form of Charcot-Marie-Tooth disease, and has also noted their presence in cases with the neuronal form. Attention to the nature of such cramps may well disclose other cases of neuromyotonia.

The EMG and histological findings in the present patients indicate that the disorder is the spinal form of Charcot-Marie-Tooth disease, whereas our previous patients (Lance et al., 1979) showed the features of the axonal (neuronal) form. The only other detailed histological report of a nerve biopsy in neuromyotonia was that of Welch et al. (1972) who reported changes of segmental demyelination in a sporadic

case. However, in this report, the authors did not indicate the percentage of fibres showing segmental demyelination, and indeed, stated that the majority of fibres were normal and that some myelin ovoids were found. The muscle biopsy contained small angular fibres, consistent with denervation. Motor conduction velocities were normal. Thus, the evidence for a significant degree of segmental demyelination in this case is not strong. Whether segmental demyelination can result in neuromyotonia remains to be established.

The molecular changes responsible for the neural hyperexcitability are unknown, but there is ample evidence that the spontaneous impulses may arise anywhere along the course of the motor axon from anterior horn cell to nerve terminal. The response of neuromyotonia to carbamazepine, which has been noted previously (Bady et al., 1969), can be explained by the action of this drug on peripheral nerve. In the rabbit, the intravenous injection of carbamazepine 20mg/kg in divided doses at 30-minute intervals (Krupp, 1969), decreases conduction velocity in the sciatic nerve, reduces the amplitude of the nerve action potential and therefore presumably diminishes the tendency to spontaneous discharge.

Summary

The term neuromyotonia has been applied to spontaneous activity of peripheral motor nerves which gives rise to pseudomyotonia, muscular fasciculations and myokymia.

A family is described in which 8 members of 3 generations suffer from the spinal form of Charcot-Marie-Tooth disease (distal type of chronic spinal atrophy). 5 of the 8 members were examined and found to have myokymia, accentuated by voluntary muscle contraction. Pseudomyotonia was present in 2 patients and, in the 1 patient treated, was abolished by carbamazepine. The association between neuromyotonia and Charcot-Marie-Tooth disease has been reported in only 7 patients before but may be more common than previously thought because muscle cramps are reported to be a feature of this disorder.

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Contribution of Single Motor Units to the Surface Electromyogram

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McComas (1977) has put forward a neurophysiological method for the estimation of the number of motor units in human muscle. The method involves placing a recording surface electrode over the end-plate region of the muscle in question; this ensures diphasic recordings of motor units. If the relevant peripheral nerve close to the muscle is stimulated, latency variations will be small, and there will be simple algebraic summation of the maxima and minima of the motor unit potentials recorded at the surface. One then takes measurements from 2 procedures:

1) The peripheral nerve is sufficiently stimulated to give a maximal contraction and, of course, a maximal surface electromyogram (EMG). The peak-to-peak voltage of this maximal EMG is measured.

2) The peripheral nerve is then stimulated around threshold. The surface EMG varies in discrete steps as individual motor units are recruited or dropped. The peak-to-peak amplitude changes are measured for each unit that can be distinguished, and thus an estimate of the mean amplitude of single motor units in the muscle is reached. Finally, the maximal EMG amplitude is divided by this mean single-unit amplitude to obtain an estimate of the number of motor units present.

We wish to concentrate on 2 of the assumptions of this method, both discussed by McComas:

1) That the motor units recruited at and just above threshold are typical, in their contribution to the amplitude of the EMG, of all motor units in the muscle

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2) That the latency from peripheral nerve stimulation to surface EMG is sufficiently constant throughout all motor units to justify the assumption of simple summation.

We have attempted a test of the first point by recording, during a voluntary contraction of the muscle, both the discharge of a single motor unit in the muscle with a needle electrode, and the continuing surface EMG of the muscle. The discharge of the motor unit is then used to initiate averaging of the surface EMG, both before and after the discharge of the unit. In this way, it is possible to measure the contribution to the surface EMG of individual motor units that have been selected by the needle electrode, instead of by nerve stimulation close to threshold.

Our results suggest that the peak-to-peak variability in units contributing to the EMG is much greater than would be estimated from nerve stimulation near

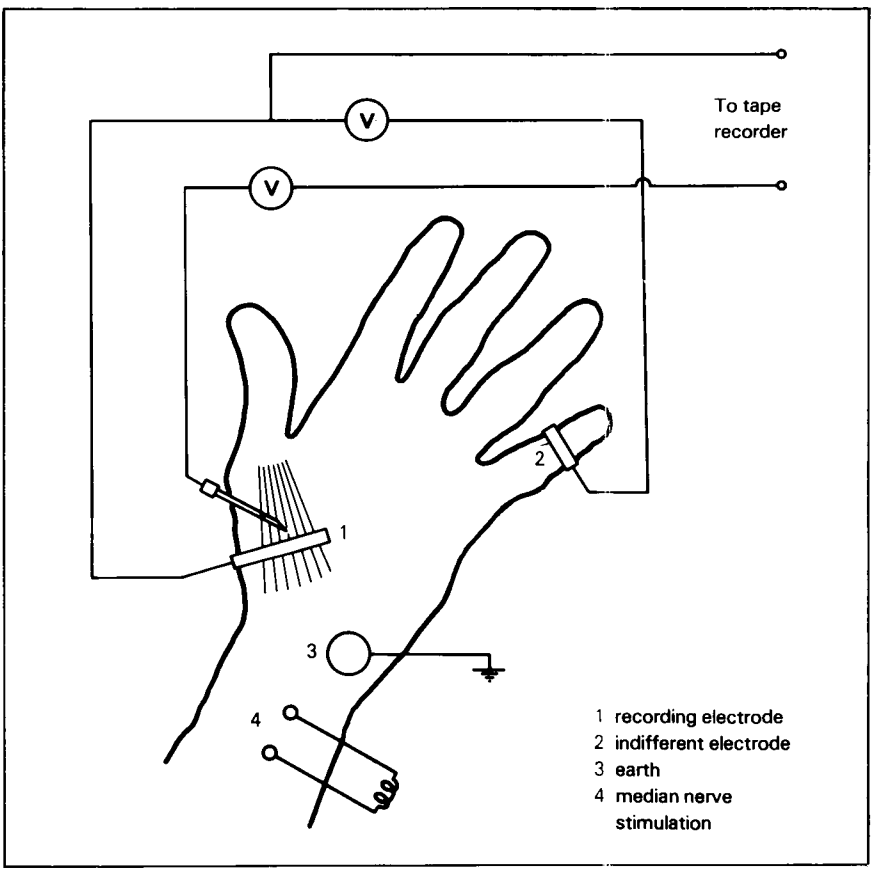


Fig. 1. Diagram of the experimental arrangement of stimulating and recording electrodes.

threshold. This implies that the method could carry a considerable error. Also, simple summation of peaks may not occur because of timing differences in the occurrence of the peaks.

Method

The results reported here are from tests on the abductor pollicis brevis, though we have also used the extensor digitorum brevis and the hypothenar muscles. Figure 1 illustrates the arrangement. The active surface recording electrode was a strip of silver 7cm × 0.8cm placed transversely over the proximal region of the thenar muscles. The indifferent electrode was a similar silver strip wound round the middle phalanx of the little finger. The earth was a disposable silver/silver chloride electrode on the hypothenar eminence. Stimulation of the median nerve at the wrist was via a pair of spherical brass knobs 3mm in diameter, covered with a cloth moistened with 10% sodium chloride.

Skin preparation was by swabbing with chloroform, scrubbing with abrasive soap, and (if necessary) additional abraiding until the inter-electrode resistance was less than 30KΩ. The needle electrode was a Medelec SF25 single fibre needle.

Amplification for both sources was through Isleworth pre-amplifiers with an input resistance of 10MΩ. For the surface EMG, the bandwidth was set at 2Hz to 1kHz, for the needle electrode 200Hz to 5kHz. With subsequent amplification, the signals were stored on a Hewlett-Packard HP3968A tape recorder.

Stimulation was with a Devices Digitimer (1/sec) and associated stimulus isolation unit. Pulse widths of 0.2msec were used, and voltage levels needed for stimulation were in the 10 to 30 volt range.

Finger movement was restrained by a plaster-of-Paris mould which held the fingers extended. The stimulating electrode was immobilised with clamps so that consistent stimulation of the median nerve was obtained.

The measurements, recorded on the tape recorder, fell into 2 groups:

1) Median nerve stimulation around threshold yielded recordings of the surface EMG.

2) Voluntary contraction yielded recordings of single motor unit discharges (with the needle electrode) and of the concomitant surface EMG.

Subsequently, the recordings were transferred to a PDP 11/40 digital computer, using a Laboratory Peripheral System peripheral. For stimulation records, a sampling rate of 10kHz was used for the surface EMG. With voluntary contraction records, the 2 channels were recorded at 5kHz each. In both cases, records of 25msec duration were stored. When stimulating the median nerve, several hundred records of 25msec following the stimulus were stored. For voluntary activity, with discharge of the unit, 200 records of 10msec preceding and 15msec following the discharge were stored.

Subsequent analysis of the records consisted of inspecting individual records (on a Tektronix 611 storage oscilloscope) for classification. Some programs were written to facilitate machine sorting of recordings, but in all cases visual inspection was the final check and ultimate arbiter. Recordings secondary to stimulation were sorted into groups of nil, 1 unit, 2 units, etc., according to the responses in the surface EMG.

The recordings during voluntary contractions were sorted according to presence of a consistent motor unit consistently triggering the averaging of the surface EMGs. This was, in general, a simpler task, though cases did occur with 2 units present, and so 2 averages could be obtained. After sorting, machine computation of averages and the standard deviations was done. Programs were written to permit addition, subtraction and averaging of individual recordings, and the manipulation of averaged recordings. Final output was written on a HP7004B XY plotter.

Averages of responses secondary to nerve stimulation involved at least 8 initial recordings. Averages of responses which were secondary to individual motor unit responses, involved at least 100 initial recordings.

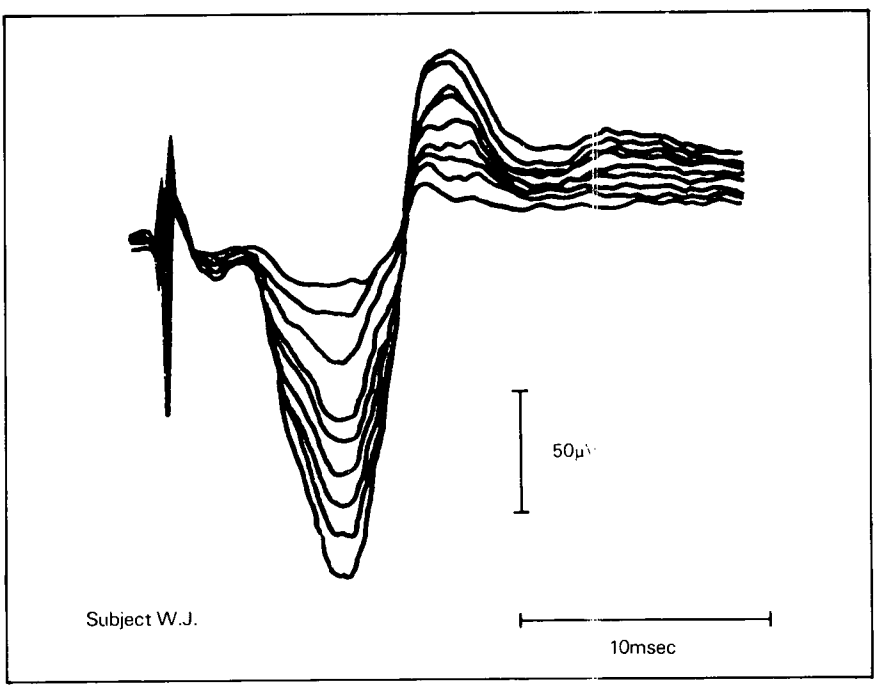


Fig. 2. Subject W.J.: Superposition of averages of records secondary to nerve stimulation, the averages being of records judged to indicate activity in a constant number of motor units. For clarity, the average for no responses has been omitted.

Results

2 experiments have been analysed in detail.

1. Subject W.J.

Averaged surface EMGs subsequent to stimulation are shown in figure 2. Each curve is the average of between 8 and 40 or so recordings, judged by inspection to belong to a group of a constant number of motor units. For clarity, the average of no responses has been omitted. A clear sequence of recruitment of motor units can be seen.

Figure 3 illustrates the results of subtraction of sequential averages displayed in figure 2. Thus these curves are the averages of single motor units. A general consistency of amplitude, shape and latency can be seen. Figure 4 shows the averages of surface EMGs triggered by single motor unit activity in the muscle. Biphasic responses, generally comparable to those in the recordings secondary to nerve stimulation, can be seen. However, there are some important observations:

a) The variability is markedly greater in the responses of figure 4 compared with figure 3.

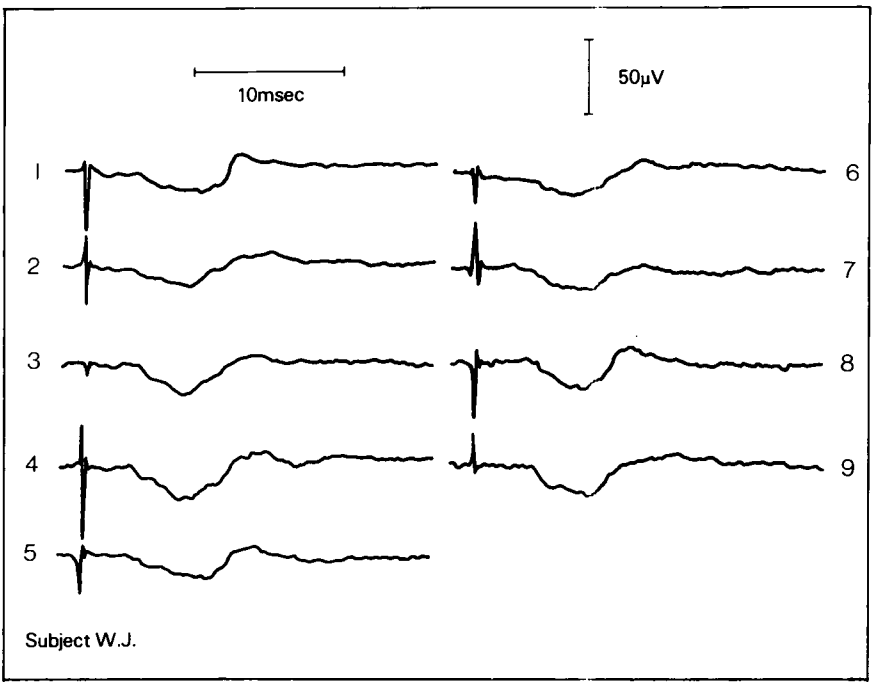
b) The absolute magnitude of the smallest responses is of the order of 5μV, which is close to the general noise level.

c) The peaks and troughs of the responses show no marked consistency in timing; that is, the timing of minima and maxima is not consistent between units.

2. Subject J.L.

Figures 5, 6 and 7 correspond to figures 2, 3 and 4 for Subject W.J. The recruitment sequence (fig. 5) is present, but, as figure 6 also shows, individual units have a wider range of amplitude. This variability is also shown in figure 7 with the surface EMGs averaged secondary to voluntary motor unit activity. Again, there are small units (close to noise), and a lack of consistency in timing of maxima and minima.

Table I gives a summary of the parametric statistics for the 2 subjects. For both subjects there is no statistical significance in the difference of the means of surface EMG responses secondary to nerve stimulation when compared with the responses averaged from motor unit discharge. However, for Subject W.J. there is a marked difference in the variability of the 2 categories of response: the responses to voluntary activity are markedly (and statistically significantly) larger than those secondary to nerve stimulation.


10msec
50μV
1
2
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7
8
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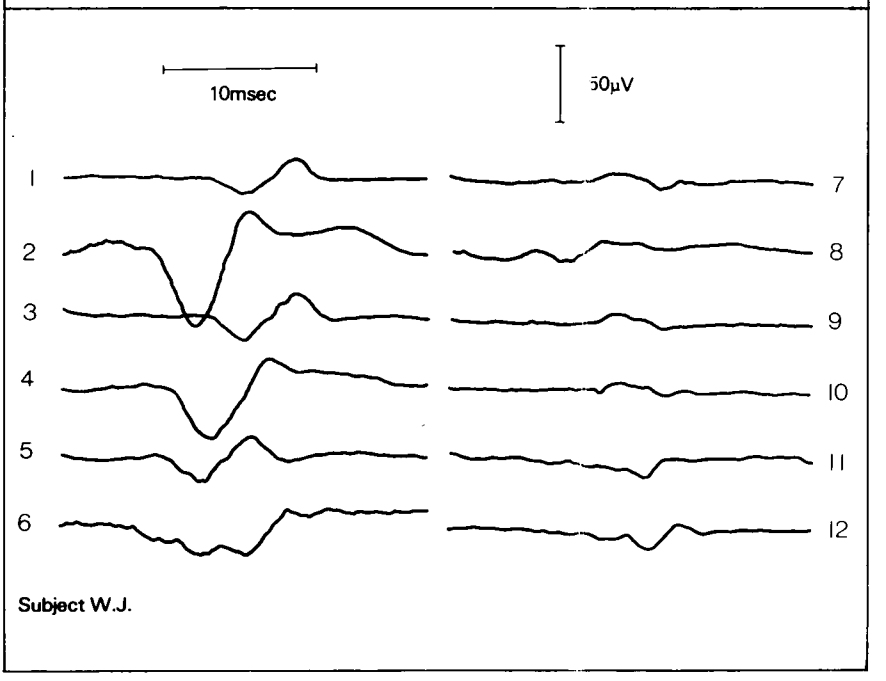
Subject W.J.

3


10msec
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Subject W.J.

4

Table I. Statistics of motor units isolated in Subjects W.J. and J.L.

Motor unit analysis	Subject W.J.	Subject J.L.
Following nerve stimulation		
number	9	7
mean amplitude (μV)	24.7	32.9
standard deviation (μV)	4.1	21.2
Following voluntary activity		
number	12	14
mean amplitude (μV)	25.9	37.8
standard deviation (μV)	19.8	17.6

F = 22.3 for 11/8 and is significant at the 1% level for the variances of Subject W.J.

Discussion

The technique of McComas uses one method (nerve stimulation) to estimate the mean size of single motor units. By its nature it is restricted to motor units activated close to threshold, and distinguishable in the EMG, and this in practice is generally around 10 or so units. Our method has much wider scope, because sampling can be continued indefinitely. The bias here will be towards units easily recorded with an EMG needle.

Superficially, the lack of any statistically significant difference between the means with the 2 methods in our 2 subjects supports the view that both methods yield the same estimate of the number of motor units. However, we draw attention to the far greater variance of the second method in Subject W.J. The range in the standard error of the mean shows that in the estimated number of motor units the variation is considerable. The real value could be half or twice the estimate.

We draw attention to units whose contribution to the surface EMG is small, for example, units 10 and 11 in Subject W.J. These are close to the noise level, and it is debatable, if such a unit were activated by nerve stimulation, whether it could be distinguished from the background noise.

Finally, we draw attention to the relative temporal positions of the units in figures 4 and 7. The units are averages generated by consistent triggering from a unit.

Fig. 3. Subject W.J.: The average EMG of 9 single motor units activated by nerve stimulation, obtained by subtraction of successive records of figure 2.

Fig. 4. Subject W.J.: Averages of the surface EMG triggered 10 msecs after the start of the traces by single motor units, voluntarily activated, and isolated with a needle electrode. 12 different motor units were isolated, and 12 averages of the surface EMG obtained.

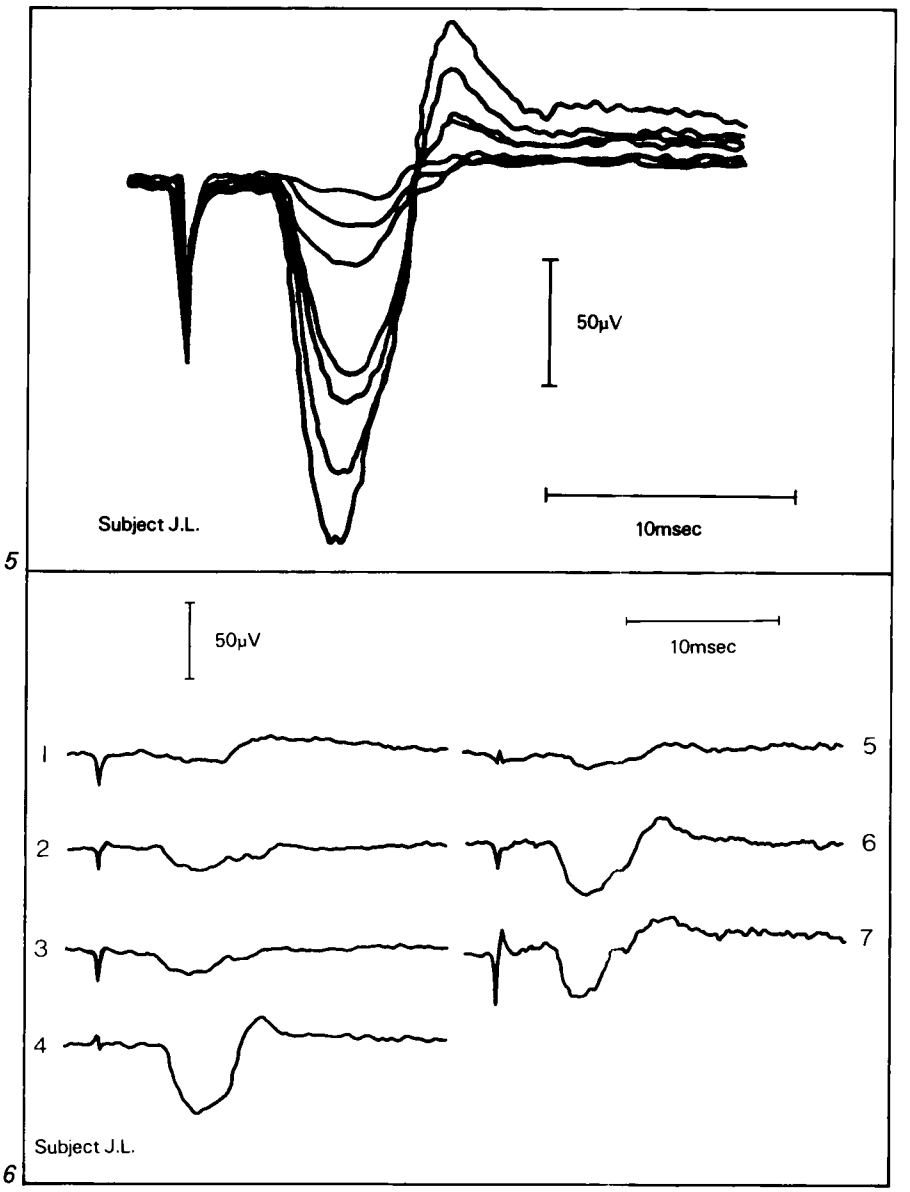

Fig. 5. Subject J.L.: Superposition of averages of records secondary to nerve stimulation, the averages being of records judged to indicate activity in a constant number of motor units. For clarity, the average for no responses has been omitted.

Fig. 6. Subject J.L.: The average EMG of 7 single motor units activated by nerve stimulation, obtained by subtraction of successive records of figure 5.

The needle tip has been kept, as far as possible, in a single plane transverse to the presumed direction of the muscle fibres, which should eliminate variations in temporal position of the surface EMG with conduction velocity in the muscle fibres. In any case, this effect is small: 5m/sec (a high value for muscle) is 5mm/msec. Thus if the tip position of the needle varied between different motor units by 0.5cm along the muscle, variations in latency of up to a millisecond in the time of arrival of the muscle action potential could be expected. But the range of variation in temporal position of the surface EMG is much greater than this.

Figure 8 illustrates this point further. The upper part of traces are the averaged surface EMGs from units 1 and 2 of W.J., and the voltage calibration applies to these only. Underneath each is the average of the unit activity that generated the surface EMG in each case. In relation to the peak deflexion of the unit recorded in the lower tracing, the maxima and minima occur at different times in the 2 cases. Thus, for the left-hand unit, the first maximal deflexion (downwards) occurs after the peak in the unit recording, whereas in the right-hand unit it precedes it.

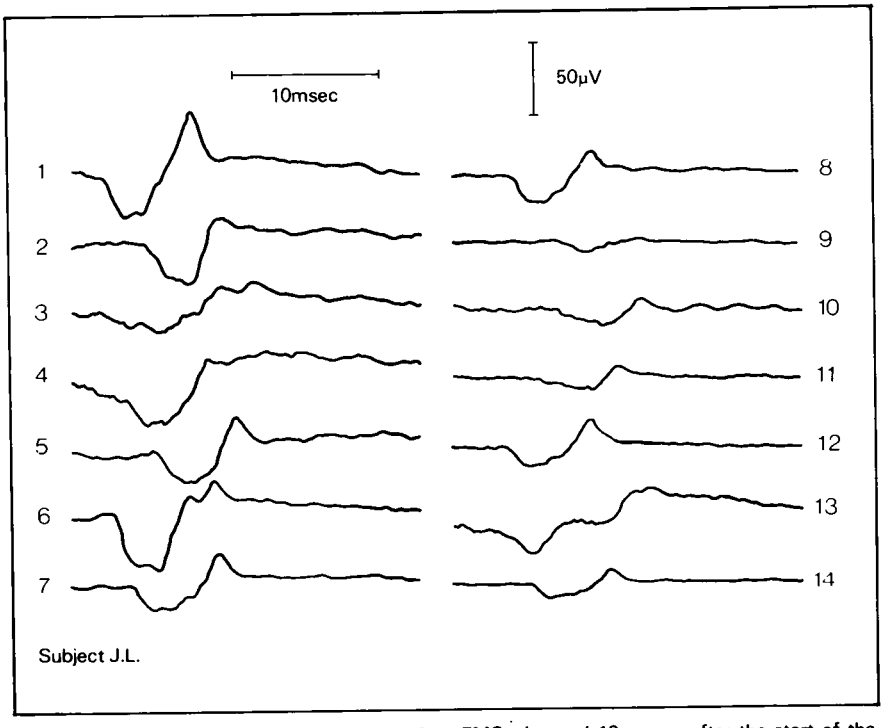

Fig. 7. Subject J.L.: Averages of the surface EMG triggered 10 msecs after the start of the traces by single motor units, voluntarily activated, and isolated with a needle electrode. 14 different motor units were isolated, and 14 averages of the surface EMG obtained.

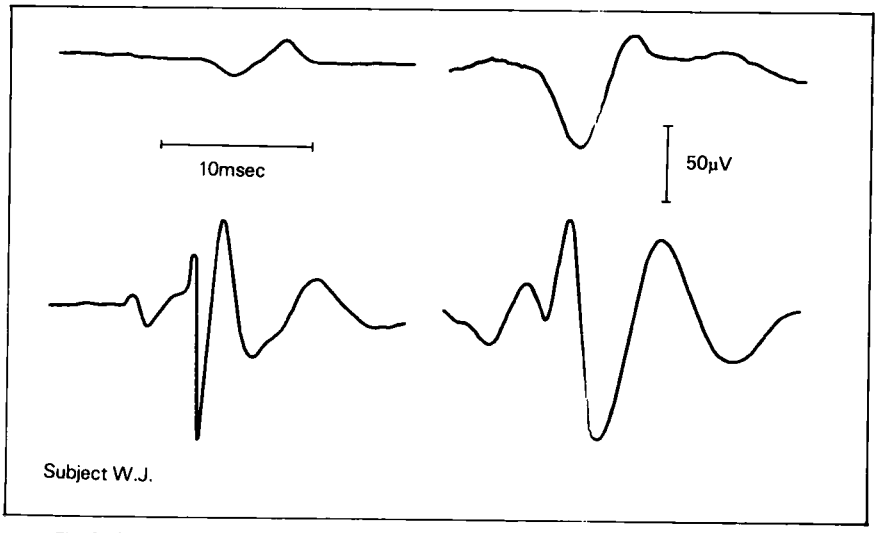

Fig. 8. Subject W.J.: The upper pair of traces are surface EMG averages, and the voltage calibration applied only to them. They are (from left to right), units 1 and 2 of figure 4. The lower pair of traces are the simultaneous averaged needle EMG records which triggered the averaging. The first minima in the surface EMG of the left hand tracing trails the maximal deflexion in the needle recording, but precedes the maximal deflexion in the right hand tracing.

The implication is that, even if 2 units were activated simultaneously in the muscle, the maxima and minima of their surface EMGs need not occur at the same time. Simple voltage summation of peaks and troughs would not occur, which implies that division of the maximal EMG response by the mean size of a single response to obtain the number of motor units is invalid.

We do not at present have enough data from fully analysed experiments to draw firm conclusions. However, our results suggest that:

a) The variability in the contribution of a single motor unit to the surface EMG is much greater than one would conclude from nerve stimulation at threshold.

b) There are units whose individual contribution to the surface EMG is below noise level, and so are not estimated.

c) There is enough temporal dispersion of the maxima and minima in the surface EMGs to invalidate the assumption of simple summation of the maxima and minima.

Summary

McComas (1977) has published a method of estimating the number of motor units in human skeletal muscle, based on peripheral nerve stimulation and recording

of the surface electromyogram (EMG). One assumption of the method is that individual motor units, recruited by peripheral nerve stimulation just above threshold, give discrete observable increments to the surface EMG which are typical of motor units in the muscle.

We have investigated this assumption in the thenar muscle. An EMG needle was inserted into the muscle and a series of individual motor units, activated voluntarily, was isolated. The discharge of these units was then used to trigger averaging of the concurrent surface EMG.

Our results suggest that motor units activated by peripheral nerve stimulation close to threshold are not representative, in amplitude or timing, in their contribution to the surface EMG, of all motor units in the muscle.

Acknowledgements

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Brain Infarction in Young Men

R.J. Burns, P.C. Blumbergs* and M.R. Sage†*

Brain infarction in men under 40 years of age is uncommon, especially if one excludes those cases where there is a likely embolic source or an underlying systemic disease. There have been numerous reports of brain infarction in young people (Sprofkin and Blakely, 1956; Wells and Timberger, 1961; Louis and McDowell, 1967; Humphrey and Newton, 1969; Abraham et al., 1971; Seneviratne and Ameratunga, 1972). In certain areas of the world, infarction is sometimes consequent on a disease peculiar to a particular race, such as aorto-arteritis which occurs in Sri Lanka (Wickremasinghe et al., 1978). In young women thrombo-embolic infarction occurring with pregnancy, the puerperium and oral contraceptives is well documented (Collaborative Group for the Study of Stroke in Young Women. 1973).

Brain infarction in young males in Western societies has not been widely described. When underlying diseases such as the recognised arteritidies, trauma, disturbances of blood coagulation and cases where there is an obvious embolic source are excluded, there remains a large group in whom the pathogenesis is speculative. In some reports (Louis and McDowell, 1967; Abraham et al., 1971) emphasis has been placed on the importance of atheroma. Others (Sprofkin and Blakely, 1956; Levine and Swanson, 1969; Grindal et al., 1978) have stressed the role of thrombo-embolism especially of cardiac origin. There have even been detailed autopsy studies performed in young males who have died of brain infarction, as a result of thrombotic

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arterial occlusion, in whom no embolic source or arterial disease could be found (Graham and Adams, 1972). Infarction possibly attributable to migraine or arterial spasm has received little consideration in most reports of this type. It is clear from most series that there is a significant number of patients in whom an adequate explanation for the infarction could not be found.

It is the purpose of this paper to describe the clinical and, where appropriate, pathological features of 8 males under the age of 40 with brain infarction.

Case Reports

The clinical features of 5 males under the age of 40 with brain infarcts are described. They were seen in a 2-year period (1976-1978) at the Flinders Medical Centre. 3 further cases were examined pathologically at the Institute of Medical and Veterinary Science in 1979. The study was not intended to be comprehensive and those males in whom there was an obvious cause for infarction, such as trauma or collagen disease, were not included.

Case 1

Left cerebral infarction, cause unknown.

This 36-year-old carpenter awoke one morning with difficulty in speaking and mild weakness of his right hand. There was no previous history of neurological symptoms including migraine, nor was there a family history of premature vascular disease.

On examination there was marked motor speech disturbance, a right lower facial weakness, hyperactive deep tendon reflexes in the right arm and mild hypokinesis of the right hand. An isotope brain scan was normal but a CAT scan showed a round, low density lesion in the left parietal lobe. 8 days after the infarct a left carotid angiogram was performed and was normal. Other investigations, including haematological and biochemical screening tests, an EEG, ECG and CSF examination, were normal.

His condition steadily improved over a period of weeks. 15 months later examination of the nervous system was normal. 2.5 years later he remained normal with no transient symptoms of any sort; a CAT scan at this time was normal.

Case 2

Bilaterial occipital cortical infarction due to vertebrobasilar arterial atheroma.

This 38-year-old warrant officer suddenly felt strange and lost consciousness for about 1 minute. He was subsequently confused and complained of a right hemicranial headache, blurred vision and perioral paraesthesiae. When he was examined a few hours later no signs could be found. Over the next few days he experienced a number of transient neurological symptoms including blurred vision, vertigo and paraesthesiae in the left arm and leg, and he complained of persistent impairment of his peripheral vision. He gave a history of borderline arterial hypertension. There was no family history of vascular disease.

On examination he looked prematurely old with a blood pressure of 140/90mm Hg. He was in sinus rhythm. His visual acuity was 6/6 and N5 in both eyes and although the visual fields were difficult to assess there appeared to be a right homonymous defect with a constriction of his left field as well.

Routine biochemical and haematological screening tests, radiographs of his chest and an ECG were normal. An isotope brain scan showed an area of uptake in the left parieto-occipital region. A subsequent CAT scan showed bilateral low density occipital lesions. A second isotope scan 6 weeks later was normal. A vertebral angiogram 3 months after the onset of his symptoms showed a hypoplastic left vertebral

artery with a dominant vessel on the right side. Stenosis of the right vertebral artery at its site of entry into the subarachnoid space was demonstrated. The basilar artery was tortuous.

6 months after the onset of his symptoms he remained well although he had a persistent constriction of his visual fields.

Case 3

Migrainous right cerebral infarction and subsequent right cerebellar infarction.

This 34-year-old clerk suddenly lost consciousness for a brief period and on awakening complained of right orbital pain. Almost immediately he was aware of left-sided weakness and numbness. There was a history of approximately monthly migraine headaches for 10 years, usually located over the right eye, lasting for hours and accompanied by vomiting. He had never experienced neurological symptoms prior to the headaches. There was a family history of migraine.

When he was examined he was noted to have a left hemiparesis, hemisensory loss and hemianopia. Investigations included a CAT scan which showed a right cerebral lesion consistent with infarction (fig. 1). An isotope scan showed an abnormality in the same area. A right carotid angiogram was normal. His neurological deficit cleared within a few weeks although he subsequently developed occasional focal and grand mal seizures.

6 months after the infarct the CAT scan was repeated and showed an area of previous infarction in the right temporoparietal region superficial to the basal ganglia and a further area of low density, presumably infarction, deep in the basal ganglia on the right side.

14 months after the original infarct he developed acute vertigo, vomiting, right-sided clumsiness and ataxia without headache. Examination revealed a horizontal nystagmus with saccadic eye movements, dysarthria and ataxia in the right arm and leg. At this time his blood pressure was mildly elevated at 140/90mm Hg. Routine haematological and biochemical screening tests were normal. His triglycerides

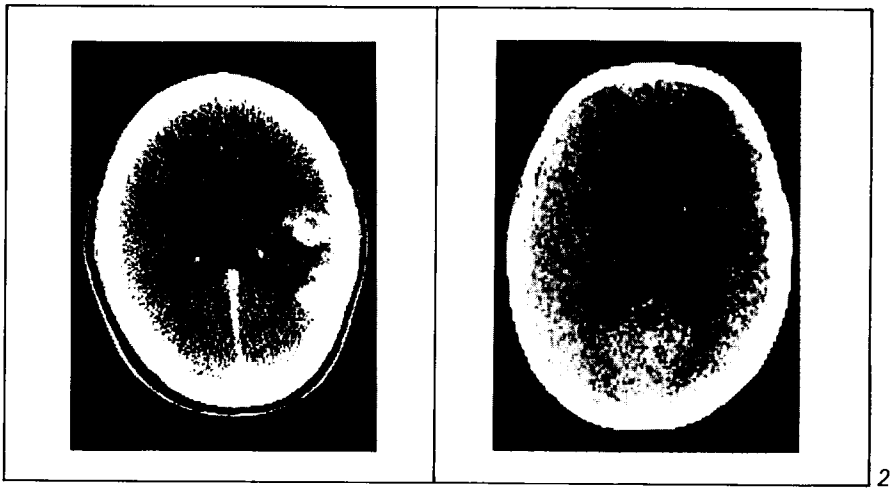

Fig. 1. Case 3. Enhanced CAT scan demonstrating extensive peripheral enhancement in the right parietal region consistent with recent infarction.

Fig. 2. Case 5. CAT scan demonstrating residual infarction with compensatory dilatation of the anterior horn of the left lateral ventricle.

were elevated at 2.3mmols/litre (normal range 0.3-1.7). An ECG showed sinus rhythm with some minor ST-T wave changes. An echocardiogram was normal. A repeat CAT scan showed the previously observed lesions in the right cerebral hemisphere and a further area of low density in the right cerebellar hemisphere.

He was advised to stop smoking, his mild hypertension was treated and he was given migraine prophylaxis. His neurological signs gradually improved and 4 months after the second infarct he was back at work, still exhibiting a mild right-sided cerebellar ataxia. There have been no further seizures or headaches.

Case 4

Left lateral medullary infarct, cause unknown.

This 39-year-old lecturer was admitted to hospital with the abrupt onset of vomiting, vertigo and ataxia. There was no headache and his past health had been excellent with no significant family history.

On examination he was fully alert. There was spinothalamic sensory loss involving the left side of his face and right side of his body, a left tenth nerve lesion and a left-sided cerebellar ataxia. Cardiovascular examination was normal with a blood pressure of 100/60mm Hg and a regular pulse.

Investigations included routine haematological and biochemical screening tests, CSF examination, radiographs of his chest and an ECG, which were all normal. Isotope and CAT brain scans showed no abnormality.

No treatment was given and his condition gradually improved. When examined 1 year later he was noted to have a horizontal nystagmus on left lateral gaze and the spinothalamic signs were still present although less marked. A mild degree of left-sided ataxia was also demonstrable. There have been no transient neurological symptoms.

Case 5

Migrainous left cerebral infarction.

This 37-year-old left-handed foreman developed a severe left frontal headache after taking a hot shower, and soon afterwards was noted to be dragging his right arm and leg. For the next 48 hours he remained in bed, drowsy, confused and with slurred speech. Since the age of 20 he had experienced periodic right periorbital headaches usually without vomiting and not associated with any neurological symptoms. There was no family history of migraine. When examined 3 days after the onset of his symptoms he was drowsy with a nominal dysphasia and a mild right hemiparesis. There was a right visual and sensory inattention. His blood pressure was 125/80mm Hg and he was in sinus rhythm.

Routine haematological and biochemical screening tests were normal. His serum triglycerides were elevated at 3.5mmols/litre (normal range 0.3-1.7). An ECG was normal. An isotope brain scan on the fourth day showed a slight delay in perfusion of the left middle cerebral artery with a relative increase in activity suggesting collateral circulation. The late images revealed an abnormally increased uptake in the left basal ganglia. A CAT scan showed an area of low density in the basal ganglia on the left side anteriorly, involving the head of the caudate nucleus, adjacent limb of the internal capsule and extending to the external capsule. There was no enhancement following contrast. A left carotid angiogram was normal.

Within 10 days his signs had resolved although there was amnesia for the first 3 days of his illness. 6 months later there had been no further neurological symptoms, nor had he experienced further headaches. The CAT scan in figure 2 showed a residual left cerebral abnormality consistent with previous infarction.

Case 6

Haemorrhagic left medullary infarct, cause unknown.

A 29-year-old lawyer suddenly developed paraesthesiae involving the left side of his tongue, left arm and both legs, with faintness, slurred speech and difficulty in swallowing. He had complained of a persistent left hemicranial headache for the previous 3 weeks. There was no history of migraine. Ex-

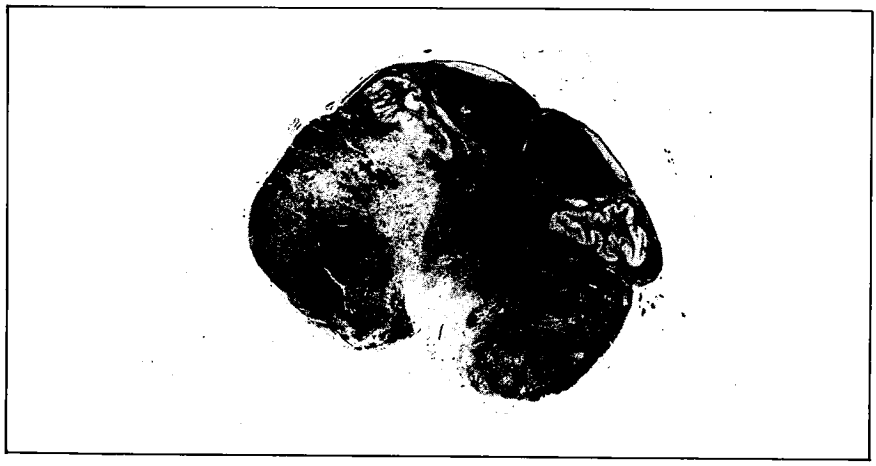

Fig. 3. Case 6. Extensive haemorrhagic infarction in the left medulla.

amination revealed rotatory nystagmus, a mild left ptosis, an absent left corneal reflex, a left lower motor neurone facial palsy, a left tenth and twelfth nerve lesion, loss of pinprick sensation possibly on the right side of the face but definitely involving the arm, trunk and leg on the right, and a gross left-sided ataxia. The deep tendon reflexes were hyperactive on the right side with an equivocal extensor plantar reflex on the right. His initial blood pressure was 170/120mm Hg with sinus tachycardia.

A complete blood picture showed a mild leucocytosis but was otherwise normal; biochemical screening tests showed a mild elevation of serum urate and a glucose level of 11.2mmols/litre (range 4.4-6.4), radiographs of his chest and skull were normal and an ECG showed sinus tachycardia only. Examination of the CSF was normal apart from 49 red cells per cubic millimetre. A CAT scan was normal.

He was fed with a nasogastric tube. His condition deteriorated over the next few days with respiratory difficulties. His blood pressure soon returned to normal. He became hypotensive and hypoxic on the fourth day prior to his death.

General pathological examination revealed diffuse, acute pulmonary oedema and early consolidation in both lower lobes. Histological section showed widespread early bronchopneumonia with abscess formation in which Gram-positive cocci were seen and meat fibres consistent with aspiration. The heart weighed 300g and was completely normal. The coronary arteries were free of atheroma. The middle ears and sinuses were opened and were normal.

Neuropathological examination showed a recent haemorrhagic infarct (6 × 6 × 15mm) involving the left side of the medulla with upward extension into the pontomedullary junction and downward extension to the level of the pyramidal decussation (fig. 3). Histologically the infarct was of several days' duration and encroached across the midline in the lower medulla to involve the right gracile nucleus and surrounding structures. There was no infarction of the cerebellum. The vessels of the circle of Willis were of normal anatomical configuration and free of atheroma. In particular, the left inferior posterior cerebellar artery and the left vertebral artery were widely patent and histologically normal. Occasional small blood vessels in the infarcted area were plugged by amorphous eosinophilic material.

The haemorrhagic nature of the infarction suggested that it might be embolic in origin but no source of embolism could be demonstrated. Moreover, emboli in the vertebrobasilar system usually lodge in the posterior cerebral arteries and rarely affect the brain stem. Therefore, arterial spasm is suggested as another possible explanation in this case.

Case 7

Left cerebral embolic infarction.

This 30-year-old Aborigine developed a sudden right-sided weakness and difficulty in speaking which progressed further over 12 hours. There was a history of heavy alcohol consumption. There was no significant family history. On examination he was drowsy, aphasic and there was a dense right hemiplegia. Cardiovascular examination was normal and his blood pressure was 135/80mm Hg.

Routine biochemical and haematological screening tests were normal. A CAT scan showed widespread areas of abnormally low density in the left cerebral hemisphere, especially in the frontal region. The septum pellucidum was displaced 12mm and the pineal 6mm to the right of the midline. There was marked compression of the left lateral ventricle, especially of its frontal horn. On the third day he suddenly developed a fixed, dilated left pupil and a small non-reactive right pupil, combined with deterioration in his state of consciousness, and despite treatment with dexamethasone and glycerol he died.

General pathological examination revealed a heart weighing 350g with left ventricular thickness at the level of the anterior papillary muscle of 15mm. A small area of roughening (4mm in diameter) was noted on the ventricular surface of the central cusp of the aortic valve well clear of the line of closure. This roughening microscopically consisted of fibrin containing a small number of degenerate cells projecting beyond the valve surface. There was partial endothelialisation at one margin. The underlying valve showed no significant abnormality and the remainder of the heart was normal. The coronary arteries showed only minimal atheroma. Isolated non-ulcerated plaques of atheroma were present throughout the aorta. There was complete occlusion of the supraclinoid portion of the left internal carotid artery by antemortem thrombo-embolus. The internal carotid artery showed no significant atheroma. The liver showed mild steatosis.

Neuropathological examination showed massive recent ischaemic infarction in the distribution of the left middle and anterior cerebral arteries. There was severe oedema of the infarcted region with transtentorial and subfalcine herniation. Compression and disruption of the rostral brainstem by multiple secondary haemorrhages were evident.

Case 8

This 38-year-old motor mechanic suddenly experienced difficulty in speaking, blurred vision and left-sided weakness. There was an 8-year history of arterial hypertension requiring treatment. A left nephrectomy had been performed 2 years previously for a non-functioning kidney. There was no history of any previous neurological symptoms. There was a family history of hypertension. On examination he was drowsy with a dense left hemiplegia and hemianaesthesia. Cardiovascular examination was normal. His blood pressure was 180/130mm Hg.

An ECG was normal apart from sinus bradycardia. Biochemical screening tests were normal. His blood film showed a mild leucocytosis. A CAT scan showed a large, low density lesion in the right frontal, temporal and parietal regions with compression of the right lateral ventricle and displacement of the pineal and septum pellucidum to the left.

A fatal respiratory arrest occurred on the fourth day despite intensive treatment with dexamethasone and intravenous glycerol.

General pathological examination revealed a heart which weighed 370g and showed mild left ventricular hypertrophy. The endocardium was intact and there were no defects in the cardiac septa. There was mild atheroma of the left anterior descending coronary artery and the right coronary artery without stenosis. The aorta showed a few scattered, isolated plaques of atheroma.

Neuropathological examination showed a large recent infarct in the territory of the right anterior and middle cerebral arteries. The infarct was anaemic apart from an area of haemorrhagic infarction 10mm in diameter in the putamen. There was severe swelling of the infarcted area with transtentorial herniation and disruption of the upper brainstem by numerous secondary haemorrhages. The right internal carotid artery was widely patent and only a few isolated non-ulcerated plaques of atheroma were present. The anatomical configuration of the circle of Willis was normal and there was minimal cerebral artery

atherosclerosis. Systematic microscopic examination of the right anterior and middle cerebral arteries and their branches showed fragments of thrombus in the posterior branch of the trifurcation of the right middle cerebral artery and in the right anterior cerebral artery 15mm distal from the junction with the anterior communicating artery. The fragments consisted of amorphous eosinophilic material containing degenerate cell nuclei with no attachment to the adjacent blood vessel wall.

It was postulated that embolic occlusion of the right internal carotid artery occurred with massive ischaemic infarction and that the embolus then fragmented to lodge distally in the anterior cerebral artery and a branch of the middle cerebral artery, explaining the haemorrhagic nature of the infarction involving the putamen, as the initially occluded lateral striate arteries would be unblocked with the distal passage of the embolus.

Discussion

Of the 3 patients who came to autopsy, 1 (Case 6) had a haemorrhagic infarct which in itself is an unusual lesion. Haemorrhagic infarction was not seen in the 16 cases of lateral medullary infarction studied by Fisher et al. (1961) even though 3 of their cases were embolic in origin. No vessel occlusion was seen in this case nor could any primary source for an embolus be found.

In Case 7 the infarction was embolic in nature. Embolic occlusion of the internal carotid artery most often involves the supraclinoid portion (Bladin, 1964) and in this case the only demonstrable source of embolism was the central cusp of the aortic valve. This in itself was an unusual lesion. Small endocardial deposits of fibrin are commonly found on the aortic and mitral valve cusps of people of all ages, even in early adult life, but these usually occur along the lines of valve closure and are not usually associated with embolism (Pomerance, 1961). The massive nature of the infarct in this case also suggests embolism as a result of cardiac disease. Embolic infarction is also postulated in Case 8, although failure to demonstrate the source is not an infrequent occurrence (Fisher et al., 1970). The diagnosis of infarction in the 5 patients who survived was made on clinical grounds with the help of brain scanning and CSF examination especially. In 1 patient (Case 4) the lateral medullary location made infarction the likely diagnosis even though arteriographic studies were not performed. The remaining 4 patients had arteriographic studies and in 1 (Case 2) significant atheromatous changes were seen which were probably related to the infarction. The remaining 3 patients had normal cerebral vessels without demonstrable arterial occlusions. 2 of these (Cases 3 and 5) had a history of migraine, while no satisfactory explanation for the infarction could be found in 1 (Case 1).

The incidence of brain infarction in young men in our community is hard to determine although there is every reason to believe that it is uncommon. In a survey in Sweden (Sjostrom, 1967) 2% of 'stroke' patients were under the age of 40 years, and this figure includes both males and females. Louis and McDowell (1967) found that 56 of 966 stroke patients reviewed retrospectively were under the age of 50 and 0.5% were males under 40. These figures include all the causes of stroke and so it is

reasonable to assume that the incidence is even less when discussing those cases in whom no underlying cause could be found. Moreover, Louis and McDowell (1967) did not have the assistance of CAT scanning to enable more accurate diagnosis. On the other hand, the incidence of brain infarction in young people is probably higher in certain geographic areas. For example, in India Abraham et al. (1971) prospectively studied 407 consecutive patients with cerebrovascular disease and found that 127 (32 %) were under the age of 41 years. A similar high incidence was also found in Sri Lanka where Seneviratne and Ameratunga (1972) found 44 young adults in a period of 4 years with infarcts due to occlusions of either the internal carotid or middle cerebral arteries.

There is a large number of conditions which are associated with brain infarction especially in the young, including arteritis, arterial trauma, cardiac disease with cerebral thrombo-embolism, and hypercoagulable states. Usually it is possible to exclude these diseases but even when this is done there remains a large group in whom no cause is apparent. Hindfelt and Nilsson (1977) studied 64 young adults aged 16 to 40 with brain infarcts and in 19 no cause could be found although an underlying systemic infection was postulated in some. A significant number of brain infarcts of unknown cause is found in other reports (Abraham et al., 1971; Seneviratne and Ameratunga, 1972; Grindal et al., 1978). Adams and Graham (1967) described 12 cases of fatal brain infarction due to arterial occlusion in the absence of atheroma or an embolic source, and in 4 of these patients the cause of the thrombosis was unknown. Graham and Adams (1972) described 'idiopathic' thrombosis of the vertebrobasilar arterial system in 2 young men.

There have been numerous studies such as those of Blackwood et al. (1969) which have emphasised the frequency of cryptogenic cerebral embolism as a cause for infarction and it seems likely that this was the explanation in 2 of the 3 patients who came to autopsy. While no embolic material was seen in the arteries of those patients who were studied with angiograms, this does not of course exclude the possibility of thrombo-embolism, as there was usually a delay of at least a week between the infarct and the angiogram. Nevertheless, no source for an embolus could be found clinically although again it should be appreciated that this does not always exclude such a possibility as exemplified by the patient with the aortic valve lesion found at autopsy. It is generally accepted that arterial spasm can cause brain infarction in migraine sufferers. This is seen in the rare familial hemiplegic migraine (Bradshaw and Parsons, 1966; Neligan et al., 1977).

It is a common experience for neurologists to see patients with infarction attributable to migraine, and there is recent CAT scan evidence (Cala and Mastaglia, 1976; Hungerford et al., 1976) that brain infarction in migraine sufferers might be more common than previously suspected. The number of pathologically verified cases is few (Buckle et al., 1964; Guest and Woolf, 1964). Pearce and Foster (1965) described 40 cases of complicated migraine, 33 of whom were investigated in detail. Angiographic studies were performed in many patients but no significant abnor-

malities were found. No pathological data were available. Arterial spasm due to migraine has been rarely demonstrated angiographically (Buckle et al., 1964) but the infrequency of this observation radiologically in no way negates the theory that arterial spasm may occur in migraine. In the majority of patients there is probably no residual neurological deficit but if the spasm is particularly severe, prolonged and perhaps widespread, infarction can occur. There may be other factors also which could be relevant to the development of infarction with migrainous spasm, such as minor degrees of atheroma with an inability of adjacent blood vessels to establish proper collateral supply, and impaired local autonomic vascular responses. Hyperlipidaemia, smoking, hypertension and transient unrecognised disturbances of blood coagulability could also be factors in some instances.

Conclusion

The particular points of interest which arise from the study of these 8 patients are:

1) The demonstration of extensive infarcts in 2 patients with a history of migraine.

2) The observation, noted by others, that the cause of brain infarction is often difficult to establish even at autopsy and that the source of an embolus might not be found.

3) In only 1 patient could atheroma be implicated on the angiograms. Although mild atheroma was found in 2 patients who came to autopsy, it was regarded as not being significant in the development of the infarction.

4) The demonstration of an unusual and clinically silent aortic valve thrombus in 1 patient.

5) The demonstration of an extensive haemorrhagic medullary infarct in 1 patient without evidence of thrombo-embolism or atheroma.

6) The 2 deaths due to massive brain infarction were the result of the effects of rostrocaudal herniation, while those who survived made good recoveries with minimal or no neurological deficits.

A thoughtful editorial (1978) concluded with the following statement: 'Surely it is time to look afresh at cerebral infarction — and stop regarding it as a mere variant of myocardial infarction'.

It is postulated that infarction due to spasm, such as occurs in migraine or for other reasons as yet unknown, might be more common that we generally appreciate. It would appear that migraine sufferers who have brain infarcts are not necessarily those with a classic migraine history, and one possible explanation of brain infarction in young people might be spasm even when there is no history of migraine. There

also may be other factors as yet not recognised which could be relevant. The frequency, degree, extent and duration of arterial spasm occurring in migraine sufferers is still not fully understood.

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The Application of Prolonged EEG Telemetry and Videotape Recording to the Study of Seizures and Related Disorders

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The diagnosis and management of patients who have attacks of disturbed consciousness or loss of consciousness is a common clinical problem. The diagnosis of epilepsy may be clearly established by history alone in some patients, and by the combination of history and appropriate interictal epileptic discharges in the electroencephalogram (EEG) in others. However, in a number of patients the interictal EEG may be normal on many occasions or may contain nonspecific abnormalities (Ajmmone-Marsan and Zivin, 1970). It may therefore not be possible to determine if the patient has epilepsy, syncope, an episodic cardiac arrhythmia or a functional disturbance of some kind.

Many of the limitations inherent in the standard techniques of EEG recording may be overcome by telemetering the EEG activity and combining the EEG recording with a simultaneous videotape recording of the patient (Bowden et al., 1975). It is possible with this technique for the patient to be completely mobile, and for very long recordings to be made without discomfort or restraint. An attack is therefore more likely to be recorded, and both EEG and ECG changes may be correlated with the behaviour of the patient.

In this study we report the results of combined telemetered EEG and videotape recordings on 115 patients.

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Table I. Age distribution of the 115 patients on whom EEG telemetry-videotape recording studies were conducted

Age (years)	No. of patients
0-10	9
11-20	28
21-30	35
31-40	17
41-50	16
51-60	8
61-70	2

Patients Studied

Over a period of 22 months, from 16 March 1977 to 31 January 1979, 128 telemetric studies were done on 115 patients. 1 patient had 4 separate examinations, and 10 had 2 separate studies each. The ages of the patients ranged from 6 to 67 years (table I). 60 patients were male and 55 were female. Patients were interviewed before the test in order to obtain a detailed clinical history and familiarise them with the examination procedures. The EEG telemetry and videotape recordings were performed in a room where the patients were free to move about, sit on a couch or recline in a chair, and read or watch television. In each case, conventional EEG studies had not provided sufficient information for diagnosis. The reasons for referral to the telemetry service are summarised in table II.

Method

Silver/silver chloride scalp electrodes were applied with collodion according to the 10-20 system, and additional electrodes were used when appropriate. The 4 commonly used montages and the clinical problems in which they were used are set out in table III. When a recording of the ECG was required, electrodes were placed at the midsternum and at the left fifth intercostal space at the midclavicular line. The electro-oculogram was recorded via a bipolar derivation from each eye in which one electrode was placed above and medial to the outer canthus, and a second electrode was placed below and lateral to the outer canthus. In some patients the submental electromyogram was recorded to allow differentiation between the wakeful state and REM sleep. 2 electrodes were placed below the chin and the signal was pre-amplified in a small amplifier with 2 sensitivity settings, a time constant of 0.01 second and a 3db drop at 75Hz. Nasal airflow was monitored via a thermocouple at the external nares to record respirations.

The signals were processed, displayed and recorded by a modified Kaiser-Disa 25A06 Videograph system. The biological signals derived by the above electrode

Table II. Reasons for referral of 115 patients for EEG telemetry-videotape recording

Reason for referral	No. of patients
Episodic psychomotor or psychosensory symptoms resembling complex partial seizures	20
To define the type or types of seizure	17
Absences or blackouts	14
To determine the cause of syncope or drop attacks	13
Intermittent psychiatric symptoms: bizarre behaviour, violent outbursts, prolonged experiential phenomena and automatisms following alcohol abuse	13
To determine the cause of excessive daytime sleepiness	11
Episodic motor symptoms resembling grand mal, tonic, myoclonic or adversive seizures	9
To determine if a new 'turn' is an epileptic seizure and its type	5
To lateralise the seizure focus	3
Sleep-apnoea due to complex partial seizures	1
Loss of consciousness after intercourse	1
Vague episodic cardiac symptoms	1
Laboured breathing on waking	1
Intermittent nocturnal autonomic symptoms	1
To determine the frequency of seizures	1
Speech lateralisation	1
Sleep paralysis	1
Insomnia	1
Episodic amnesia for recent events	1

placements were fed into an 8-channel FM transmitter (25B04) which was carried in a vest or belt pack. The coded signals were received by a unit (25B05) which would pass them directly to one sound track of a videotape recorder and to a decoding unit (25B11) which displayed the 8 channels of data on a television monitor. Thus a simulated 'page' of data moved continuously from right to left across the screen at a rate equivalent to 30mm/sec in a hard copy write-out. The EEG, ECG and EOG signals were displayed at a gain of 50μV/cm with a time constant of 0.3s, and the EMG signals were displayed at a gain of 20μV/cm. A picture of the patient was simultaneously obtained with a Ikegami CTC 5000 camera. The picture was both

Table III. The 4 montages used in the telemetric studies, and the clinical problems for which they were used

Montage	Symptoms evaluated
1) F_3-F_7 or F_{p1}-F_7 F_7-T_3 T_3-T_5 T_5-O_1 F_4-F_8 or F_{p2}-F_8 F_8-T_4 T_4-T_6 T_6-O_2	Absences and blackouts; symptoms resembling complex partial seizures; episodic psychiatric symptoms
2) F_{p1}-F_3 F_3-C_3 C_3-P_3 P_3-O_1 F_{p2}-F_4 F_4-C_4 C_4-P_4 P_4-O_2	As for montage 1; elementary motor symptoms
3) F_3-F_7 F_7-T_3 T_3-T_5 F_4-F_8 F_8-T_4 T_4-T_6 ECG	Syncope and drop attacks
4) Lt. EOG Rt. EOG EMG T_3-C_3 C_3-C_4 C_4-T_4 T_5-O_1 O_2-T_6	Excessive daytime sleepiness

superimposed on the monitor with the telemetered data, and recorded on the videotape. Sound from the study area was recorded on the second sound track of the video recorder. A digital time code was added to the video recordings which were made using 2 National NV9500 video-cassette recorders controlled by a NV-A950 Edit system. This video recording equipment replaced the Philips domestic video recorder which was supplied with the equipment.

Table IV. 4 criteria by which results of EEG telemetry-videotape recording were regarded as 'useful'

Ictus	Ictal EEG	Interictal EEG		
		epileptic discharges	nonspecific abnormality	normal
Recorded	Characteristic changes	±	±	∓
Nil	Nil	+	±	−
Recorded	Normal *or* obscured by artefacts	+	±	−
Recorded: motor a) complex and stereotyped b) occur in circumstances where voluntary mimicking impossible e.g. sleep	Normal *or* obscured by artefacts	−	±	∓

The duration of the studies was related to the clinical problem. About 6 to 8 hours of recording were obtained for diurnal studies, 10 to 12 hours overnight for nocturnal studies and as long as was necessary to obtain 2 periods of 1.5 hours' continuous diurnal sleep in patients with excessive daytime sleepiness.

Various provocative tests were used where appropriate, such as natural sleep, hyperventilation, blinks and eye closures, reading both silently and aloud, television viewing, photic and non-patterned light stimulation and pattern stimulation using closely ruled lines. Clinical assessment was performed during an ictus.

Results

The results of the study were assessed as useful, doubtful, or not useful, for the purpose of evaluating this type of investigation. A useful result either enabled a definite diagnosis to be made, or answered the question posed by the referring doctor. Useful results were defined by 4 criteria as shown in table IV.

Diagnosis of Epilepsy

The 2 main diagnostic problems were:

1) To determine whether or not a patient had epilepsy.
2) To define the type or types of seizure in a patient suspected of being an epileptic but in whom the history and standard EEG had failed to define the seizure type clearly.

Table V. Results of investigations into the presence and type of epilepsy

Diagnostic problem		Value of investigations	
		no. useful (%)	no. doubtful and unhelpful (%)
?Epilepsy	*Symptoms*		
	absences, blackouts or disturbed consciousness	6 (43)	8 (57)
	complex partial seizures	10 (50)	10 (50)
	resembling complex partial seizures adversive and myoclonic seizures	4 (45)	5 (55)
	intermittent psychiatric symptoms	0	13 (100)
	others	2 (40)	3 (60)
Type of epilepsy		15 (89)	2 (11)

The results of the studies on these 2 diagnostic problems are summarised in table V.

The following are some illustrative case histories.

Case 1

K.A., a male aged 35 years, had suffered a serious head injury in 1964 and had been unconscious for 12 days. Since 1967 he had suffered from attacks that consisted of a strange feeling during which he was seen to become flushed and to swallow his saliva repeatedly. The examination and EEG were normal. During telemetry a single seizure occurred and consisted of the patient becoming flushed and agitated; he fumbled with his hands. The ictal EEG showed semirhythmic slow waves from the frontotemporal areas and the study confirmed a diagnosis of complex partial seizures.

Case 2

F.B. was a female of 27 years. In 1972 soon after the birth of a child she was said to have had a major motor convulsion when confronted with the tragic news that her husband had suddenly died in an accident. In August 1978 she lost consciousness twice in circumstances that made the neurologist suspect that her symptoms were psychogenic. Clinical examination was normal and the EEG nonspecifically abnormal. During telemetry right temporal slow waves with frequent right temporal epileptic discharges in sleep suggested a diagnosis of complex partial seizures.

Case 3

For 1 year P.J.E., a 10-year-old boy, had suffered frequent nocturnal complex automatisms which woke him up from sleep. An initial EEG had shown a right temporal epileptic focus. With anticonvulsants the seizures initially improved but later became refractory to treatment. His repeat EEG was normal. During EEG telemetry-videotape recording, while in NREM 4 sleep, he suddenly sat up in the chair with

the left arm raised above the head; then both arms were tonically flexed and the legs were extended. These events were rapidly succeeded by semipurposeful movements resembling a searching action, the whole seizure lasting less than 30 seconds. The mother recognised the seizure as similar to his usual ones. The ictal EEG was obscured by artefacts, but the complex stereotyped automatism in sleep enabled the diagnosis of nocturnal complex partial seizures to be made.

Case 4

M.O'B., a 7-year-old boy, suffered major motor fits at the age of 6 weeks, the seizures gradually being controlled with anticonvulsant drugs. At the age of 4 years he developed frequent upward eye-rolling and eyelid flutters while apparently fully conscious. These attacks failed to respond to a variety of anticonvulsant drugs. The eyelid flutters closely mimicked a habit tic and they were intensified while eating and in bright sunlight. There was also a suggestion that he suffered absences and tonic seizures on watching television. EEG telemetry-videotape recordings revealed that the rapid eye flutters were associated with generalised epileptic discharges. He remained alert and orientated during these brief attacks and a diagnosis of eyelid myoclonia (Jeavons, 1977) was made.

Case 5

H.J. was a woman aged 35 years. This patient developed myoclonic jerks when aged 11. Later she developed major motor fits and episodic confusion in the morning. Her seizures were poorly controlled despite an adequate trial of drugs. EEG telemetry-videotaping revealed an additional interesting but minor seizure that consisted of a stereotyped complaint of 'a funny twitch in the forehead and behind the eye either on the left or the right side' with generalised short bursts of atypical 3Hz spike and wave epileptic discharges.

Case 6

M.B., a 23-year-old woman, had had a grand mal fit initially preceded by jaw-clicking while reading a letter, 5 years previously. Since then she suffered jaw clicks and uncontrolled jaw movement while reading silently and while viewing pop art drawings. EEG telemetry with videotape recordings revealed that her reading-triggered seizures were initially rare, but after she had smoked a cigarette the focal seizures were easily triggered for a couple of hours. Further cigarette smoking again facilitated the triggered seizures.

Episodic Psychiatric Symptoms

In 13 patients with episodic psychiatric symptoms, nonspecific interictal EEG abnormalities were seen in 3. 2 patients had their symptoms during the telemetric study but their ictal and interictal EEG remained normal. In the other 8 patients no symptoms were recorded during the study and the EEG remained normal throughout.

Case 7

J.W.M., aged 25, was a schizophrenic, on treatment for 4 years. For 6 months he had suffered episodic symptoms that consisted of a 'funny, fearful, strange feeling' with auditory hallucinations that lasted hours. His examination and repeated EEGs were normal. During EEG telemetry-videotape recording similar symptoms were associated with a normal EEG and he appeared fully conscious and orientated during the attack.

Lateralisation of Seizure Focus

In 3 patients with complex partial seizures who had failed to respond adequately to anticonvulsant drugs, a telemetric study was requested to lateralise the seizure focus with a view to possible surgical extirpation. In 1 patient telemetry was not successful in lateralising the seizure focus. In the other 2 patients, surgery was considered unsuitable on the basis of the telemetric study. (A young female with frequent minor psychomotor seizures arising from the dominant hemisphere had prominent bilateral independent temporal epileptic discharges, the latter not being apparent in earlier EEG studies. In a male with long standing temporal lobe epilepsy, who had undergone 2 surgical excisions of his left temporal lobe 10 years earlier, further surgery was precluded because his temporal lobe seizures also arose from the right hemisphere, and because frequent bitemporal independent epileptic discharges were seen in sleep.)

Evaluation of Additional Seizures in Known Epileptics

In 5 epileptics telemetry was requested to evaluate 'new seizures' that were not responding to current medication. In the first case, the frequent bizarre motor manifestations, which had been interpreted by the attending staff as functional 'turns' were shown to be partial seizures arising from the right hemisphere. Readjustment of medication controlled these new seizures. In the second case symmetrical tonic posturings were not associated with the ictal EEG changes of tonic seizures; her seizures were interpreted as functional attacks. In the third case episodic prolonged experiential phenomena were not associated with scalp EEG seizure discharges. Her seizures were interpreted as functional. In 2 other patients the study was negative as the infrequent new seizures were not recorded during the telemetric study.

Seizure Frequency

In 1 patient aged 14 years with petit mal absences, thought to be on adequate anticonvulsant medication, there was some doubt about the mother's description of continuing frequent absences. EEG telemetry over 6 hours revealed 13 spontaneous absences which supported the correctness of the mother's observations and the need for reviewing the patient's medication.

Excessive Daytime Sleepiness

11 patients were referred for evaluation of excessive daytime sleepiness. The results are shown in table VI.

3 of the patients with narcolepsy had a history of cataplexy and 1 of them had a family history. 2 patients with sleep-apnoea syndrome had a history of snoring in

Table VI. Diagnoses made after EEG telemetry-videotape recording assessment in 11 patients presenting with excessive daytime sleepiness

Final diagnosis	No. of patients
Narcolepsy	4
Sleep-apnoea	2
Subwakefulness syndrome of Mouret	1
NREM sleep disorder requiring further tests for classification	3
Unsuccessful	1

sleep, with apnoeic spells. 1 of them had a very short neck, dwarfism and a narrow mouth, and had difficulty with breathing even while alert.

Syncope and Drop Attacks

13 patients presented with syncope or drop attacks. The study was unsuccessful in 7 as no syncopal attacks occurred during the test and the EEG and ECG remained normal throughout the study. In 2, nonspecific interictal EEG abnormalities were seen. In one woman aged 26 years, interictal epileptic discharges from the temporal lobe suggested that the attacks could be of temporal lobe origin and anticonvulsant drug trial was recommended. In a 25-year-old woman the ECG contained frequent atrial ectopics which were considered by the cardiologist to be a benign finding.

In 2 other females (aged 35 and 40) with frequent syncope not related to postural changes, the clinical examination and prolonged interictal EEG and ECG were normal. During syncopal attacks no EEG or ECG changes were apparent. It was not possible to identify any reflex-evoking factors for their syncopes.

Miscellaneous Conditions

EEG telemetry-videotape recordings were also useful in the following instances:

1) In the patient with sleep paralysis the demonstration of sleep-onset REMS in a polygraphic study identified the problem as narcolepsy.

2) In a 21-year-old male with a left hemisphere arteriovenous malformation, who presented with subarachnoid haemorrhage, speech lateralisation was requested prior to surgery. A Wada intracarotid sodium amylobarbitone test (Wada and Rasmussen, 1960) lateralised the speech centres to the right hemisphere in this left-handed person.

3) A 47-year-old man with 'cardiac irregularities' following a viral infection developed 7 'nocturnal seizures', all of which necessitated hospitalisation. The

seizures were signalled by his wife's being woken up in the early hours of the morning by her husband's strange noisy breathing. The patient on admission was partially obtunded and had an irregular pulse that became gradually normal. The EEG and ECG on prolonged telemetry remained normal until hyperventilation induced multifocal and bigeminal ventricular ectopics. This finding suggested that the nocturnal seizures could have been of cardiac origin and related to the respiratory changes of REM sleep. However, nocturnal polygraphic studies were declined.

4) In a female aged 50 with episodic amnesia for recent events, persistent bitemporal slow waves suggested bitemporal structural disorder as the basis of her symptoms.

5) In a patient with sleep-apnoea in whom a permanent tracheostomy was being contemplated, the telemetric study suggested that the symptoms were probably not due to temporal lobe epilepsy.

Discussion

Prolonged EEG monitoring over several hours increases the probability of recording a seizure and of demonstrating interictal epileptiform discharges as a direct consequence of increasing the EEG sampling time. A simultaneous videotape recording of the ictus allows repeated replay and detailed analysis of the clinical events in the seizure. Thus prolonged EEG studies combined with videotape recordings can be used as an important diagnostic tool in epileptic disorders, especially in the circumstances where the usual EEG tests and history have been unhelpful.

The Disa 25A06 Videograph system provides one method of obtaining EEG and the television images of patients over several hours. Systems such as these have been used for several purposes:

1) To diagnose epileptic seizures and to determine whether seizures are associated with focal or generalised EEG abnormalities (Bowden et al., 1975).

2) To conduct intensive inpatient therapeutic re-evaluation of intractable epileptics with the aim of achieving better seizure control (Porter et al., 1977).

3) To obtain an objective estimate of absence seizure frequency (Browne et al., 1974).

4) To determine the clinical manifestations of frontal lobe seizures (Geier et al., 1977).

5) To determine the clinical accompaniments of absences and other seizures (Kiffin Penry et al., 1975; Porter et al., 1976).

6) To localise a seizure focus (Stevens et al., 1969; Adams and Rutkin, 1972; Lieb et al., 1976).

7) To evaluate environmental influences on the occurrence of petit mal absences (Guey et al., 1969).

8) To determine the relationship of absences to activities (Bureau et al., 1968).

9) To conduct research into somnambulism (Broughton and Gastaut, 1975).

The present study suggests that the 3 main applications of prolonged EEG telemetry-videotape recording are:

a) the diagnosis of epilepsy
b) identifying the type or types of seizure
c) identifying the cause of excessive daytime sleepiness.

The studies confirmed a seizure disorder in approximately half the patients who presented with absences, blackouts, symptoms resembling complex partial seizure and tonic-clonic, tonic, adversive or myoclonic episodic symptoms. Recording a seizure during the study, with its characteristic ictal EEG changes, allowed identification of a seizure disorder and its type in 25% of positive results. Obviously the more frequent the seizure and the longer the EEG telemetry-videotape recording time, the greater is the likelihood of recording a seizure. By identifying trigger factors, seizure frequency and their relationship to sleep, time of day and menstrual periods, one could choose the appropriate time for the telemetric study and improve on the positive yield of this test. Nevertheless, our data suggest that prolonged EEG telemetry is also useful in patients with infrequent seizures, as a diagnostic conclusion may still be made from characteristic and appropriately distributed interictal paroxysmal abnormalities.

In seizures where the ictal EEG is normal or obscured by artefacts and the interictal EEG is normal or nonspecifically abnormal, a videotape record of a motor seizure and its analysis may still provide diagnostic information either because of the resemblance of the recorded ictus to known motor seizures, or if it is bizarre by its complexity, and its occurrence in situations where voluntary mimicking is impossible.

The situation, however, is quite different in patients in whom the ictus is a psychosensory or psychiatric manifestation with a normal interictal and ictal-telemetered EEG. In these instances, although one could conclude that the study did not suggest a seizure disorder, it is not possible to be entirely certain of this conclusion, as partial seizures may occur without producing scalp EEG abnormalities (Abraham and Ajmmone-Marsan, 1958; Ajmmone-Marsan and Abraham, 1960; Klass, 1975; Thomas et al., 1977).

The videotaping of seizures is an excellent method of correctly identifying the seizure type. Correct identification of seizure type has important therapeutic and prognostic implications. In addition the test could reveal important clinical details which are generally not available in the history from lay observers. Some of these clinical details, such as the seizure occurrence in relation to specific states (mental inactivity or alertness, physical activity, sleep and environmental factors) and the identification of specific seizure triggers, have relevance to therapy and advice on the avoidance of seizure-provoking factors or situations. Thus in the patient with reading epilepsy it was conclusively demonstrated that reading-triggered seizures were readily

facilitated after smoking cigarettes, and she was advised not to smoke before or while reading. Gloor (1975) drew attention to the frequency of minor seizures recorded by prolonged depth EEG recordings, which are not apparent to even the most astute clinical observer. Observations, such as those on Case 5. and their documentation help to increase the awareness of clinicians of the possibility that repetitive and stereotyped symptoms, however bizarre or innocuous, may be epileptic.

The present study confirms the observations of other workers (Stevens, 1969; Adams and Rutkin, 1972; Browne et al., 1976; Lieb et al., 1976) of the value of prolonged telemetered EEG videotape recordings in:

a) determining the frequency of absence seizures

b) localising epileptic foci in patients being evaluated for surgery for epilepsy.

One particular area where this test was especially important was in patients known to be epileptics who over the years developed new seizures which failed to respond to the initial drug regimen. Videotape recordings with telemetered EEG may help decide whether these new seizures are organic or functional.

In syncopal conditions both the EEG and ECG can be monitored continuously and the relevant portions of the ECG and EEG preceding and during the syncope easily identified. These portions of both electrical parameters can then be carefully scrutinised to determine if the syncope is an atonic seizure or due to a cardiac arrhythmia. In 2 patients not only was the interictal EEG and ECG normal but the ictal portions were also normal. The syncopes were unrelated to posture, and reflex factors were unidentifiable. These attacks were not due to an electrical abnormality of the heart and were not atonic seizures. Although partial seizures may occur without scalp EEG changes we are reluctant to ascribe these attacks to epileptic seizures in view of the persistently normal EEG, the absence of other seizures, the onset in adult life and failure to respond to adequate trials of anticonvulsant drugs. It remains to be seen whether intermittent autonomic failure with postural hypotension or intermittent failure of postural muscle tone underlies these attacks.

The causes of excessive daytime sleepiness (Guilleminault and Dement, 1977) may be identified by prolonged EEG telemetry. Several hours of polygraphic data can be scanned on the television monitor, allowing samples of relevant data on tape or paper to be saved for subsequent detailed analysis by the electroencephalographer. The test is comfortable for the patient, noise-free, saves paper wastage, and does not commit an EEG machine to just one patient for hours.

The Disa Videograph system has some disadvantages. The connections of the electrodes to the transmitter are prone to produce greater artefacts than cable transmission, and the videotape recordings can only be replayed in real time. In practical terms, therefore, on-line analysis of data is necessary, and a highly trained and knowledgeable technician is required throughout the study, to facilitate tape editing and the correlating of relevant portions for further analysis.

Alternative methods are available for obtaining prolonged EEG records. 24-hour EEG cassette recordings of ambulatory patients with accelerated replay analysis

of the tapes (Ives and Woods, 1975; Apple and Burgess, 1976; Ives, 1976) is one method. However, this technique lacks a video component, is limited to 4 channels of information and the technical quality of the records is inferior to that of the Disa Videograph system. Prolonged cable EEG and videotape recordings with automatic computerised sampling of recorded seizures (Ives et al., 1976) are excellent for seizure monitoring, but the equipment is expensive and complex.

Summary

The clinical application of prolonged monitoring by the combined EEG and videotape recording of patients was evaluated. This test was found to be useful in diagnosing epileptic seizures in patients in whom both the history and diurnal EEG studies were unhelpful, and it assisted with the accurate classification of seizure types. It enabled seizure focus lateralisation in medically intractable epileptics who were being evaluated for surgery, and it also provided an objective estimate of minor seizure frequency.

Prolonged EEG telemetry and videotape recording was especially useful in assessing additional seizures that develop in known epileptics. In some patients with syncope and drop attacks this technique helped to exclude atonic epileptic seizures and intermittent cardiac tachy-brady-arrhythmia as the underlying cause. As a method for identifying sleep disorders it has greater merits than conventional methods of polygraphic recordings.

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The Epoxide of Carbamazepine

*L. McKauge, J.H. Tyrer and M.J. Eadie**

There are several unresolved questions concerning the clinical pharmacology of the anticonvulsant carbamazepine. Two of these questions are:

1) Why have authors repeatedly found no correlation, or only a very poor correlation, between steady-state plasma carbamazepine levels and carbamazepine dose in patients treated with the drug?
2) What is the mechanism of the well documented interaction in which increasing dosage of phenytoin is associated with a fall in steady-state plasma carbamazepine levels in patients receiving anticonvulsants (e.g. Christiansen and Dam, 1973; Hooper et al., 1974)?

In an attempt to answer these questions we have measured simultaneous steady-state plasma levels of carbamazepine and of its metabolite carbamazepine-10,11-epoxide. The epoxide is a first stage biotransformation product of carbamazepine, and in animals it is an anticonvulsant in its own right (Morselli et al., 1975). Measurement of plasma carbamazepine epoxide levels might not only help answer the questions raised above, but might also provide information of more immediate clinical relevance to the control of epilepsy.

Carbamazepine Biotransformation

According to Faigle et al. (1975) the molecule of carbamazepine may be oxidised, either at the C = C bond of the central ring to form carbamazepine-10,11-epoxide, or

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at one of the C atoms in the peripheral aromatic rings to form a phenolic derivative (fig. 1). Carbamazepine epoxide may be further biotransformed to a dihydroxy derivative or possibly to a hydroxymethyl acridan derivative. The dihydroxy derivative is the main metabolite of carbamazepine found in human urine.

Materials and Methods

Measurement of Carbamazepine and Carbamazepine Epoxide

Epoxides are often rather unstable thermo-labile compounds. Carbamazepine epoxide cannot be measured satisfactorily by the gas chromatographic techniques that are used to measure carbamazepine. The epoxide decomposes at the temperatures necessary for gas chromatography. However, both carbamazepine and its epoxide can be measured simultaneously by high pressure liquid chromatography carried out at room temperature, using a methoxy derivative of carbamazepine as an internal standard.

The technique employed in the present study was as follows: 1ml plasma was mixed with 1ml 0.2M.Na_3PO_4 solution and with 5ml chloroform containing the internal standard 10-methoxycarbamazepine in a concentration of 2mg/litre. The organic layer was removed and evaporated to dryness. The residue was taken up into 50µL and 25µL were injected into the injection loop of a Tracor liquid chromatogra-

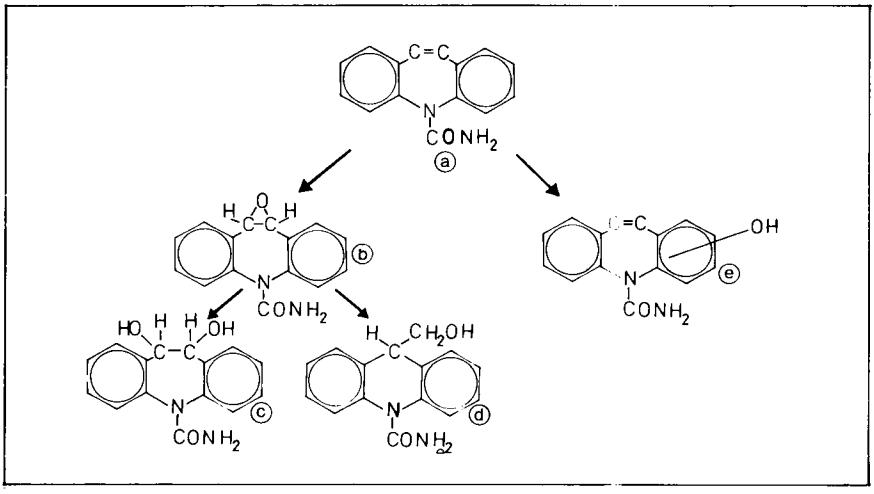

Fig. 1. Biotransformation pathway for carbamazepine. a) carbamazepine b) carbamazepine-10,11-epoxide c) 10,11-dihydroxycarbamazepine d) 9-hydroxymethyl-10-carbamoyl acridan e) 1,2 or 3-hydroxycarbamazepine.

phy system which utilised a 50% methanol-water mobile phase with a flow rate of 2ml/min, and an octadecyl silane column (Waters C-18μ Bondapak). The effluent from the column was scanned at 215nmm in a Varian spectrophotometer equipped with a micro-flow cell. Quantitation of carbamazepine and its epoxide was effected by measurement of the relevant peak-heights relative to that of the internal standard.

Plasma carbamazepine levels in the steady-state show relatively little fluctuation across a dosage interval (Eadie and Tyrer, in press). Therefore the timing of plasma carbamazepine level measurement in relation to the timing of drug intake was relatively unimportant for the purposes of the present study. The data of figure 2 suggest that, under steady-state conditions, plasma carbamazepine epoxide levels also show little fluctuation over a dosage interval. Therefore the exact timing of the measurements of the epoxide plasma levels was also probably unimportant.

Statistical Analysis

Plasma level data were analysed by various linear, curvilinear and multiple variable linear regression techniques, using a programmable Hewlett-Packard 9810 desk calculator.

Patients Studied

Measurements of simultaneous steady-state plasma carbamazepine and carbamazepine epoxide levels were carried out on 101 epileptic patients. These patients ranged in age from 1 to 68 years (mean 26.4 ± SD 16.4 years). They comprised 52 males and 49 females. Body weights, and doses of any concurrent therapy, were known for all patients. Only a single set of values for each patient was used in the analysis of data.

Results

The Relation Between Carbamazepine Dose and Plasma Levels of Carbamazepine and Carbamazepine Epoxide

10 variable linear regression analysis was used to study the relation between plasma levels of a) carbamazepine, b) carbamazepine epoxide, or c) carbamazepine to carbamazepine epoxide ratios, and doses of carbamazepine, phenytoin, phenobarbitone, methylphenobarbitone, primidone, sulthiame, ethosuximide, clonazepam, nitrazepam and valproate. For simplicity, at this stage, only the regressions for the various plasma levels on carbamazepine dose are shown (plasma levels are expressed in mg/litre, and drug doses in mg/kg/day):

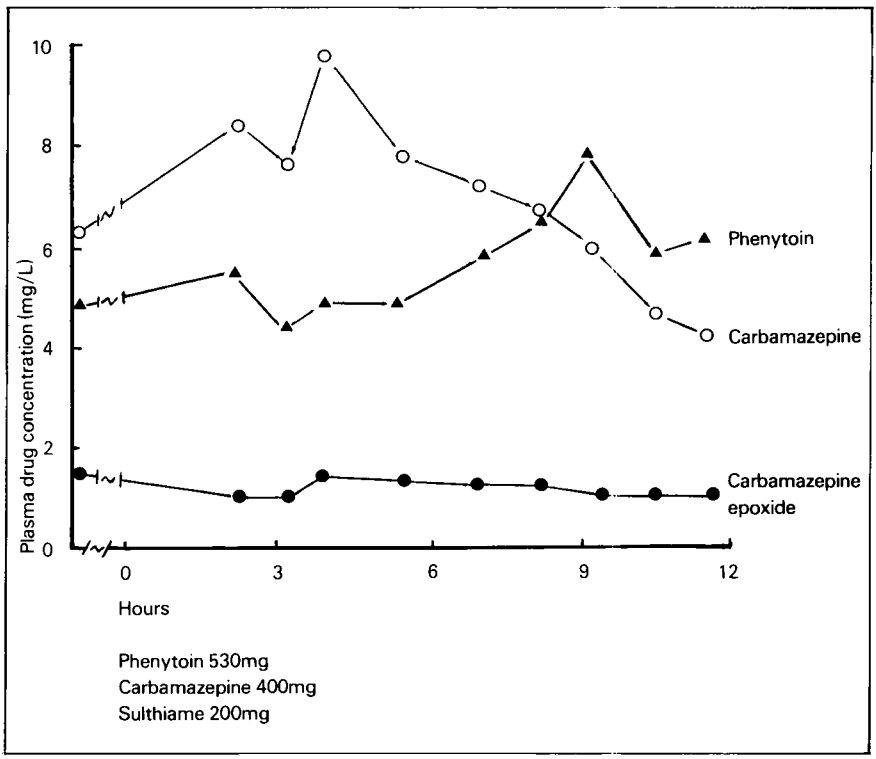

Fig. 2. Steady-state time-courses of plasma concentrations of carbamazepine, carbamazepine-10,11-epoxide and phenytoin in 1 patient.

a) plasma carbamazepine level = 6.0980 + 0.0285 carbamazepine dose
b) plasma carbamazepine epoxide level = 0.9377 + 0.0240 carbamazepine dose
c) plasma carbamazepine/carbamazepine epoxide ratio = 6.0781-0.0365 carbamazepine dose.

The partial correlation coefficients for the 3 equations are, respectively, 0.0253 ($p > 0.10$), 0.2780 ($p < .01$) and 0.1902 ($0.05 < p < 0.10$).

Thus the plasma carbamazepine levels, and plasma carbamazepine/-carbamazepine epoxide ratios, do not correlate with the carbamazepine dose, but plasma carbamazepine epoxide levels do correlate, though not particularly well (fig. 3).

In view of the latter correlation, the possibility of a correlation between the sum of simultaneous plasma carbamazepine and carbamazepine epoxide levels in each patient and carbamazepine dose was investigated. Neither a linear regression nor a

variety of curvilinear regressions could be fitted to the data at a statistically significant level of confidence.

The Relation between Simultaneous Plasma Level of Carbamazepine and its Epoxide

There was a statistically significant ($r = .416$, $p < .001$) linear relationship between plasma levels of carbamazepine and carbamazepine epoxide in the population studied (fig. 4). The data could be fitted even more closely ($r^2 = .3002$) by a power curve of the form $y = .5294\ x^{.5309}$, where $y =$ plasma carbamazepine epoxide level and $x =$ plasma carbamazepine level.

The Effects of Phenytoin on Plasma Carbamazepine Levels

The multiple variable linear regression analyses referred to above showed that, while carbamazepine dose did not correlate with plasma carbamazepine level, pheny-

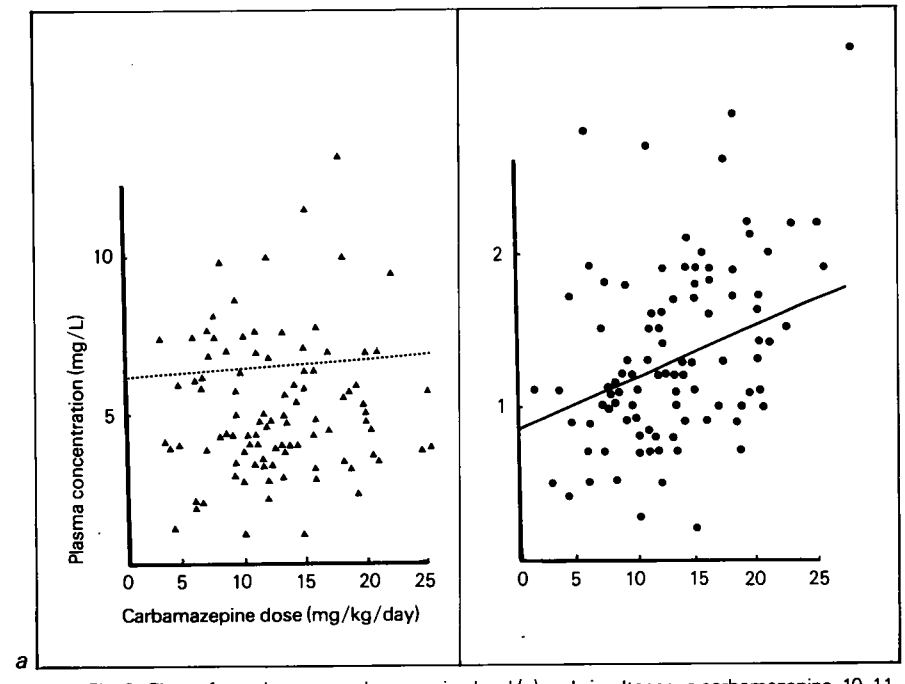

Fig. 3. Plots of steady-state carbamazepine level (a) and simultaneous carbamazepine-10-11-epoxide level (b) against carbamazepine dose. No statistically significant regression can be fitted for the plasma carbamazepine level data, though there is a statistically significant regression for the epoxide data.

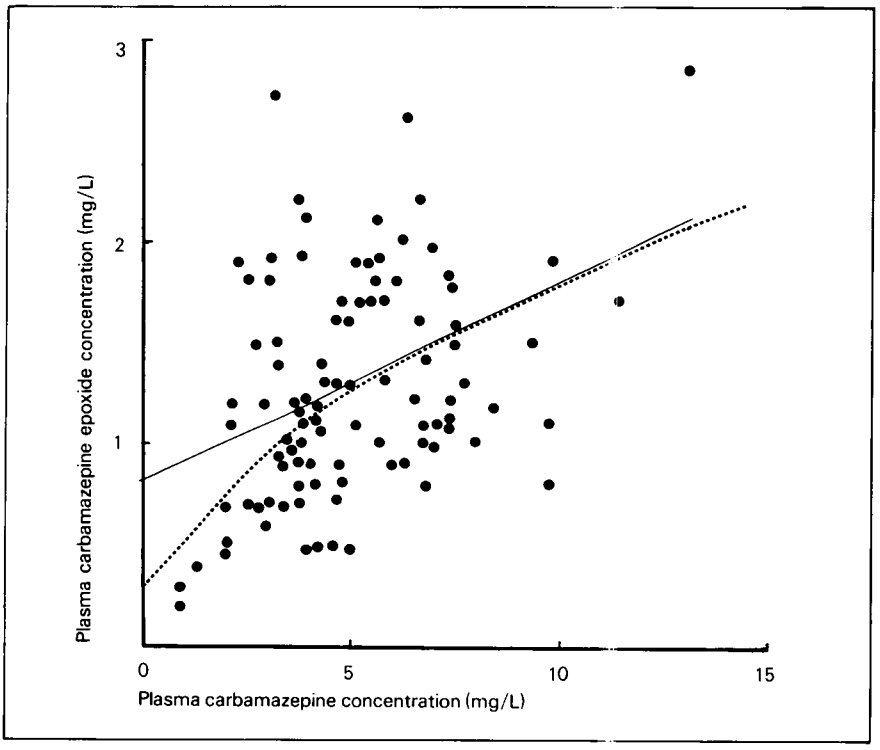

Fig. 4. Relation between simultaneously measured plasma carbamazepine and plasma carbamazepine epoxide levels.

toin dose had a statistically significant negative ($r = .449$, $p < .001$) correlation with plasma carbamazepine level. The regression equation, omitting the terms referring to drugs other than carbamazepine (x_1) and phenytoin (x_2), was:

$$\text{Plasma carbamazepine level} = 6.0980 + 0.0285\ x_1 - 0.3882\ x_2.$$

However, similar regression analysis showed that phenytoin dose had no statistically significant ($r = 0.0892$, $p > 0.10$) effect on the relation between plasma carbamazepine epoxide level and drug doses. This regression had the form:

$$\text{Plasma carbamazepine epoxide level} = 0.0377 + 0.2441\ x_1 - 0.0003\ x_2.$$

Phenytoin dosage had a statistically significant effect on the plasma carbamazepine to carbamazepine epoxide concentration ratios ($r = 0.500$, $p < .001$).

The relevant terms of the regression equation were:

$$\text{Carbamazepine/carbamazepine epoxide ratio} = 6.0781 - 0.0365_{x_1} - 0.02809_{x_2}.$$

As shown in figure 5, plasma carbamazepine epoxide levels were plotted against simultaneous plasma carbamazepine levels in 62 subjects taking phenytoin as well as carbamazepine, and in 33 subjects taking carbamazepine, but not phenytoin, valproate, phenobarbitone or a drug metabolised to phenobarbitone (since the multivariate regression analyses, or previous work, had raised the possibility that any of these drugs might affect plasma carbamazepine levels). The 2 regressions were each statistically significant ($p < .001$), and the lines differed in elevation to a statistically significant extent ($p < .001$). Plasma carbamazepine epoxide levels tended to be higher relative to plasma carbamazepine levels when subjects took phenytoin.

Plasma carbamazepine epoxide levels were plotted against carbamazepine dose in patients taking carbamazepine alone, and carbamazepine with phenytoin (fig. 6). No statistically significant regression could be fitted to the data for patients taking carbamazepine alone, so the comparison of the 2 regressions was not possible. However, it may be seen from figure 6 that, for the usual carbamazepine dose of 10 to 15mg/kg/day, mean plasma carbamazepine epoxide levels in the 2 groups of patients would have been similar if one were prepared to accept the non-statistically significant regression line.

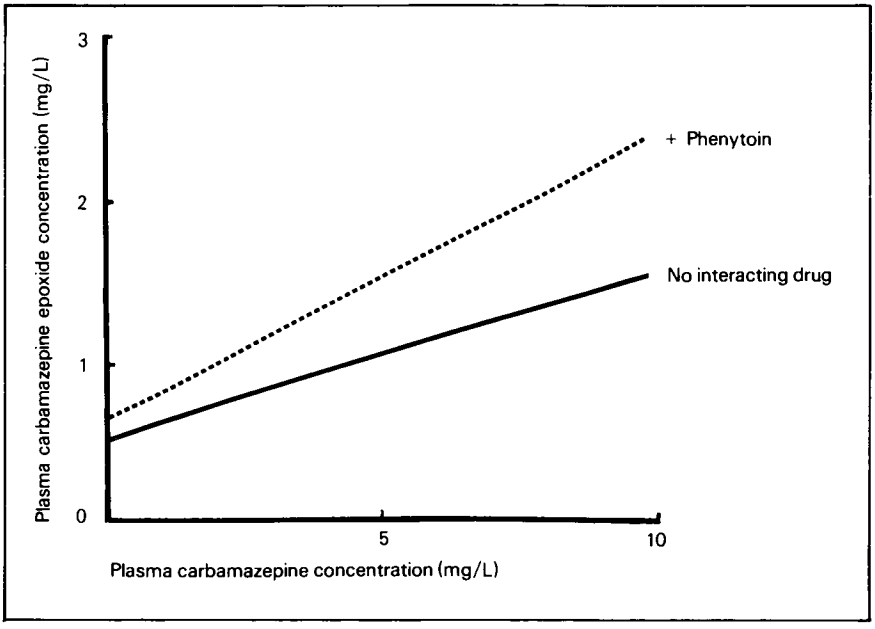

Fig. 5. Linear regressions for plasma carbamazepine epoxide level on plasma carbamazepine level in patients taking carbamazepine with phenytoin, and in patients taking carbamazepine alone, or with drugs known not to interact with it.

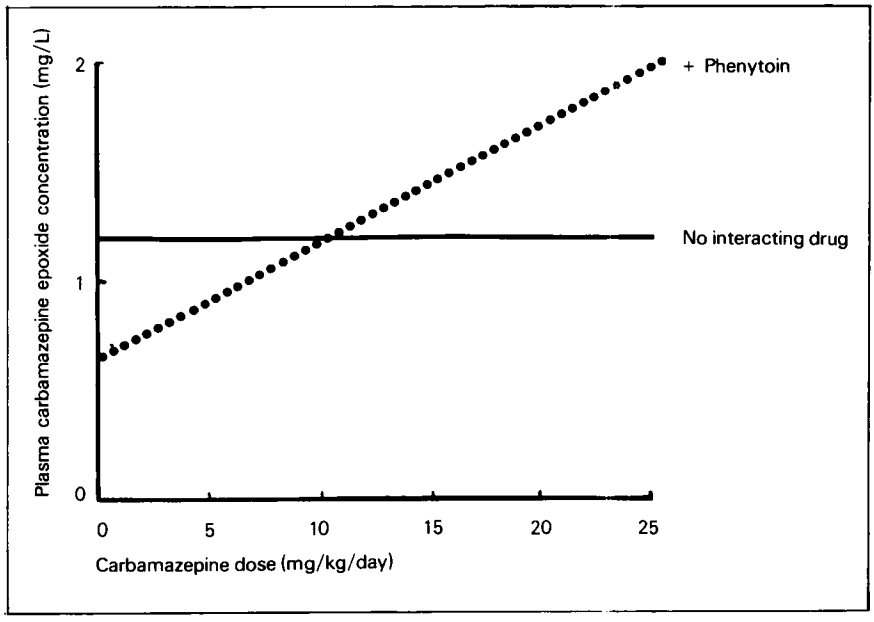

Fig. 6. Linear regression for plasma carbamazepine epoxide level on carbamazepine dose in patients taking carbamazepine with phenytoin and in patients taking carbamazepine alone. It should be noted that the regression in the latter patients is not statistically significant.

Discussion

The present study, like previous investigations (Reynolds, 1973; Hooper et al., 1974; Eichelbaum et al., 1976; Johanessen et al., 1976; Rane et al., 1976; Lander et al., 1977) has demonstrated a lack of correlation between steady-state plasma carbamazepine levels and carbamazepine dose. The reasons for this lack of correlation have not been determined. There is a poor but statistically significant correlation between plasma carbamazepine epoxide level and carbamazepine dose. Carbamazepine epoxide is derived from carbamazepine and the plasma levels of the two have been shown to correlate in the present study. These results make it unlikely that widely differing capacities in the population for biotransforming carbamazepine to its epoxide account for the absence of correlation between plasma carbamazepine level and carbamazepine dose. Inevitably one would suspect that the bioavailability of carbamazepine might be incomplete and variable, and some previous work has suggested that this may be so (Cotter et al., 1975, 1977; Morselli, 1975).

The present study has also shown that phenytoin intake is related to a fall in plasma carbamazepine levels in the treated population, but not to a change in plasma carbamazepine epoxide levels. If the interaction between the 2 drugs has a single

mechanism it seems that phenytoin may increase the elimination of carbamazepine by converting more of a carbamazepine dose to metabolites other than the epoxide (since plasma carbamazepine epoxide levels show no statistically significant change when phenytoin is taken with carbamazepine). However, if the interaction involves multiple mechanisms there could be, for instance, altered bioavailability of carbamazepine in the presence of phenytoin, and also altered carbamazepine epoxide elimination. Measurements of metabolite excretion should clarify the question. However, the findings of the present study imply that the mechanism previously suggested for the interaction — increased conversion of carbamazepine to its epoxide in the presence of phenytoin (Dam et al., 1975; Schneider, 1975) — may not be correct.

Summary

Simultaneous steady-state plasma concentrations of carbamazepine and carbamazepine-10,11-epoxide have been measured by high pressure liquid chromatography in 101 epileptic chidren and adults taking the drug. There was either no statistically significant correlation, or only a very poor correlation, between drug dose and steady-state plasma levels of a) carbamazepine, b) its epoxide, and c) the sum of drug and epoxide. Plasma concentrations of carbamazepine correlated with those of its epoxide. Plasma carbamazepine levels were lower in patients taking phenytoin with carbamazepine than in patients taking carbamazepine alone. Plasma carbamazepine-10,11-epoxide levels were not definitely altered when carbamazepine and phenytoin were used together. This finding is consistent with the hypothesis that phenytoin enhances the metabolism of carbamazepine to a metabolite other than its epoxide.

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The Neurological Aspects of Atrial Myxoma

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The origin of atrial myxomas is uncertain. They are thought to be endothelial or subendothelial, and the myxoid component is thought to represent degenerative change consequent to mechanical trauma (Yufe et al., 1976). Myxomas are covered by a thin endothelial layer surrounding an amorphous basophilic centre, which includes scattered spindle-shaped and stellate cells plus thin-walled blood-filled spaces and multinucleated cells (Schwarz et al., 1972).

In 1965 there were 352 cases of intracardiac myxomas reported in the literature, but by December 1977 this figure was well over 1,000 (Wharton, 1977). The incidence of atrial myxomas varies, with figures such as 0.2% of all necropsies according to Bauman and Clavedetscher's series in 1969 (Koikkalainen et al., 1977) and 0.025% (Heath, 1968). It has been suggested that the accepted incidence would be about 0.05% of all necropsies (Silverman et al., 1962; Joynt et al., 1965; Yufe et al., 1976).

This paper reports 2 cases of left atrial myxoma that were diagnosed at the Queen Elizabeth Hospital in Adelaide in 1978.

The recent literature is reviewed to emphasise the varied presentations of atrial myxomas and to highlight the role of echocardiography in establishing the diagnosis and hence determining management.

Case Reports

Case 1

A woman aged 33 presented in January 1978 with the sudden onset of right-sided facial and upper limb dysaesthesia associated with a sensation of 'flashes of light', blurring of vision and a left occipital

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headache. The character of the headache was not reported at the time. Following the onset of the headache she vomited.

She was referred to hospital with the comment from her private doctor that it was probably a mild CVA. She described 'migraines' occurring at 6-monthly intervals, affecting the occipital region and lasting for 24 to 48 hours, since childhood. She had occasional nondescript chest pain when lying flat in bed. There was no history of regular medication, other than occasional paracetamol, and she was not using oral contraceptives. She smoked 10 cigarettes daily and abstained from alcohol. There was no relevant family history.

Examination at the time of her initial assessment revealed slight weakness in the right upper limb. The distribution of this weakness was not reported in detail. The rest of the examination was reported as normal. Only 2 investigations were performed at this time. An EEG showed a left anterior temporal theta wave focus (fig. 1) and nucleotide brain scans performed in January and February 1978 were normal. A provisional diagnosis of migraine was made in February 1978, and she was followed in the general medical outpatients. She subsequently had 12 episodes of migraine.

5 days prior to her second admission she attended her private doctor because of 'heart thumping', and was reassured. On 10 June 1978, she was admitted following a collapse. At this stage the referring note reported a loud first heart sound, a diastolic murmur, a complete left hemiparesis and left hemianalgesia. The admission history was that after a few seconds of light-headedness, while brushing her teeth, she collapsed into the bathtub. She remembered falling and hitting her occiput and denied loss of consciousness. Left-sided weakness and loss of sensation was apparent to her within seconds of the fall. Following this she vomited and became aware of right-sided occipital headache which was constant in nature. No visual symptoms or significant neck stiffness were experienced. Examination at the time of her admission confirmed the above features, as well as revealing a left homonymous hemianopia. A diagnosis of cerebral embolus of cardiac origin was made.

During admission further evidence of arterial emboli was observed in the toes of the left foot and in the right thigh. Results of investigations carried out during this admission are set out in table I. Echocardiograph and cardiac catheterisation (figs. 2 and 3) confirmed the presence of left atrial myxoma and she was referred for cardiac surgery.

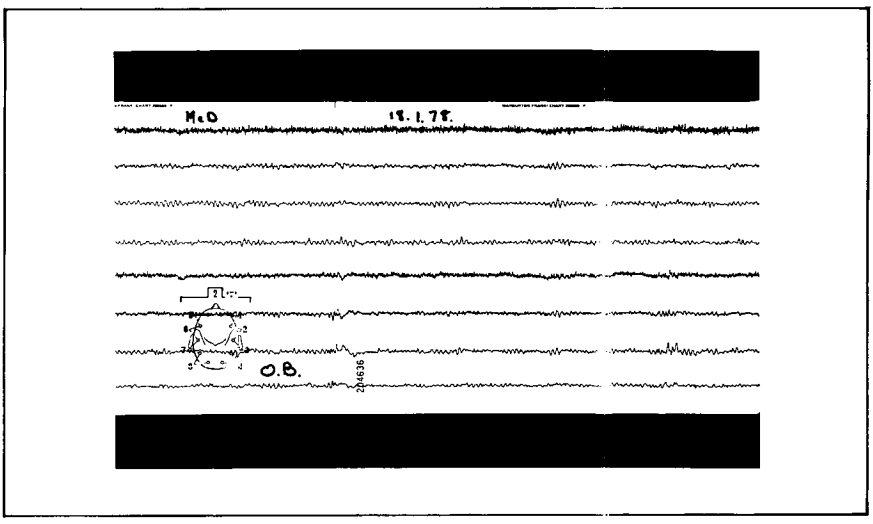


Fig. 1. EEG performed on Case 1 showing a left anterior temporal theta wave focus.

Table I. Results of investigations performed on Case 1

Investigation	Results	Normal range
Blood picture	Normal, but white cell count $13.1 \times 10^3/mm^3$	$4\text{-}12 \times 10^3/mm^3$
	ESR 19mm in 1st h	2-7mm 1st h
Biochemical profile	Normal, but serum alkaline phosphatase 137U/L	25-90U/L
Chest radiograph	Normal	
Skull radiograph	Displaced pineal gland 4mm to the left of the midline	
Electrocardiograph	Normal	
Protein electrophoresis	Albumin 31g/L	35-50g/L
	Beta globulin 12g/L (nonspecific pattern)	4-10g/L
Echocardiograph	See figure 2	
Cardiac catheterisation	See figure 3	

Case 2

A 53-year-old woman was brought to hospital at 1800 hours on 5 July 1978, having been found slumped over the steering wheel of her car which was parked awkwardly and facing in the wrong direction by the roadside. She had vomited en route to hospital.

At the time of admission she was stuporose with eyes opening spontaneously, commands being obeyed and with stable observations (Teasdale and Jennett, 1974). Her head and eyes were deviated to the right. There was generalised muscle hypertonicity, but it was impossible to be certain of localising signs at this time. She had no neck stiffness and Kernig's sign was absent. The plantar responses were equivocal. Cardiovascular examination revealed no clinical abnormality. Initial management involved administering oxygen, parenteral antibiotics, and parenteral steroids. The results of investigations are shown in table II. 5.5 hours later she was more alert and able to give a history. She stated that over the preceding months she had experienced dyspnoea and decreasing effort tolerance, over the week prior to presentation. She also reported transient episodes of blurring of vision. There was no history of drug abuse. She was a non-smoker and her alcohol consumption was minimal.

Examination revealed spastic posturing and lack of movement on the right side. There was a suggestion of a left homonymous hemianopia and some weakness of the left finger extensor and abductor muscles. The right plantar response was extensor and there was impaired sensation to light touch and vibration in the right lower limb. It was suspected that there was more than one lesion, and a CAT head scan was performed (fig. 4).

The results of other investigations are set out in table II. Echocardiography and cardiac catheterisation (figs. 5 and 6) confirmed the presence of left atrial myxoma, and the patient was referred for cardiac surgery.

Table II. Results of investigations performed on Case 2

Investigation	Results	Normal range
Blood picture	Normal, but white cell count $15.3 \times 10^3/mm^3$, falling to normal during admission.	$4\text{-}12 \times 10^3/mm^3$
	ESR 78mm in 1st h, rising to 90	2-7mm 1st h
Biochemical profile	Normal, but blood glucose rising to 10.8mmol/L	3.1-8.3mmol/L
	Amino aspartate transferase 88U/L	0-50U/L
	Serum alkaline phosphatase 114U/L	25-90U/L
	Lactate dehydrogenase > 835U/L	120-250U/L
Chest radiograph	Suggestive of infection or aspiration	
Skull radiograph	Calcified pineal gland midline and no significant findings other than calcification noted in the carotid syphon	
Electrocardiograph	See figure 7	
Protein electrophoresis	Albumin 33g/L	35-50g/L
	A_2 globulin 13g/L	5-10g/L
	Beta globulin 12g/L	4-10g/L
Carboxyhaemoglobin	None detected	
Immunoelectrophoresis	IgG 20.8g/L	6-18g/L
	IgA 2.2g/L	0.5-3.5g/L
	IgM 6.75g/L	0.5-3.5g/L
Serum complement levels	Normal	
Serum lipid studies	Normal	
Antinuclear factor	Negative	
Blood culture	Negative	
Drug screen	No drugs detected in plasma	
Echocardiograph	See figure 5	
Cardiac catheterisation	See figure 6	

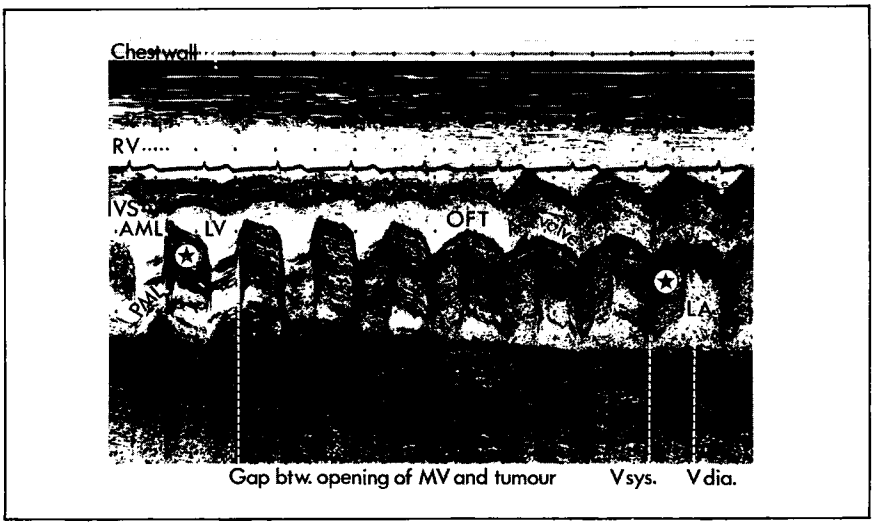


Fig. 2. Echocardiographic scan performed on Case 1 demonstrating the prolapsing left atrial myxoma with the mass of reflecting tumour passing between the left atrium and left ventricle. ★ Atrial myxoma. AML Anterior mitral leaflet. AO Aorta. IVS Interventricular septum. LA Left atrium. LV Left ventricle. MV Mitral valve. OFT Outflow tract. PML Posterior mitral leaflet. RV Right ventricle. V dia. Ventricular diastole. V sys. Ventricular systole.

Discussion

Intracardiac neoplasms are rare. The most common primary intracardiac tumour is a myxoma, which accounts for 50% of intracardiac neoplasms (Joynt et al., 1965; Finegan and Harrison, 1970; Yufe et al., 1976).

Both cases reported here were female, and it is reported that females are affected 3 times as commonly as males (Kyllonen et al., 1976; Yufe et al., 1976; Meller et al., 1977). Onset occurs most commonly in the 30- to 60-year age group (Silverman et al., 1962; Yufe et al., 1976; Wharton, 1977) and this range includes both cases reported here. Familial cases have been reported (Kyllonen et al., 1976; Yufe et al., 1976). Though myxomas are thought to be rare in childhood, this may in fact be the result of inadequate investigation.

Atrial myxomas may be asymptomatic or may present with constitutional symptoms (Morgan et al., 1977). These include fever, malaise, Raynaud's phenomenon, weight loss, anaemia, leukocytosis, protein abnormalities and raised serum globulins (Goodwin, 1963, 1968; Schwarz et al., 1972; Koikkalainen et al., 1977). Both patients reported here had leukocytosis and elevated sedimentation rates. Both cases demonstrated abnormal serum protein levels, and Case 2 was investigated for the possibility of a vasculitis (tables I and II). Joynt et al. (1965) make the point that there is no definite pathognomonic clinical syndrome.

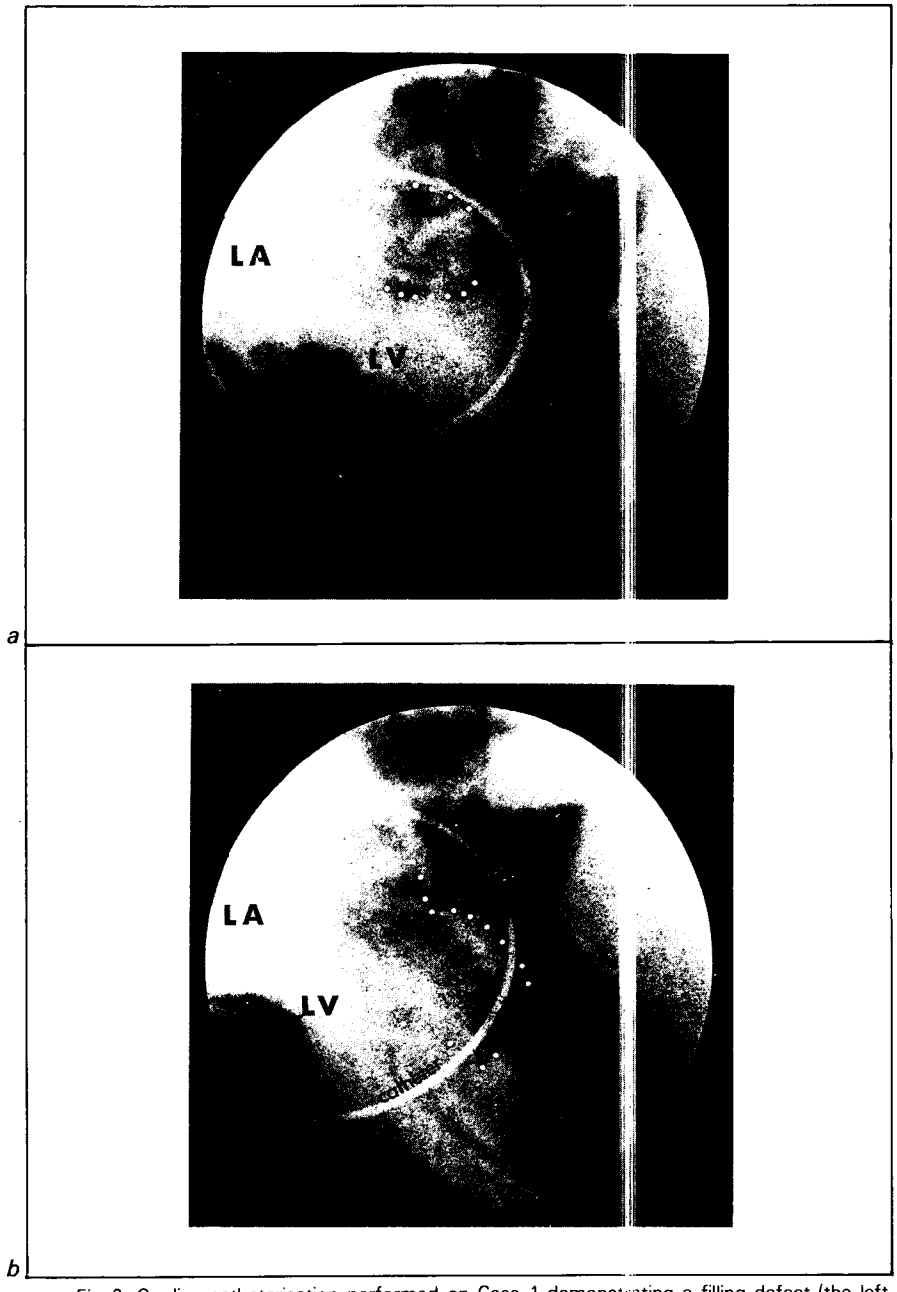


Fig. 3. Cardiac catheterisation performed on Case 1 demonstrating a filling defect (the left atrial myxoma) passing a) from the left atrium (LA) to b) the left ventricle (LV).

Though myxomas are histologically benign lesions they behave in a malignant fashion (Kokkalainen et al., 1977) with more than 50% leading to emboli (Kyllonen et al., 1976). These emboli may be formed by tumour fragments or by thrombi dislodged from the tumour surface (Morgan et al., 1977; Nishimura, 1977) and may finally rest in any organ or vessel. The brain is described as the target site in at least half of the cases, especially in the middle cerebral artery or internal carotid artery territory (Schwarz et al., 1972; Yufe et al., 1976). Both of our cases demonstrated the effects of cerebral infarction subsequent to embolisation.

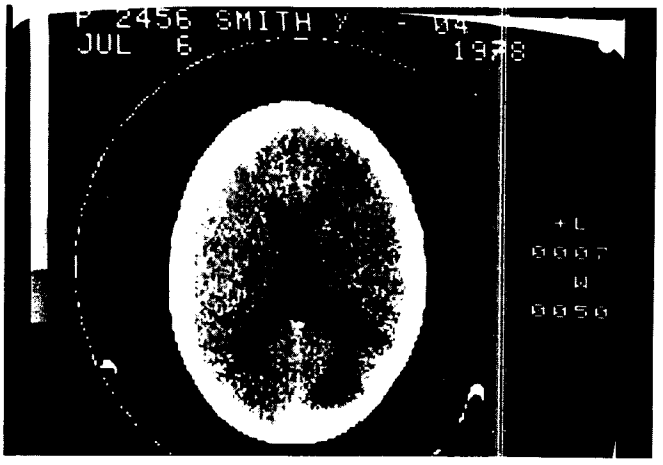
Neurological manifestations of myxomas sometimes antedate definitive diagnosis (Joynt et al., 1965). Kyllonen et al. (1976) reported 19 years between initial symptoms and final diagnosis in one case. Case 1 presented at least 6 months prior to diagnosis and had had migraine for as long as she could remember. Case 2 gave a history of transient visual disturbance which could have been the result of small emboli. This seems probable since an occipital infarction seemed indicated by CAT scans of the head (fig. 4).

Cerebral emboli often leave permanent neurological deficits (Koikkalainen et al., 1977). There is evidence that smaller tumour emboli may continue to grow *in situ*, resulting in arterial wall invasion with subsequent development of multiple aneurysms (Schwarz et al., 1972; Damasio et al., 1975). Progress CAT scanning and cerebral angiography may be of value to assess this possibility, and it is contemplated that these procedures will be performed in our reported cases.

Another neurological manifestation of myxoma is epilepsy. This has been ascribed to cerebral anoxia resulting from either valvular obstruction, cardiac arrhythmia, or from embolism (Schwarz et al., 1972). Syncope and vertigo, often related to posture, have been reported in up to 19% of myxomas (Joynt et al., 1965). Case 2 may have had either or both of these problems.

Spinal cord lesions due to direct embolisation have also been reported (Schwarz et al., 1972). Neither of our cases had signs of spinal cord involvement. Goodwin (1963) emphasised that most murmurs related to atrial myxoma were atypical or difficult to hear. Case 1 was considered normal at her initial examination, though the loud first heart sound and diastolic murmur were heard subsequently. Case 2 was also described as having normal cardiovascular examination and, despite positive echocardiographic evidence of the lesion, no murmur was detected clinically. The murmur of left atrial myxoma may resemble that of hypertrophic subaortic stenosis, mitral incompetence or mitral stenosis (Schwarz et al., 1972; Morgan et al., 1977) and may change with altered posture. Another cardiac complication is progressive decompensation, often of short duration, and unresponsive to digitalis and bed rest (Joynt et al., 1965). Case 2 gave a history of dyspnoea for 1 month with decreased effort tolerance for the week prior to admission.

A past history of rheumatic fever or cardiac irregularity is considered quite rare with atrial myxoma (Joynt et al., 1965). Case 1 initially gave a history of chest pain when lying flat; as commented above, posture is a significant factor in producing



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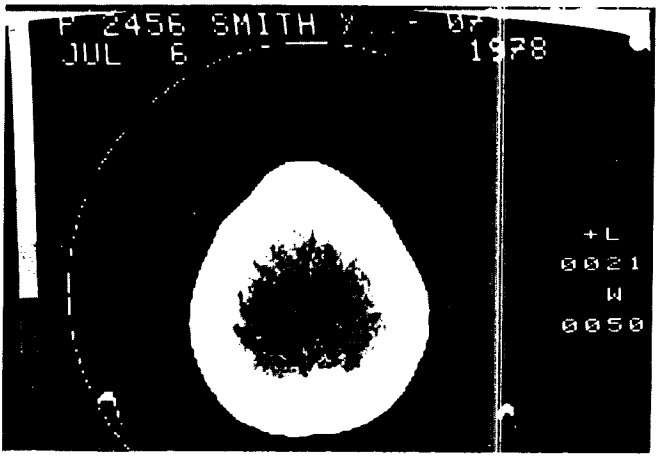

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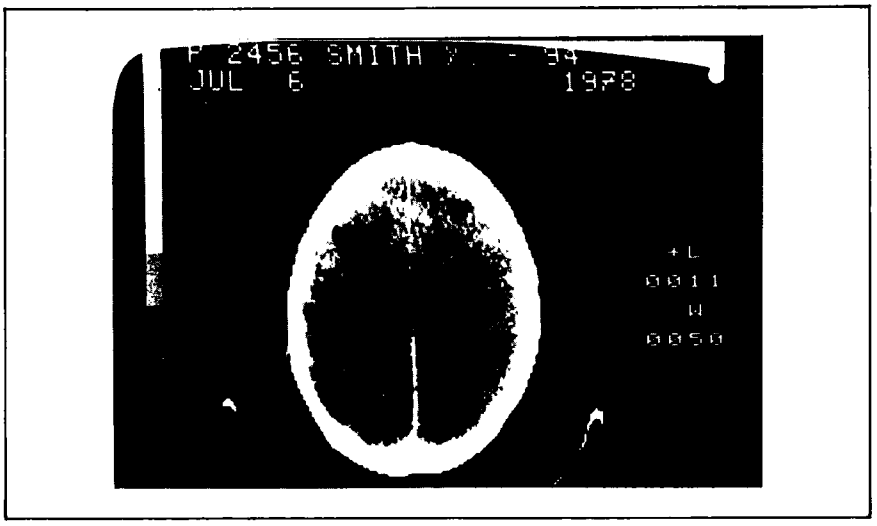

4c

symptoms. Only 1 week prior to her ultimate diagnosis, Case 1 had presented with palpitations suggesting cardiac irregularity. Neither patient had a history of rheumatic fever. Sudden death in this condition may result from acute outflow obstruction, or as a consequence of lethal embolisation (Joynt et al., 1965; Koikkalainen et al., 1977).

Diagnosis of atrial myxoma depends on awareness of the condition and of its varied clinical presentations. Certain investigations may help to guide the clinician towards the diagnosis. Blood tests may show raised gamma globulins, as shown in both cases in this report (tables I and II). This is thought to result either from antibody formation to the polysaccharide component discharged by the tumour, or from haemorrhage and degeneration within the tumour with subsequent muscle emboli (Damasio et al., 1975; Yufe et al., 1976). The first explanation seems more acceptable and is the basis for the concept that elevated CSF gamma globulin is indicative of active myxomatous tissue within the nervous system (Damasio et al., 1975).

Chest radiographs may lead to the suspicion of a tumour if there is right ventricular hypertrophy out of proportion to the enlargement of the left atrium, in the presence of left-sided cardiac failure (Joynt et al., 1965). Calcification of the tumour may also be evident on chest radiographs.

Fig. 4. (a) CAT head scan performed on Case 2 demonstrating a right occipital cortical lesion of decreased density considered to be an occipital infarct. (b) A much smaller area of slightly decreased density in the left parasagittal parietal region thought to be a superficial cortical infarct. (c) A very small area of slightly decreased density in the right frontal area peripherally may represent a further infarct.

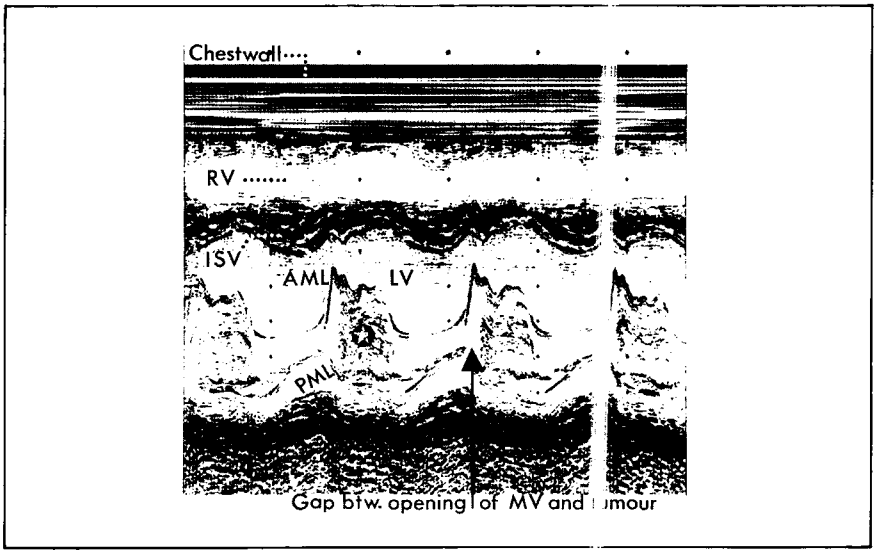

Fig. 5. Left ventricular echocardiograph performed on Case 2 demonstrating a moderately large left atrial myxoma with a mass of reflecting tumour posterior to the mitral valve.
✪ Atrial myxoma. AML Anterior mitral leaflet. IVS Interventricular septum. LV Left ventricle. MV Mitral valve. PML Posterior mitral leaflet. RV Right ventricle.

The ECG is generally normal in patients with atrial myxomas who have had no other cardiac complications. Possible variance from this may be the presence of left atrial or right ventricular hypertrophy resulting from the tumour. 'Giant T wave inversion' (Jacobsen and Schrire, 1966) is associated with 'cerebral reflexes' and periods of altered consciousness. Case 2 showed this cardiographic change (fig. 7) and though an area of decreased mobility was detected on cardiac catheterisation, coronary angiography revealed no abnormality. Though the ECG suggested that she did have a myocardial infarction subsequent to tumour embolisation, the possibility of a 'cerebral' electrocardiograph should be considered (Burch et al., 1954; Hugenholtz, 1962; Jacobsen and Schrire, 1966).

Ultrasound echocardiography is now accepted as an inexpensive, reliable, simple, non-invasive and non-hazardous technique for the diagnosis of intracardiac tumours. It may be employed to scan both the right and left sides of the heart (Meller et al., 1977; Nicholson et al., 1977; Nishimura, 1977; Wharton, 1977). Eiffert and Domanig first reported a pattern of echoes behind the mitral valve pattern in a patient with a right atrial myxoma (Schwarz et al., 1972). Mitral valve movement may be abnormal in association with a myxoma (as described with mitral stenosis) but the pathognomonic feature of the left atrial myxoma is the mass of reflecting tumour immediately posterior to the valve leaflets (Schwarz et al., 1972), as shown in figures 2 and 5.

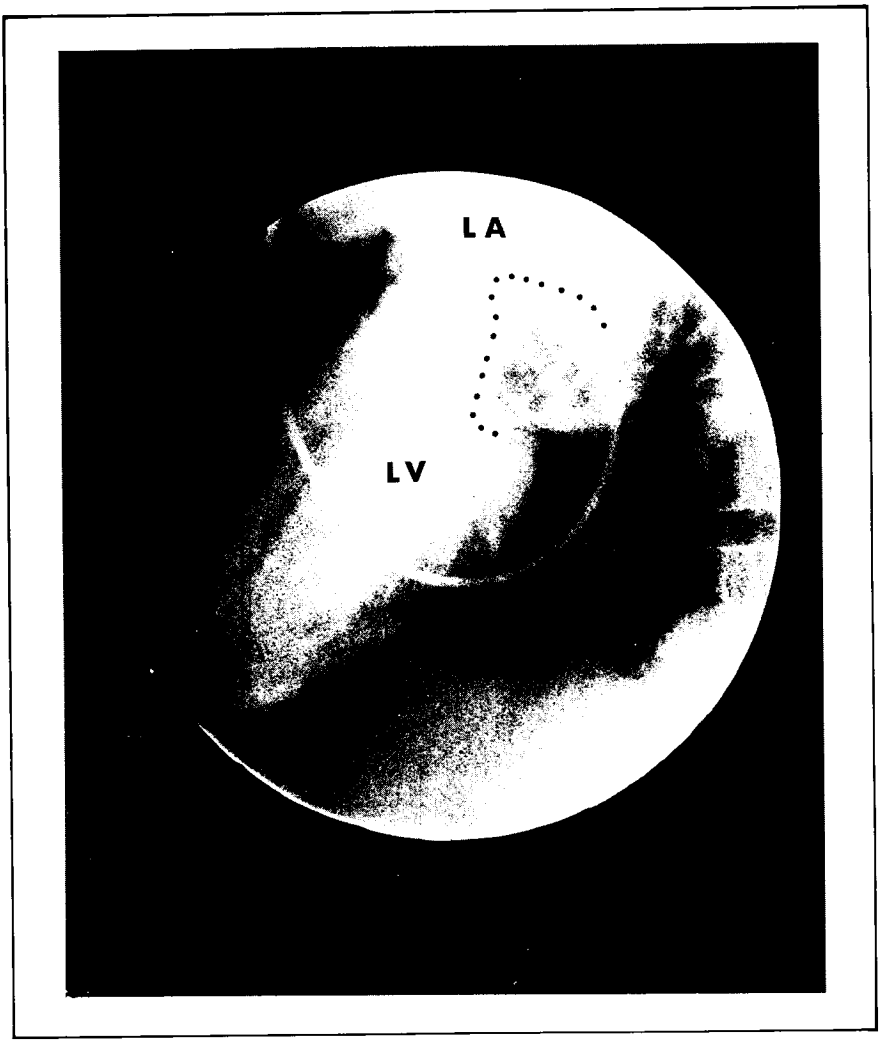

Fig. 6. Cardiac catheterisation on Case 2 demonstrated the filling defect representing the left atrial myxoma.

Prolapsing mitral valve due to myxomatous valvular degeneration should also be considered in the differential diagnosis as a cause of cerebral embolism, with the supposition that the embolus arises from the atrial surface of the myxomatously degenerated mitral valve (Guthrie and Edwards, 1976; Barnett et al., 1978). This condition may also be diagnosed by echocardiography. Cardiac angiography is also a most important method of assessment to demonstrate not only the filling defect that represents the tumour, but also to determine the state of the heart valves (Joynt et al.,

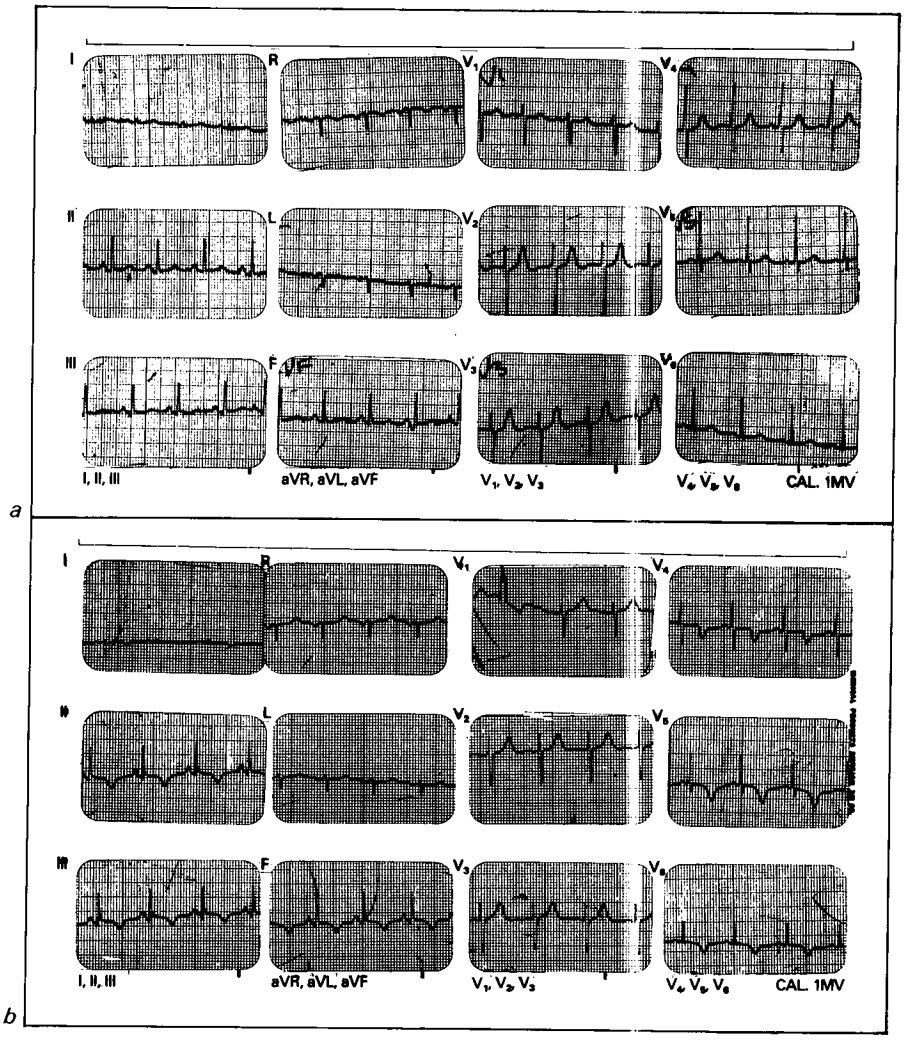

Fig. 7. Serial electrocardiographs performed on Case 2. a) Normal tracing on the day of admission. b) 2 days later: symmetrical deep T wave inversion and prolongation of the QT interval in leads II, III aVf and V4-6.

1965; Kyllonen et al., 1976; Nishimura, 1977). It is important to note that there are both false positives and negatives associated with cine-angiography and interpretation should be made in association with the echocardiograph (Meller et al., 1977).

Until recent times, cardiac myxoma was usually a necropsy diagnosis but now, with the combination of echocardiography and cine-angiography, cases such as those reported here are being diagnosed and effectively treated. The remaining considera-

tion is the proper procedure for long term follow-up, for the detection of local recurrence and of tumour emboli.

Atrial myxoma should be actively excluded in young patients presenting with stroke, especially as a minor event often heralds more serious consequences (Schwarz et al., 1972). This assumes even greater significance once carotid disease, cardiac arrhythmia and myocardial infarction have been confidently excluded.

Summary

2 cases of left atrial myxoma are presented, with a review of the recent literature on the topic, in order to bring this rare condition to the attention of clinicians. Both cases presented to the Neurological Unit of the Queen Elizabeth Hospital during 1978.

The cases helped to emphasise the role of echocardiography in the routine appraisal of the stroke patient, especially if there are multiple lesions or if the patient concerned is young. The second case raised interesting questions regarding electrocardiographic changes associated with altered states of consciousness.

Until recently cardiac myxomas were usually a postmortem diagnosis, but now with the effective combination of echocardiography and cine-angiography, cases are being effectively diagnosed and treated. It is hoped that with an increased awareness of the condition, diagnosis will be made sooner and thus prevent more severe sequelae occurring.

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Cerebellar Malformations: Some Pathogenetic Considerations

*H. Urich**

Both the definitive structure and the embryogenesis of the cerebellum have now been sufficiently explored to make it one of the best known territories in neuroanatomy. This organ therefore lends itself to a critical analysis of its malformations in the light of modern teratological concepts.

Materials and Methods

The cases presented here have been selected to illustrate specific points and are not intended to cover the entire field of cerebellar malformations. They fall into 3 groups:

1) Destructive processes
2) Chromosomal abnormalities
3) Dysraphic malformations.

The first group comprises 1 case of generalised neonatal cytomegalovirus (CMV) infection, 1 of burnt-out CMV infection and 1 of the Walker form of 'lissencephaly' (Chan et al., in press).

The chromosomal abnormalities include 1 case each of Patau's syndrome (trisomy D, 13-15), Edwards' syndrome (trisomy E, 17-18), Down's syndrome (trisomy G, 21-22) and Turner's syndrome (XO) [Molland and Purcell, 1975].

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In the group of dysraphic states the 2 most common ones, the Arnold-Chiari malformation and anencephaly, have been deliberately omitted, the former because internal derangements of cerebellar structure play only a minor part in the syndrome, the latter because more work needs to be done on the range of cerebellar abnormalities in this condition. The cases presented include 1 case of the Dandy-Walker malformation and 2 of occipital encephalocele (Karch and Urich, 1972).

In addition a surgical biopsy is included of an extra-axial ependymal cyst of the posterior fossa.

All brains removed at autopsy were cut after fixation in formol-saline, representative blocks embedded in paraffin and sections stained with haematoxylin and eosin, Kluver-Barrera's method (luxol fast blue-cresyl violet) and Holzer's stain for glial fibres. In selected cases van Gieson's stain, Mallory's phosphotungstic acid-haematoxylin (PTAH) and Gordon and Sweets' impregnation for reticulin were also used. The biopsy material was embedded in paraffin and stained with haematoxylin and eosin and with van Gieson's method.

Findings

1. Destructive Lesions

Case 1. Active CMV Infection

A very small neonatal brain with generalised polymicrogyria, moderate dilatation of the lateral ventricles, subependymal calcification and large intranuclear inclusion bodies, most abundant in the subependymal glia. The cerebellum was small and externally coarsely nodular with blurred pattern of the folia. Microscopically it showed extensive, though not ubiquitous, cerebellar microgyria with an irregular pattern of trabeculae of internal granular cells, lined with Purkinje cells and an adjacent molecular layer abutting on islands of external granule cells centred round a vessel or strands of connective tissue.

Case 2. Burnt-out CMV Infection

A hydrocephalic brain of a 4-year-old child, with generalised cerebral cortical polymicrogyria and subependymal calcification, but no inclusion bodies. The cerebellum showed asymmetrical lesions with a coarse lobular pattern in the left hemisphere and approximately normal folia in the right (Greenfield, 1976a). Microscopically the affected parts showed a trabecular microgyric pattern similar to that described above, but devoid of an external granular layer (fig. 1).

Case 3. Walker's 'Lissencephaly'

A 5-day-old infant with multiple cerebral and ocular malformations. The latter included microphthalmia, detachment and dysplasia of the retina, hypoplasia of the optic nerves, persistence of the primary vitreous, cataracts, obliteration of the anterior chamber and vascularisation of the cornea. In the brain the salient features were micrencephaly, agyria with a thick cortex intersected by deep glial and collagenous scars, hydrocephalus, persistent corpus pontobulbare, obliteration of the subarachnoid space by glial and collagenous adhesions and a midline arachnoid cyst in the posterior fossa. The small cerebellum showed a trabecular pattern of microgyria, most marked in the superficial parts of the cerebellar cortex, while the structure in the depths of the sulci appeared relatively normal

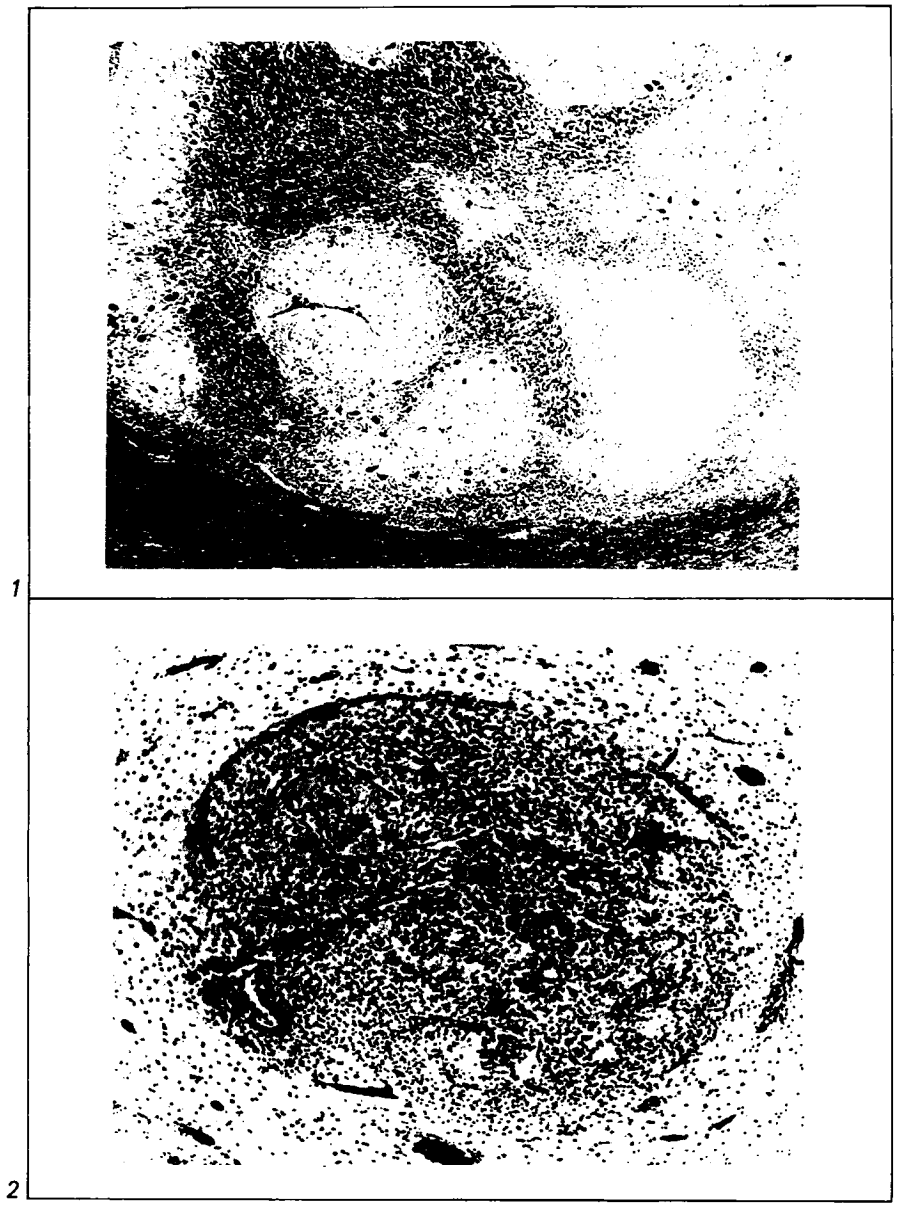

Fig. 1. Case 2 (burnt-out CMV infection). Trabecular pattern of cerebellar microgyria, consisting of granule cells, Purkinje cells and molecular layer, but devoid of external granular layer (Kluver-Barrera).

Fig. 2. Case 4 (trisomy D, 13-15). Low power view of cortical heterotopia (Kluver-Barrera).

2. Chromosomal Abnormalities

Case 4. Trisomy D, 13-15

The main abnormalities in the cerebrum were arhinencephaly and incomplete separation of the cerebral hemispheres. In the cerebellum the main abnormality was a massive aggregation of small, darkly staining cells, with oval or elongated nuclei, resembling external granular cells, in and around the dentate nuclei. In addition a small focus of ectopic cortical cells was found deep in the white matter, consisting of external and internal granular cells, Purkinje cells and molecular layer (fig. 2). Despite the apparently haphazard arrangement of the various elements, they maintained a semblance of a normal relationship to each other (fig. 3). Another ectopic focus in the roof of the fourth ventricle consisted of cells resembling those of the external granular layer interspersed with larger cells resembling those of the deep nuclei of the cerebellum.

Case 5. Trisomy E, 17-18

The abnormalities were confined to the cerebellum. They consisted of an ectopic focus in the white matter composed of large neurones, resembling those of the deep nuclei, and another in the lateral wall of the fourth ventricle containing cortical elements as described in the previous case. In the depth of one sulcus there was a small area of transposition of the internal granular and Purkinje cell layers, the order of lamination being as follows: external granular layer, a thin ribbon of molecular layer, internal granular layer, another thin zone of molecular layer and finally a layer of somewhat misshapen, elongated Purkinje cells (fig. 4).

Case 6. Trisomy G, 21-22

The only abnormality found consisted of islands of cells resembling those of the external granular layer in and around the dentate nucleus.

Case 7. Turner's Syndrome (XO)

The appearances of the posterior fossa structures were those of a Dandy-Walker malformation with a rudimentary vermis and a large cyst of the fourth ventricle. In addition the cerebellar tonsils were malformed and showed a pattern of trabecular microgyria.

3. Dysraphic Malformations

Case 8. Dandy-Walker Syndrome

This infant showed the typical appearances of a rudimentary vermis, consisting only of a few of the uppermost folia, and relatively normal cerebellar hemispheres (Greenfield, 1976b). The vermis continued upwards in a tent-like cyst extending through the tentorial orifice with its apex lying behind the splenium of the corpus callosum. Over the cerebellar hemispheres the cyst was continuous with the fourth ventricle. The cyst wall was attached to the medial and posterior walls of the hemispheres until it reached a point of reflection where it detached itself from the surface of the cerebellum. The parts of the cyst wall nearest to the fourth ventricle contained some cortical elements: an external and internal granular layer and a few Purkinje cells (fig. 5). Beyond that the cyst wall consisted of a thin layer of glia, lined on the inside by ependyma, on the outside by pia-arachnoid (fig. 6).

Case 9. Occipital Encephalocele

In this case the structures of the posterior fossa, although displaced in the hernial sac, were relatively well preserved. Most of the nuclei and tracts of the brain stem were easily identifiable as were the two cerebellar hemispheres, one of which showed extensive destructive changes, ischaemic in nature and probably postnatal. The vermis was totally absent and the hemispheres were separated by a cleft lined by the

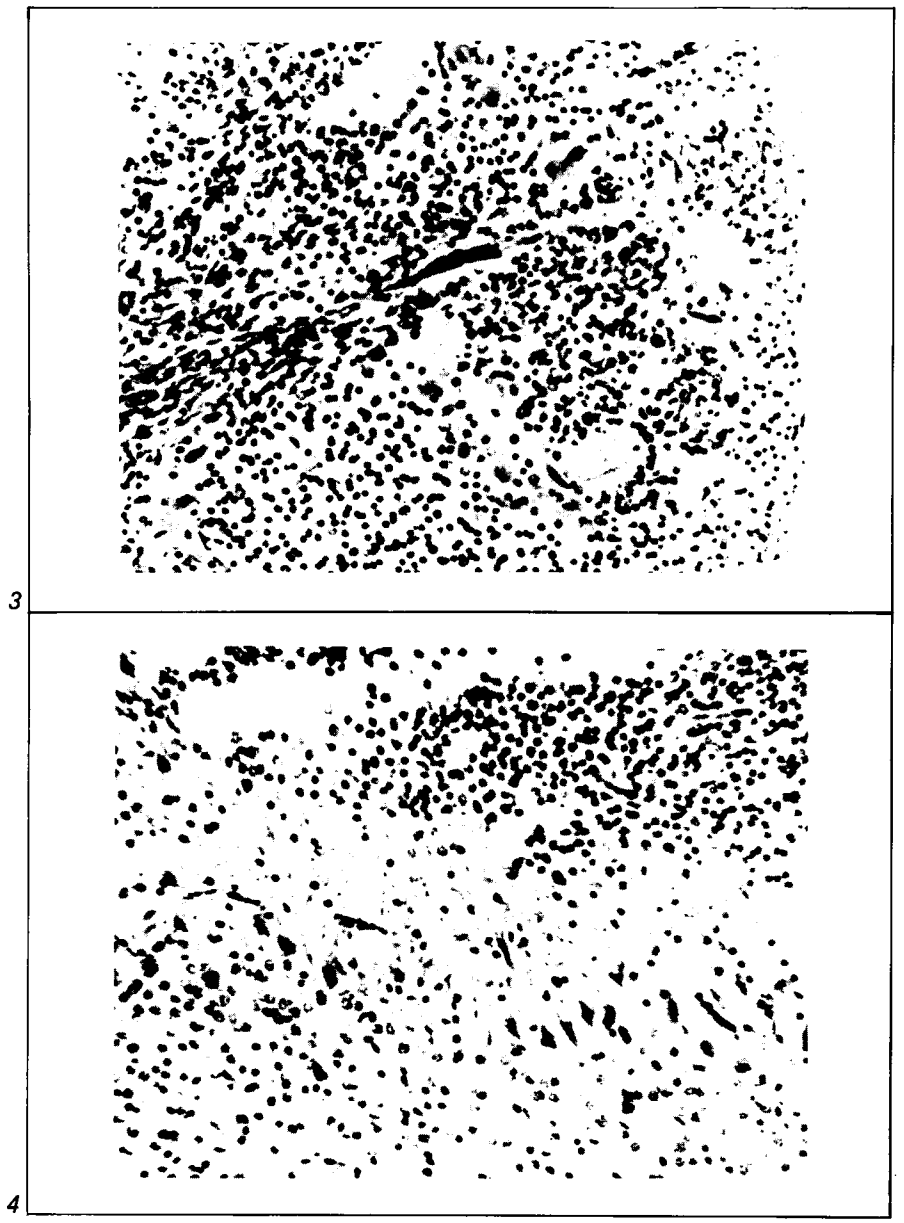

Fig. 3. Case 4. High power view of the same showing the 3 main cell types (Kluver-Barrera).

Fig. 4. Case 5 (trisomy E, 17-18). Focus of transposition of internal granular and Purkinje cell layers (Kluver-Barrera).

roof membrane of the fourth ventricle. The extent and course of this membrane could not be traced as it was damaged in removal from the hernial sac.

Case 10. Occipital Encephalocele

The posterior fossa structures were lying entirely within the hernial sac which also contained large, though asymmetrical, parts of the cerebral hemispheres. The brain stem was represented by an elongated cylindrical structure lined by ependyma of the fourth ventricle both on its dorsal and its ventral aspects (Greenfield, 1976c). The cerebellum consisted of two widely separated rudiments: one minute nodule near the base of the brain stem, and a larger spherical mass near the apex. The latter consisted largely of cerebellar cortical neurones with a small amount of white matter near one end. The cortical elements comprised external and internal granule cells, Purkinje cells and fragments of molecular layer in an apparently haphazard arrangement, yet retaining an approximately normal relationship to each other.

Case 11. Extra-axial Cyst

This large midline cyst in the posterior fossa was surgically explored and part of its thin-walled roof removed. It consisted of a layer of glia, lined on one side by ependyma, on the other by pia-arachnoid (fig. 7).

Discussion

Modern teratological concepts admirably summarised by Evrard (1977) resolve themselves into two propositions. Malformations may be due either to faulty genetic programming or to destructive processes during embryonic and fetal life. The former mechanism operates in the rare genetic malformations transmitted by simple Mendelian inheritance or in the more common cytogenetic disorders in which various chromosomal abnormalities are responsible for the disordered coding. Destructive processes in fetal life include intrauterine infections, poisons, ionising radiation, anoxia and nutritional deficiencies. At present this simple and rational classification leaves a large no man's land in which the mechanism remains obscure for lack of adequate evidence in favour of genetic or environmental factors, or perhaps of an interplay of both.

The first 3 cases presented here illustrate the operation of destructive processes. Case 1 is a typical example of cerebral malformations associated with an intrauterine CMV infection as described by Diezel (1954), Crome and France (1959) and others, and in which the occurrence of cerebellar microgyria was reported by Bignami and Appicciutoli (1964). The evidence that Case 2 represents a burnt-out case of the same condition is circumstantial. It is based on an almost identical case in the collection of the Langley-Porter Institute in San Francisco in which a definite diagnosis of generalised CMV infection had been made in the neonatal period (Malamud, personal communication).

Case 3 closely resembles that described by Walker (1942) under the name of lissencephaly. This is a complex oculocerebral malformation which differs considerably from the classical agyria. It is a mixture of migration disorders and scarring which

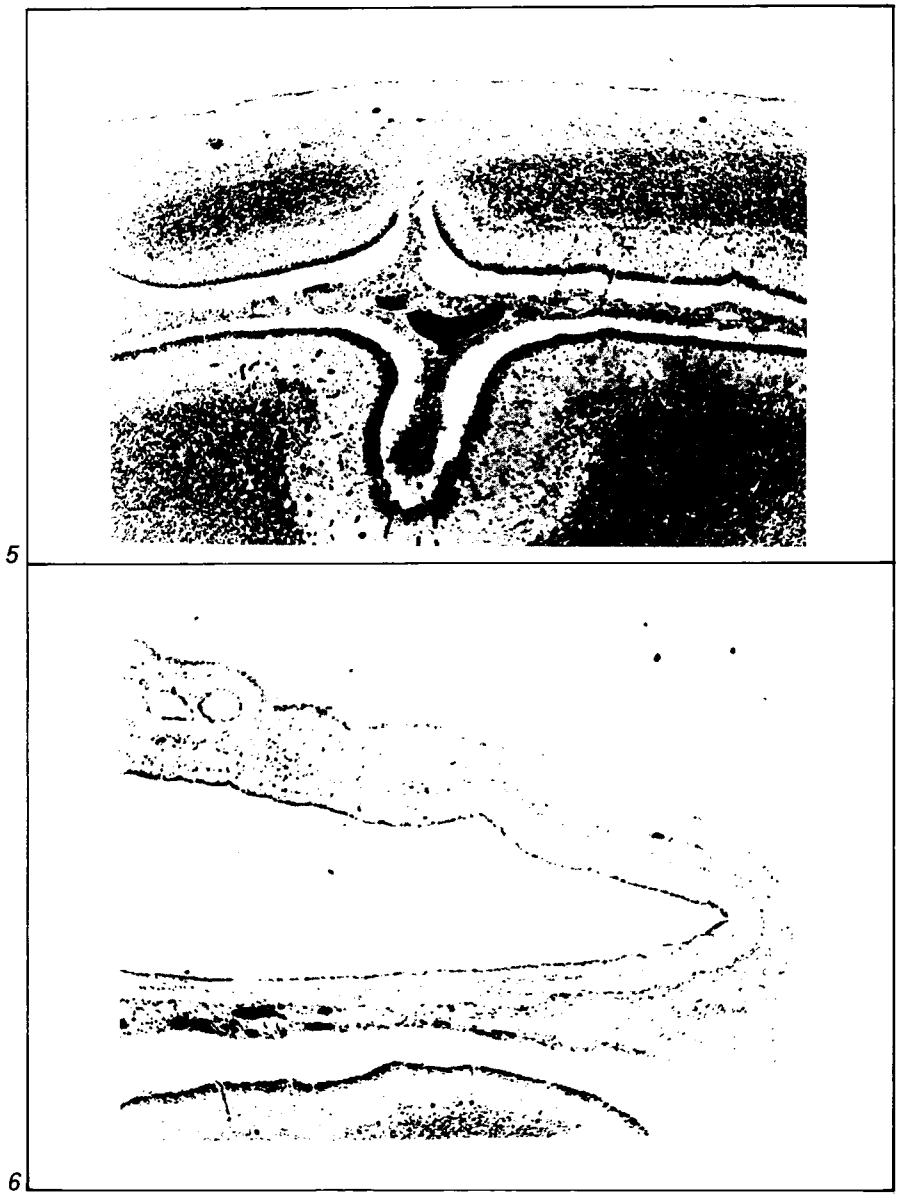

Fig. 5. Case 8 (Dandy-Walker syndrome). Proximal part of cyst membrane containing rudimentary folia (Kluver-Barrera).

Fig. 6. Case 8. Point of reflection of cyst from surface of cerebellum. The wall consists of glia lined by ependyma on the inside, pia-arachnoid on the outside (Kluver-Barrera).

can only be explained by a protracted destructive process operating over several weeks of intrauterine development (Chan et al., in press).

Evidence that destructive lesions may be responsible for some cerebral and cerebellar cortical malformations, and that these processes may operate later in fetal development than was assumed in the past, has only recently come to light. Richman et al. (1974) have shown that the classical 4-layer pattern of cortical polymicrogyria is the result of a postmigration laminar necrosis due most commonly to vascular factors operating during the sixth month of intrauterine life. Evrard and Caviness (1974) described a type of cerebellar microgyria which they ascribed to similar factors operating during the same period. Admittedly their case showed a pattern different from the common trabecular one illustrated in the present material. The evidence that this also is due to destructive lesions, particularly infections, was provided by Friede and Mikolasek (1978). This pattern is produced by erosion of the tips of the folia with subsequent fusion of their remnants. This process cannot occur until the cerebellar folia are reasonably well developed, which places its operation around or after the twentieth week of fetal life. It is of interest to note that the distorted cortex undergoes normal maturation as demonstrated by the absence of the external granular layer in Case 2.

The disorders of genetic coding are represented by Cases 4 to 7. The cerebellar lesions in the trisomies have been well described by Norman (1966), Terplan et al.

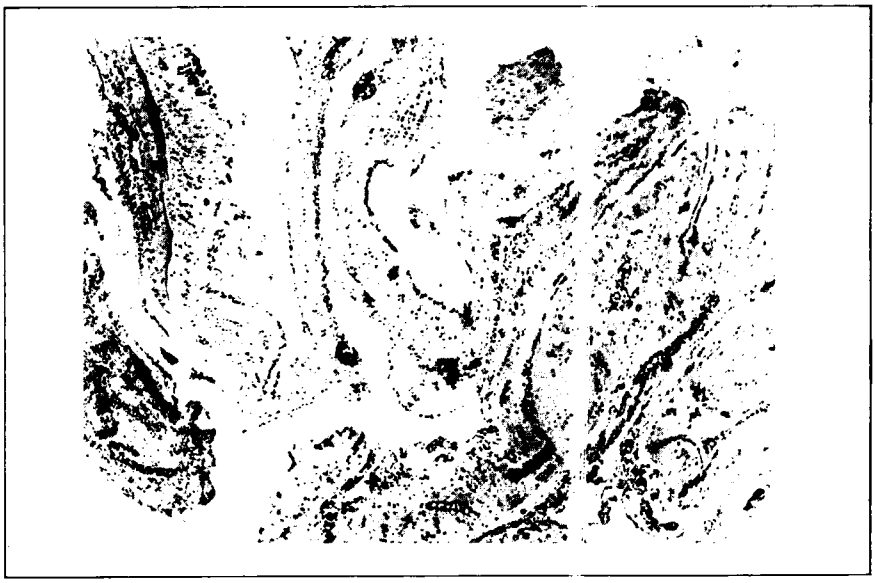

Fig. 7. Case 11. Wall of extra-axial cyst: allowing for distortion, the structure is similar to that of a Dandy-Walker cyst (haematoxylin-eosin).

(1966) and Sumi (1970). One of the most constant abnormalities is the aggregation of primitive cells, resembling those of the external granular layer, in and around the dentate nucleus. This is seen invariably in trisomy D, and occasionally in the trisomies E and G. Some caution is required in their interpretation, as minor foci of these cells may sometimes be found in normal neonates (Jellinger, 1974). Their subsequent fate is unknown — whether they mature, migrate or undergo necrosis, as do many superfluous cells in normal development. Their origin is equally obscure. They are unlikely to be derived from the external granular layer, and are best interpreted with Jellinger as persistent undifferentiated matrix cells.

The cortical ectopias showing some attempt at internal organisation are puzzling. One can speculate that one type of cortical cell, possibly the Purkinje cell, arrested in its outward migration towards the cortex, may induce the pluripotential matrix to differentiate into other cortical elements which then migrate into their appropriate positions.

The transposition of the internal granular and Purkinje cell layers in Case 5 is an unusual feature. It implies a disorder of migration of the granule cells from the external layer into their definitive position with an arrest half-way through the molecular layer. An analogous situation occurs in the weaver mouse where the disorder is caused by faulty formation of the Bergmann glia, the processes of which provide the guidelines of migration for the granule cells (Rakic and Sidman, 1973).

Turner's syndrome is not as a rule associated with malformations of the central nervous system. However, only 20% of fetuses with the XO abnormality survive, while most of the remainder undergo spontaneous abortion and show gross malformations (Carr, 1967). A few malformed fetuses may reach full term and die in infancy. Case 7 presents two points of interest: it is an example of the Dandy-Walker malformation associated with faulty genetic coding, and suggests that this may also be responsible for trabecular microgyria, although the operation of secondary destructive processes on the cerebellar tonsil cannot be ruled out.

Cases 8 to 10 represent selected examples of dysraphic malformations. The term is used here in the widest sense implying the presence of midline clefts in the neuraxis and/or its coverings, without prejudging the merits of any of the theories of their pathogenesis (Brocklehurst, 1971). They fall into that group of malformations in which it is impossible at present to disentangle genetic from environmental factors. The geographical and seasonal clustering of the common dysraphic malformations suggests the operation of a hypothetical environmental factor (Renwick, 1972). Other epidemiological studies have suggested an interplay of genetic and exogenous factors (Carter et al., 1968). It is far from proven that the dysraphic conditions form a homogeneous group of uniform aetiology.

That the Dandy-Walker malformation is due to a genuine midline defect and not to atresia of the roof foramina was demonstrated conclusively by Brodal and Haughlie-Hanssen (1959) and subsequently confirmed by other observers (Hart et al., 1972). Some comparative studies of the Dandy-Walker and Arnold-Chiari malfor-

mations have suggested a close relationship between them (Gardner, 1959; Gardner et al., 1972) while others have stressed the essential differences (Gardner et al., 1975). The sporadic occurrence of the Dandy-Walker syndrome throws little light on its aetiology. Hints at a possibility of faulty genetic coding are confined to its recorded occurrence in Turner's syndrome (Case 7) and in a genetic disorder of mice (Brodal et al., 1944).

The pathogenesis of the defect in the vermis remains controversial. Woodard (1960) challenged the orthodox theory of cerebellar embryogenesis, claiming that it was based exclusively on the study of midsagittal sections which did not reveal the early stages of development. He re-emphasised the importance of the early intraventricular phase of the growth of the cerebellum which originates from two swellings of the rostral part of the rhombic lip. These cerebellar plates grow medially into the lumen of the ventricle until they meet in the midline, fuse with each other and with the overlying part of the ventricular roof. Woodard's final conclusion that the external granular layer originates from the roof membrane is undoubtedly erroneous. The evidence of surface migration of the granule cells from the rhombic lip over the now extraventricular cerebellum is too strong to be dismissed (Rakic and Sidman, 1970; Sidman and Rakic, 1973). It is therefore not surprising that Woodard's theory has been passed over in silence by subsequent writers with the exception of Sarnat and Netsky (1974). Nevertheless an appreciation of the intraventricular phase may contribute to the understanding of midline clefts in the cerebellum. Incomplete fusion may lead to a defective vermis and a redundant roof membrane which would form the main elements of the Dandy-Walker syndrome.

Total absence of the vermis was a feature of all 4 cases of large occipital encephaloceles reported by Karch and Urich (1972). This defect was previously recorded by Ostertag (1956). Recently Caviness and Evrard (1975) questioned the dysraphic nature of occipital encephalocele, which they interpreted as a result of an 'explosion' of a hydrocephalic brain with herniation through the developing occipital squame. Their meticulous study, based on serial sections, commands respect yet a doubt remains whether their conclusions are valid for all types of occipital encephalocele. The presence of midline clefts associated with cystic dilatation of the fourth ventricle ('ventriculocele') points to a close relationship between this condition and the Dandy-Walker syndrome.

The structure of the cerebellar rudiment in Case 10 merits a brief mention. It is conceivably the end result of a destructive process which shattered the cerebellum into small fragments, which subsequently fused into an amorphous mass. On the other hand the close similarity of its internal structure to the ectopic cortical foci observed in the trisomies suggests the possibility of faulty genetic programming.

Another lesion which may be explained by incomplete fusion of the cerebellar plates with the roof membrane is the midline ependymal cyst of the posterior fossa. The so-called extra-axial cysts (without communication with the ventricular system) fall into 2 groups: the arachnoid and the ependymal. The arachnoid cysts as ex-

emplified in Case 3 are probably due to adhesions following upon an infective process. They consist of a thin collagenous wall lined on the inside by a layer of arachnoid cells. The structure of the wall of ependymal cysts resembles that of a Dandy-Walker cyst: a thin layer of glia lined by ependyma on the inside and by pia-arachnoid on the outside. It is conceivable that both of them originated from parts of the ventricular roof which failed to fuse with the underlying cerebellar primordium.

Summary and Conclusions

1) Destructive processes are responsible for most cases of cerebellar microgyria of the trabecular pattern. Erosion and subsequent fusion of the folia produce the disorganised pattern in which the various cellular elements retain their normal relationship and are capable of normal maturation. Intrauterine infection is responsible for most cases; the evidence is conclusive in some cases, presumptive in others.

2) Faulty genetic coding, as illustrated by the trisomies, may lead to formation of heterotopias. The primitive cells aggregating around the dentate nucleus should be interpreted as matrix cells and not as cells of the external granular layer. Cortical heterotopias with attempted internal organisation also occur; their origin is obscure. The unusual, possibly unique, transposition of the internal granular and Purkinje cell layers observed in one case may be ascribed to faulty formation of the Bergmann glia by analogy with the weaver mouse.

3) It is impossible at present to disentangle the role of genetic and environmental factors in the pathogenesis of the dysraphic malformations. It is possible, however, that defective fusion of the intraventricular cerebellar primordium plays a part in the development of the Dandy-Walker malformation, of midline cerebellar clefts in some cases of occipital encephalocele, and of extra-axial ependymal cysts of the posterior fossa.

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Adrenoleucodystrophy: A Study of Four Patients

*P.G. Procopis and R.A. Ouvrier**

Adrenoleucodystrophy (ALD) is a rare disease of the cerebral white matter associated with pathological changes in the adrenal cortex and other organs. It is characterised by progressive spasticity, visual loss, behaviour change and dementia in young boys and is transmitted by an X-linked recessive mode of inheritance.

We present here the details of 4 boys with this condition, seen at the Royal Alexandra Hospital for Children since 1975.

Case Reports

Case 1

J.G., from Noumea, presented at the age of 6 years having had 2 right focal fits 9 months previously. Progressive difficulty in walking ensued and examination in Noumea 4 months later showed bilateral pyramidal signs in the lower extremities. No dementia was evident. The EEG was diffusely abnormal and CSF protein was 0.56g/litre. The disorder progressed relentlessly and he was transferred to the Royal Alexandra Hospital for Children 5 months later.

On examination he responded only to painful stimuli. He appeared to be blind and did not follow a light with his eyes. The optic discs were somewhat pale but the pupils reacted to light sluggishly. A spastic quadriparesis was present and grasp and snout reflexes were easily elicited. The blood pressure was 140/80mm Hg.

After investigation he returned to Noumea. No follow-up is available.

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Case 2

P.C. presented at the age of 10 years with a 12-month progressive history of visual loss, clumsiness, slurred speech, inability to dress himself and deterioration in school performance. No significant family history was present. While he was being examined frequent absence seizures were noted. A mild right hemiparesis was present with increased tendon reflexes on the right and bilateral Babinski signs. The visual acuity was 6/36 in both eyes but the optic discs and retinae appeared normal.

Progress: Steady neurological deterioration continued until 4 months after admission he could no longer walk alone because of marked ataxia, and could only see well enough to count fingers at 1 metre. He had also deteriorated intellectually and could no longer do simple sums. Pyramidal signs were present bilaterally. Over the next 3 years steady deterioration continued so that he can now no longer speak and has little useful vision. A marked spastic quadriparesis and optic atrophy are present. It is not possible to test his intellectual functions accurately, but his mother believes he understands simple sentences; he demands certain food and he enjoys listening to television. No skin pigmentation or signs of adrenal insufficiency are present.

Case 3

S.A. presented at the age of 7 years with slowly increasing difficulty in walking for 2 years, which had worsened in the previous 6 months. His school teacher thought that his vision and writing had deteriorated in the previous 12 months but that there had been no loss in his learning ability.

2 male siblings, aged 9 and 5, seemed normal. A male cousin of the mother had died at the age of 20 years with paralysis and inability to speak.

On examination his intelligence appeared to be normal. His speech was dysarthric. The visual acuity was 6/24 in the right eye and 6/36 in the left. The pupils reacted sluggishly to light but the optic discs and fundi appeared normal. The muscle tone was normal and no weakness was present but the deep tendon reflexes were pathologically increased in the lower extremities and a Babinski response was present bilaterally. Mild intention tremor was noted in the upper limbs and there was ataxia on heel-toe walking. Seizures which occurred soon after admission were controlled with phenobarbitone.

Progress: Rapid neurological deterioration occurred in the 6 months after presentation, causing inability to speak, incontinence and spastic quadriparesis. He was able to respond to his mother by a smile, cry or grunt. It was not possible to assess visual acuity accurately but it was thought that he had little useful vision. The optic discs were pale.

18 months after presentation diffuse pigmentation of the skin, palmar creases and mucous membranes was noted. The blood pressure was 95/60mm Hg.

At present, almost 3 years after presentation, he remains in much the same state as described above.

Case 4

D.N. presented at the age of 8 years with a 3-month history of deterioration in school performance and visual loss. In the month prior to admission he showed lack of personal hygiene. On the day of admission he became disorientated in time and place, did not recognise his parents and seemed to be having hallucinations.

A maternal uncle died of 'Schilder's disease' at the age of 14.

On examination he was uncooperative at first but after several days his acute delirium settled and he could answer questions and converse in a simple manner. He could do only simple sums and could not read. The visual acuity was 6/12 in the right eye and 6/24 in the left. The optic discs and fundi were normal. He was mildly ataxic but no pyramidal signs were present.

Progress: Intellectual function and visual acuity steadily regressed so that 6 months after presentation he could say only a few words. He was hyperactive, incontinent and would obey only the simplest of

commands. It was not possible to test his visual acuity accurately, but he appeared not to see a jelly-bean 1 metre away. However, no long tract signs could be elicited until 1 year after presentation when increased tone and increased deep tendon reflexes were present in the lower extremities. Frequent multifocal seizures occurred soon after and were only partially controlled with phenytoin and diazepam. He continued to deteriorate, and now, 21 months after presentation, he is poorly responsive, requires nasogastric feeding and has marked extensor rigidity and spasms. No skin pigmentation or clinical signs of adrenal insufficiency are present.

Investigations

EEG

The EEG showed diffuse nonspecific abnormalities in all patients. Its main use was to help rule out the diagnosis of subacute sclerosing panencephalitis in these patients.

Nuclear Brain Scan

All 4 patients had an abnormal scan which showed increased areas of uptake usually in the parietal regions (fig. 1). The areas of uptake were less extensive than the

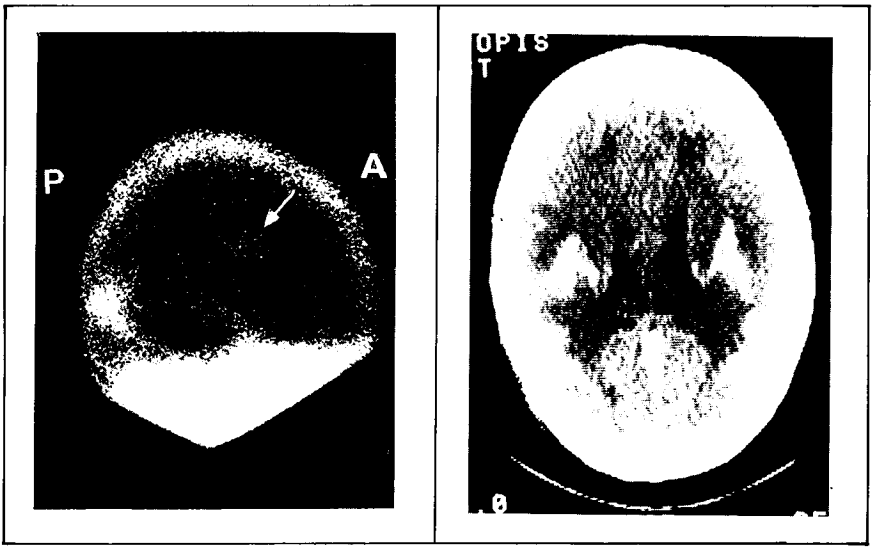

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Fig. 1. Case 3. Nuclear brain scan showing an increased area of uptake in the parietal region.

Fig. 2. Case 4. CAT scan showing low density areas in white matter with contrast enhancement at the anterior borders.

CAT scan abnormalities and probably reflected areas of active demyelination. In the series of Schaumburg et al. (1975) the scan was abnormal in 2 of 9 patients.

CAT Scan

3 patients had CAT scans and in all, large confluent low density areas were present throughout the central white matter with no particular predilection for the occipital lobes. In 2 patients symmetrical enhancement occurred at the anterior borders of the low density areas after infusion of contrast material (fig. 2). This was thought to correspond to a zone of active demyelination with associated inflammation (Greenberg et al., 1977).

Brain Biopsy

A brain biopsy (frontal lobe) in Case 1 was normal to light microscopy. However, electron microscopy showed marked disorganisation of the myelin sheaths by disrupted lamellae with accumulation of granular material that produced fusiform-like swellings of the sheath.

Adrenal Biopsy

Adrenal biopsy was performed in Case 1. Light microscopy showed a thin adrenal cortex and loss of the normal layers. Randomly arranged large cells with finely vacuolated cytoplasm and in some areas fine striations within the cytoplasm were seen. Histochemical stains showed that these cells contained cholesterol. Electron microscopy showed that a large proportion of the adrenal cortical cells contained membrane-bound, electron-lucent spicules characteristic of adrenoleucodystrophy (Powers and Schaumburg, 1974). There was a great increase in the endoplasmic reticulum and the mitochondria were hypertrophied in the cells containing the spicules.

Sural Nerve Biopsy

This was normal in the 1 patient studied (Case 3).

Neurophysiological Studies

Nerve conduction velocities were normal in the 3 patients studied. Visual evoked responses were absent or delayed in Cases 1, 3 and 4. In Case 2 the latencies were normal.

Adrenal Function Tests

Basal plasma cortisol levels were normal in all 4 patients. All except Case 2 responded normally to a tetracosactrin stimulation test. Case 2 however failed to respond even to an augmented tetracosactrin stimulation test. ACTH levels were elevated in the 2 cases in whom they were performed [Case 3 — 86ng/litre; Case 4 — 168ng/litre (normal less than 60ng/litre)].

Discussion

The term adrenoleucodystrophy was suggested by Blaw (1970) for the hereditary disorder causing demyelination of the central cerebral white matter and adrenal atrophy. The transmission is by an X-linked recessive mode of inheritance. Since then studies have shown specific abnormalities by both light and electron microscopy in the adrenal cortex, Schwann cells, testis and brain (Schaumburg et al., 1975). It is now generally believed that most of the cases of Schilder's disease in males are in fact ALD. A form of multiple sclerosis is probably responsible when females, or males without adrenal changes, are affected.

In none of our cases did adrenal insufficiency present clinically. In 1 of the children increased pigmentation occurred late in the disease. Adrenal insufficiency was recognised in 6 of the patients described by Schaumburg et al. (1975), but it antedated the neurological signs in only 2 of them. Similarly, routine tests of adrenal function may be normal (as in 3 of our patients) but plasma ACTH levels are usually elevated (Rees et al., 1975).

Definitive diagnosis of ALD, important for genetic counselling, is best done by adrenal biopsy. The cells of the zona fasciculata and reticularis show striated cells which are PAS negative. Under the electron microscope the striations consist of linear lamellar accumulations within the cytoplasm (Powers and Schaumburg, 1974). Similar changes have also been seen in the testis and sural nerve of some affected patients (Schaumburg et al., 1975).

Summary

4 unrelated boys suffering from adrenoleucodystrophy (ALD) are reported. All presented with a cerebral degenerative disorder manifested by behaviour change, dementia, progressive visual loss and spasticity. 1 child showed an excess of skin pigmentation but no other clinical features of adrenal insufficiency were present. An ACTH stimulation test indicated adrenal insufficiency in 1 patient. In the 3 patients with a normal response to ACTH stimulation, 2 had elevated resting plasma ACTH levels, and the other showed typical inclusions in the cells of the adrenal cortex when examined by electron microscopy.

Nuclear brain scans were abnormal in all 4 patients. 3 patients had a CAT scan and in all a diffuse decrease in density was shown throughout the central cerebral white matter. 2 patients had a zone of contrast enhancement adjacent to the low density areas.

In boys under the age of 10 years ALD is the commonest cerebral degenerative disease after subacute sclerosing panencephalitis.

Acknowledgement

The authors are indebted to Dr Rodney Carter of the Adelaide Children's Hospital for the pathological report in Case 1.

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Primary Lymphoma of the Central Nervous System: A Case Report

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Primary central nervous system lymphomas comprise approximately 1 % of all brain tumours (Zimmerman, 1971, 1975; Jellinger et al., 1975). Yuile (1938) and Kinney and Adams (1943) first described these tumours as primary reticulum cell or histiocytic sarcomas of the brain. In 1948, Russell et al. used various silver staining techniques to separate the cells of the reticulo-endothelial system into a mature argyrophilic type (microglia) and an immature non-argyrophilic type (reticulum cell). On this basis they expressed the view that the more primitive cell elements in these tumours probably arose from de-differentiation of the more mature forms, and called the cell proliferation microgliomatosis. The term reticulum cell sarcoma-microglioma was adopted for many years as a compromise satisfying the two alternative cytogenetic points of view (Rubinstein, 1972). However, more recent studies have attempted to classify these tumours within the sphere of the non-Hodgkin's lymphomas (Lennert, 1975; Zimmermann 1975), and this view would appear to be supported by evidence that these tumours fulfill the cytoplasmic immunoglobulin-staining requirements for B cell lymphocytes (Houthoff et al., 1978).

Clinically, these tumours often present with a rapid picture of encephalopathy or intellectual decline, together with signs of raised intracranial pressure and focal neurological disturbance, not unlike the presentation of glioblastoma multiforme (Henry et al., 1974). Until recently, most cases were diagnosed only at autopsy. However, with the introduction of computerised axial tomography (CAT) scanners, it may

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be possible to suspect this diagnosis earlier in the clinical course and to institute appropriate therapy.

This paper outlines the clinical and radiological features of a case of primary CNS lymphoma. Following the case presentation is a discussion of the relevant literature and suggestions about management of future similar cases.

Case Report

A 46-year-old female Russian immigrant was admitted to hospital on 17 January 1978 with a 1-week history of headaches, confusion and strange behaviour. 7 months prior to admission she had complained of diplopia. An EEG and a radionucleotide brain scan were normal at that time. On 8 November 1977 she consulted an ophthalmologist because of further visual disturbance, and fluorescein angiography revealed evidence of widespread focal choroiditis.

Examination at the time of admission revealed a well nourished woman who was afebrile and alert, but disorientated in time and place. Visual acuity was normal, eye movements were full and fundoscopy was normal. She was mildly ataxic and there was fine nystagmus at the extremes of horizontal and vertical gaze. The rest of the neurological examination and the general examination was normal.

Investigations

Routine haematological and biochemical profiles were normal. Lumbar puncture drained clear CSF at 140mm pressure. Microscopy revealed 50 mononuclear cells per high power field, but no other cells. The protein was grossly elevated at 4.11mmol/litre and glucose was 2.0mmol/litre (plasma glucose 4.6mmol/litre). These values were consistent, and remained essentially unchanged throughout the illness. Serological tests for syphilis were negative and procedures to detect cryptococcal and tuberculous infection were negative.

A radionucleotide brain scan using Technetium 99 was carried out 2 days after admission (fig. 1). The dynamic study was normal. In the delayed static study the lateral ventricles were clearly visualised, and there was also abnormal tracer uptake in both occipital poles. The comment was made that ventricular uptake was highly unusual but had been reported in ventriculitis.

Computerised brain scans were performed. After injection of contrast material, there was marked enhancement around the ependyma, including the septum pellucidum (fig. 2). Subsequent scans showed some ventricular enlargement and increasing periventricular oedema. There was also a suggestion of a discrete right-sided paraventricular enhancing lesion (fig. 3).

At this stage, the diagnosis was thought to be tuberculous or sarcoid meningitis. Treatment was begun with rifampicin 150mg 3 times a day, ethambutol 1,000mg/day and INAH 100mg 3 times a day. A course of streptomycin was also given. However, the patient's confusion worsened, and she complained continually of not being able to see. A gross disturbance of short term memory became apparent, and she could be easily induced to confabulate. She developed snout and grasp reflexes bilaterally, and both plantar responses became extensor. Despite her complaint of visual failure, light reflexes and fundoscopy remained normal and she responded to threat in all parts of the visual field.

Because of the continuing deterioration, a right frontal burr-hole was performed, biopsy specimens were taken from cortex and paraventricular areas, and a ventricular catheter was inserted. These and later specimens revealed no evidence of tumour. Late in the course of the illness a centrifuged specimen of CSF revealed malignant cells of indeterminate type. The last CAT scan, performed several days before her death, revealed extension of the periventricular oedema and multiple discrete areas of contrast enhance-

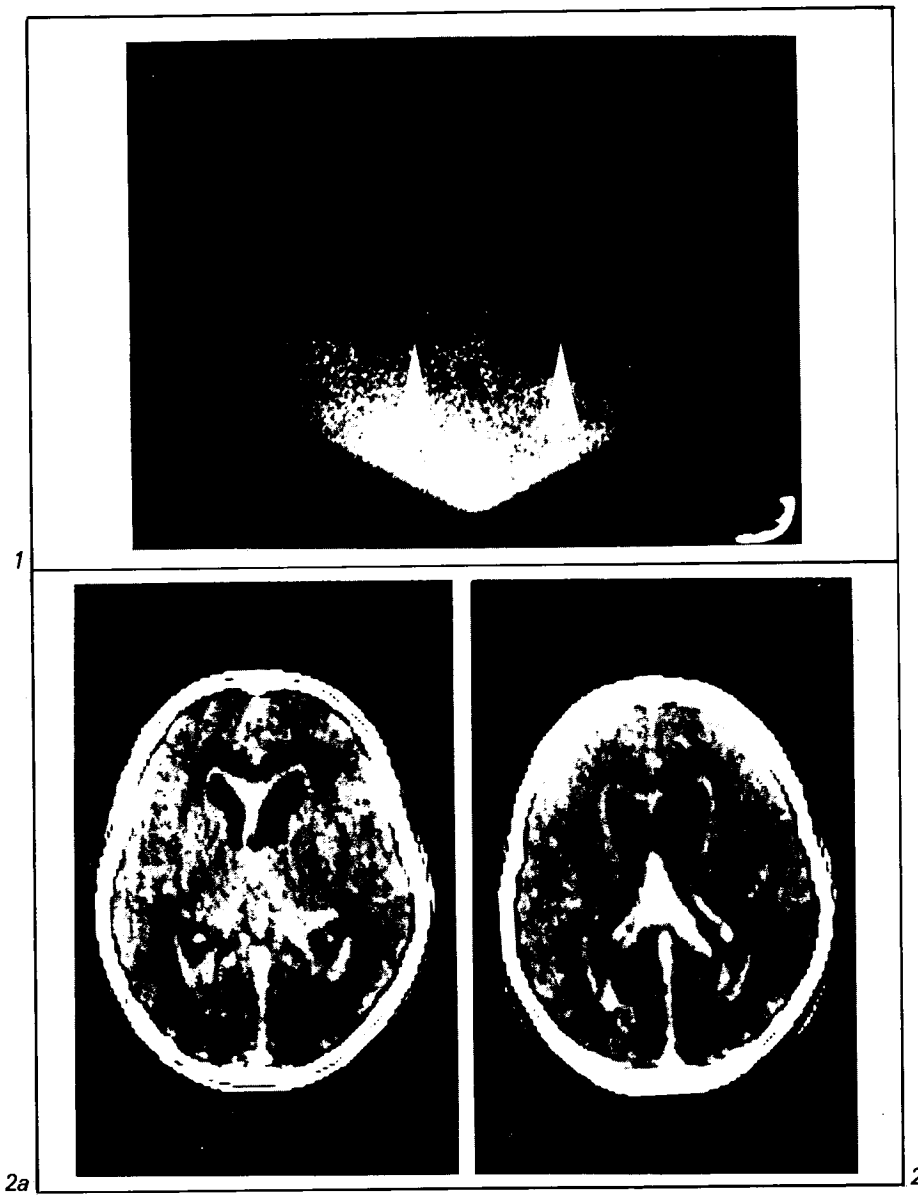


Fig. 1. Radionucleotide brain scan (PA view) showing abnormal tracer uptake around and within the lateral ventricles.

Fig. 2. Computerised tomography after contrast injection showing enhancement around the lateral ventricles and within the septum pellucidum.

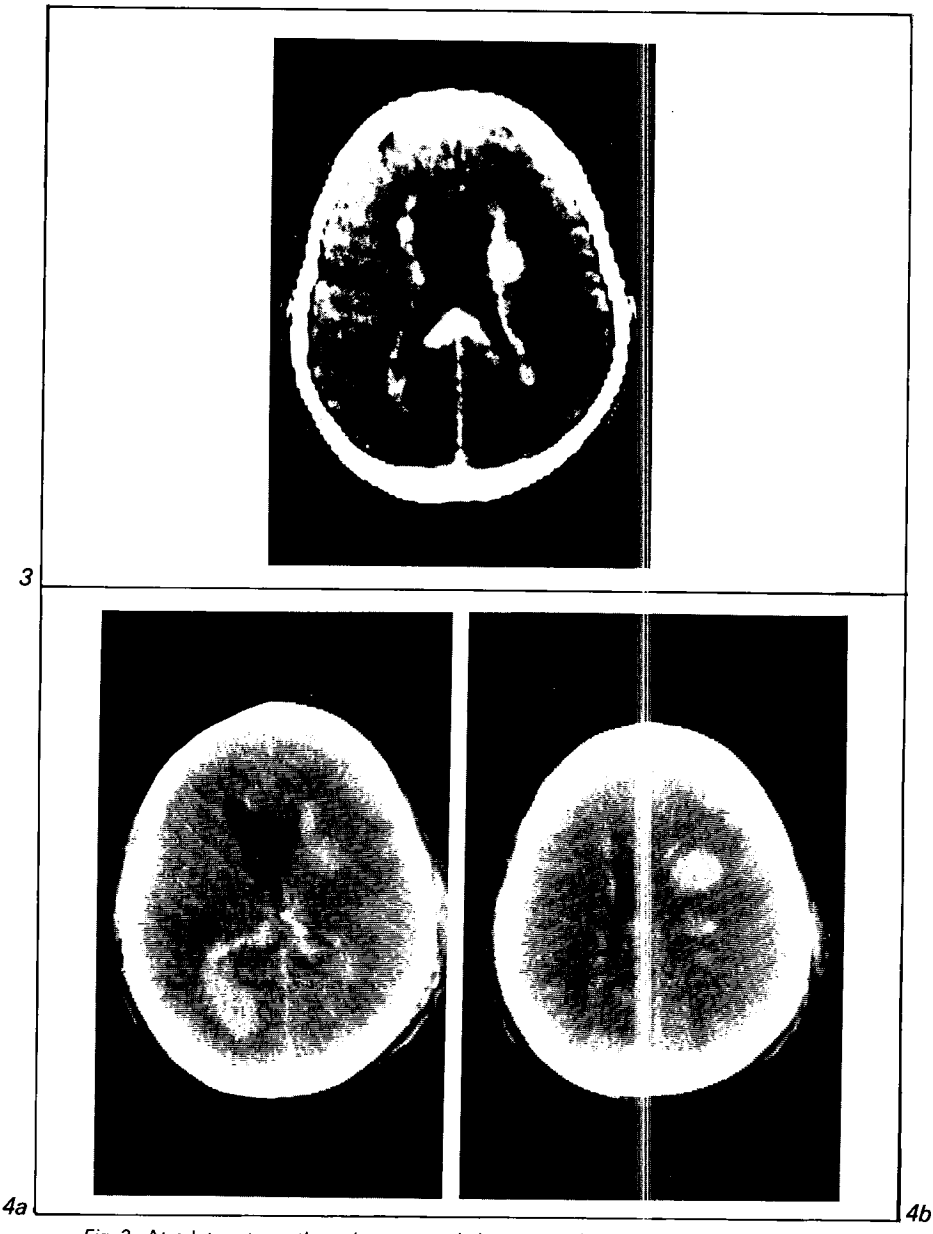


Fig. 3. At a later stage, the enhancement is in a more classical butterfly-shaped distribution and there is a mass of enhancing tissue in the right frontoparietal region.

Fig. 4. Later still, the CAT scan (different machine) shows tissue mass in the left occipital and right frontal region (a), and also along and within the corpus callosum on both sides (b).

ment extending along and through the corpus callosum (fig. 4). The patient was given high dose steroid therapy but died 12 weeks after admission.

Postmortem Findings

At necropsy, the brain weighed 1500g, and there was flattening and widening of the gyri, especially on the right side, where biopsy specimens had been taken. There was evidence of mild uncal and medullary coning, particularly on the right. Coronal brain slices confirmed the predominantly right hemisphere oedema and demonstrated soft greyish brown tumour of somewhat granular, dry texture surrounding both lateral ventricles (fig. 5). The tumour tissue extended outwards towards both cerebral cortices and across the genu of the corpus callosum. A 3cm diameter mass of tumour tissue was present in the right frontoparietal region, in continuity with the corpus callosum tumour and infiltrating the head of the right caudate nucleus. The track of the right frontal biopsy site just reached the most superficial aspect of this frontoparietal mass. Histological examination revealed densely cellular tumour tissue. The cells were predominantly of medium size, with occasional small cells. The nuclei were pleomorphic with a delicate chromatin pattern and occasionally a prominent nucleolus. The nuclear membrane was distinct. Occasional binucleate cells were seen. The smaller cells had dense, predominantly oval nuclei.

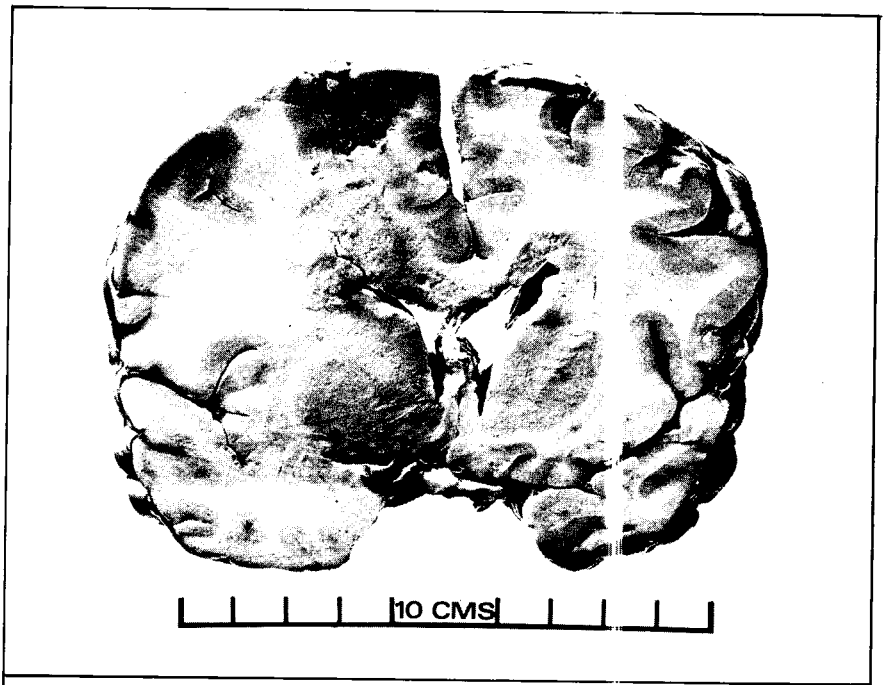
The distribution of the tumour cells was striking, with a large number of cells arranged perivascularly (fig. 6) and markedly distending the Virchow-Robin spaces. The border of the tumour was poorly defined with rays of tumour radiating out into the surrounding cerebral tissue (fig. 7).

Reticulin stain (fig. 8) showed a distinct pattern of concentric rings of perivascular reticulin. The innermost ring was the thickest and the concentric rings were connected by bridges of reticulin which in many cases appeared disrupted. Related to these rings and bridges were clumps of tumour cells. PTAH stains showed some mild astrocytosis at the tumour periphery. Both Hortegas and the Nanarembo/Feigin silver carbonate stains for microglia were performed but the results were not consistent enough for inclusion in this report, and no attempt was made to classify this tumour according to the histopathological criteria of Lennert (1975) or Lukes and Collins (1975). No evidence could be found, macroscopically or microscopically, of lymphoma tissue outside the brain.

Discussion

This report details the clinical course of a patient with a primary CNS lymphoma. The diagnosis was initially thought to be a form of granulomatous meningitis, and later, primary or secondary neoplastic invasion of the brain was considered. Because attempts to obtain a specific histological diagnosis were unsuccessful, no specific therapy was given. However, recent reports suggest that many of the features of this case were typical enough of primary CNS lymphoma to justify cranial irradiation in the absence of a specific histological diagnosis.

Pathologically, these tumours are known to occur in a periventricular distribution, with the septum pellucidum commonly involved (Ebels, 1972; Schaumberg et al., 1972; Houthoff et al, 1978). Therefore the CAT scan appearance of a 'butterfly tumour', tumour multicentricity and corpus callosal involvement from genu to splenium extending bilaterally, should strongly suggest the diagnosis of primary CNS lymphoma.



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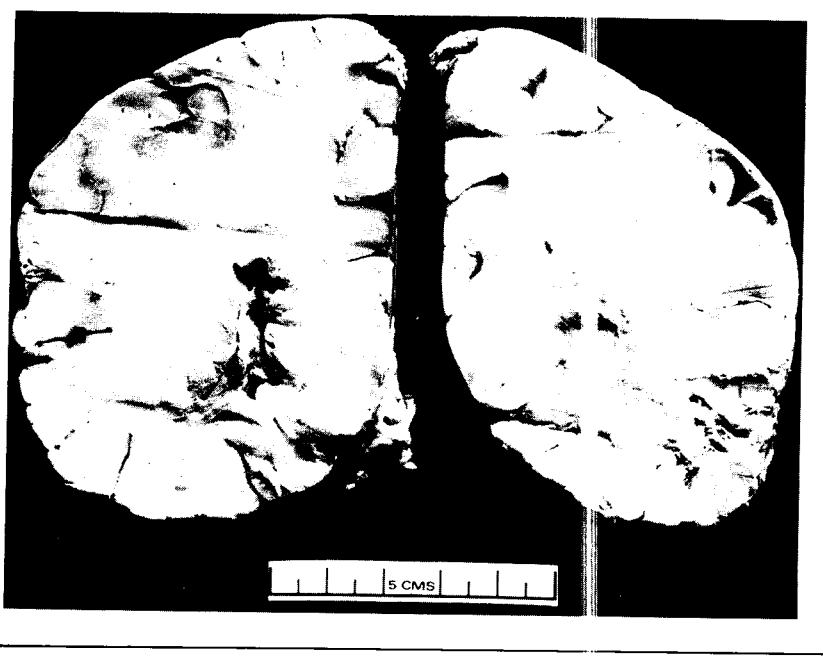

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Fig. 6. Microscopic appearance of tumour, showing the striking perivascular distribution, with distension of Virchow-Robin space. The subependymal distribution can also be seen.

Recently, Radvany and Levine (1978) compared the CAT scan appearances of 295 cases of proven glioblastoma with the appearances of 2 histologically proven primary CNS lymphomas. They concluded that the demonstration of a large, homogeneously dense, contrast-enhancing lesion with smooth margins, very little surrounding oedema and tendency for subependymal or intraventricular growth was very suggestive of CNS lymphoma. Similar CAT scan appearances were described in a case of secondary involvement of the CNS by systemic malignant lymphoma (Dubois et al., 1978).

Without treatment, most recorded cases of primary CNS lymphoma pursue a fulminating course with a survival of 3 to 5 months after the appearance of the first symptoms (Rubinstein, 1972). There is evidence that the tumour is radiosensitive (Fisher et al., 1969; Rubinstein, 1972), and a few patients are alive and well with no evidence of recurrence several years after operation or biopsy followed by radiotherapy (Kernohan and Uihlein, 1962).

Fig. 5. a) Coronal section of the brain showing tumour mass in right frontoparietal region which is continuous with tumour involving septum pellucidum and corpus callosum.

b) Coronal section through occipital region, showing granular tumour tissue surrounding the lateral ventricles and completely obliterating the left occipital horn.

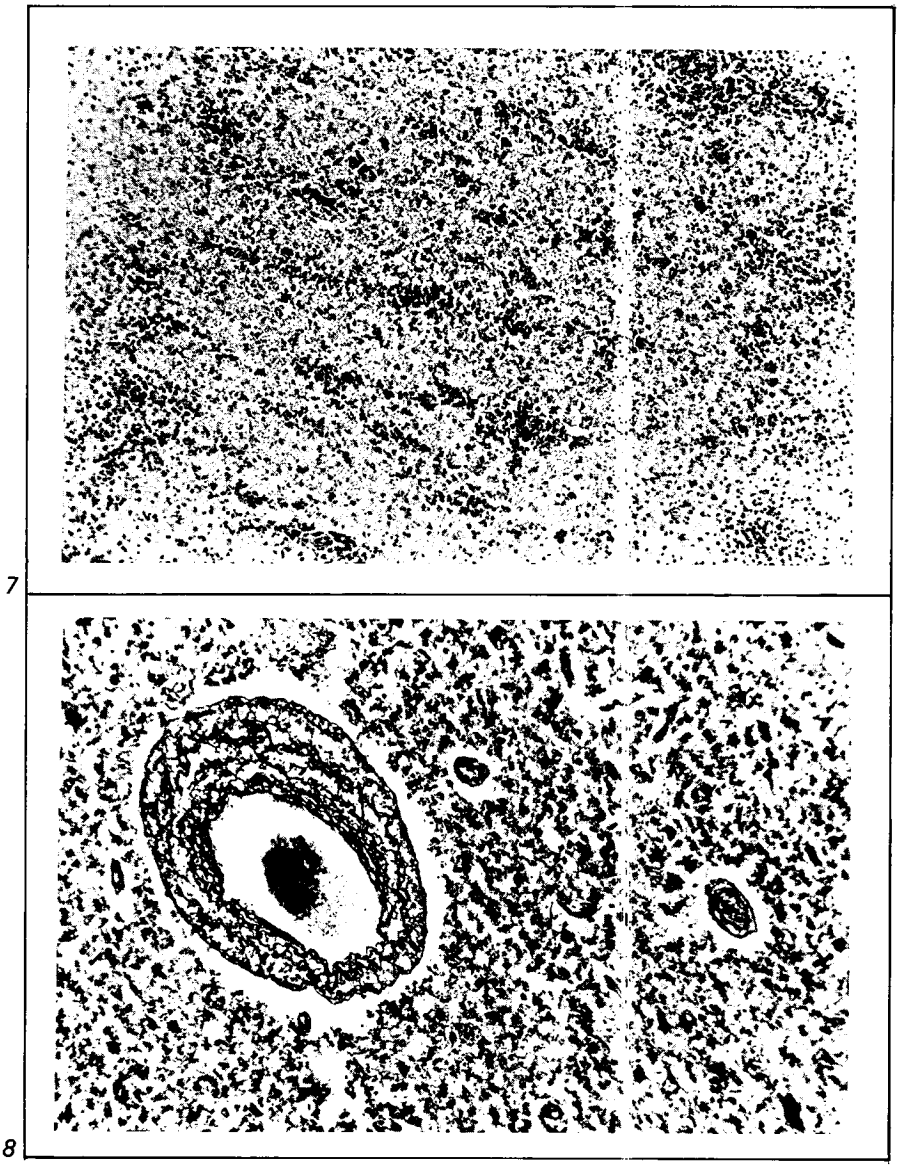

Fig. 7. Section from the periphery of the tumour, showing the finger-like extensions of tumour tissue into the surrounding brain.

Fig. 8. Reticulin staining demonstrating the characteristic pattern of concentric rings of reticulin fibres around blood vessels, within the Virchow-Robin space. Related to the rings and bridges of reticulin are clumps of tumour cells.

Patients presenting with clinical and radiological features suggestive of primary CNS lymphoma should have appropriate CSF and tissue examination in an attempt to confirm the diagnosis. However, if these procedures are non-diagnostic and the patient's condition is deteriorating, in our view a course of cranial irradiation is justified while appropriate investigation and monitoring is continued.

Summary

A 46-year-old female presented with a 1-week history of mental change, confusion and headaches. Investigations revealed evidence of sterile meningitis. CAT scanning of the brain demonstrated marked contrast enhancement around the ependyma, and later examinations showed extension of the process deep into the white matter. Cerebral biopsies were non-diagnostic and, despite ventricular drainage and treatment with antibiotics and high dose steroids, the patient died. At postmortem there was extensive tumour tissue distributed in a butterfly shape around the ventricles, and microscopy revealed typical appearances of primary CNS lymphoma.

On the basis of the experience of this case and a review of recent literature, it is suggested that the CAT scan appearances of this tumour are quite typical, and that cranial irradiation may be justified in the absence of specific histological diagnosis.

Acknowledgements

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Hypoglycaemia Secondary to Pancreatic Islet Cell Adenoma

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Functioning pancreatic islet cell tumours are uncommon and excite great clinical interest because of the diagnostic challenge they present, and because the disabling syndromes produced are potentially completely curable by surgical resection. The neurologist is particularly concerned with the diagnosis of the insulin-secreting islet cell adenoma presenting with recurrent hypoglycaemic episodes. He has the added concern that delays in diagnosis can lead to the development of permanent neurological and intellectual sequelae and in rare instances even a fatal outcome (Lawrence et al., 1942; Howard et al., 1950; Mulder et al., 1956; Gautier-Smith, 1965).

As was amply demonstrated by Best et al. (1978) the clinical recognition of this syndrome presents the major problem in diagnosis, even bearing the complexities and difficulties of the relevant endocrinological laboratory investigation in mind. Clinical recognition ultimately depends on obtaining a full and detailed medical history, as has been stressed by numerous authors (Moersch and Kernohan, 1938; Breidahl et al., 1955; Longmire et al., 1968).

Moersch and Kernohan (1938) have stressed that the physician be 'hypoglycaemia conscious' (as otherwise bizarre neurological and psychiatric symptoms of the syndrome may go unrecognised for long periods) and that the diagnosis is 'usually easy if the condition is simply kept in mind'. Indeed, detailed case reports from various studies (Howard et al., 1950; Richardson and Russell, 1952) are all rather stereotyped from case to case and in retrospect are virtually diagnostic. Yet it is precisely this information which is often lacking initially when the patient may be

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Table I. Fasting serial plasma glucose and serum insulin levels recorded in Case 1

Duration of fast (hrs)	Glucose (mmols/L)	Insulin (micro-units/ml)
12	3.5	16
24	2.4	14
25	3.9	12
30	2.7	9
31	2.0	9

drowsy, confused or in coma. A history here requires the detailed questioning of relatives, friends and family doctor, as stressed by Sutherland et al. (1966), because the patient himself often cannot remember events leading up to and during his attacks.

Case Reports

The case histories of 5 patients with pancreatic islet cell adenoma are presented to illustrate these features.

Case 1

This 58-year-old woman presented with a 6-month history of episodes of confused behaviour, usually occurring in the late morning and cut short by eating lunch. She did not experience palpitations or sweating in these attacks. For the previous 2 to 3 years she had had occasional episodes of diplopia during which objects would appear to be distorted. She would feel confused and would be unable to judge time. Hypoglycaemia was suspected as a possible cause of her attacks and her fasting plasma glucose was found to be 2.1mmol/litre.

She was admitted to hospital for investigation. On several occasions during a fast the fasting plasma glucose fell to 2mmol/litre or below and at these times the patient behaved in a vague, disorientated manner. The serum insulin levels on these occasions were persistently in the range usually seen in normoglycaemia. The results of a prolonged fast with combined serum insulin and plasma glucose levels are shown in table I. The fast was terminated with the plasma glucose at 2mmol/litre, at which stage the patient became quite confused, restless and agitated.

A CAT body scan of the pancreas and coeliac angiogram were both normal.

At exploratory laparotomy an islet cell tumour 13mm in diameter was located in the tail of the pancreas and resected. This tumour was reported histologically as being a benign islet cell adenoma.

Postoperative convalescence was uneventful and no further attacks have occurred.

Case 2

3 months before admission to hospital this 18-year-old male patient had an episode of confusion followed by collapse one morning while he was walking through his local shopping centre. The patient remembered nothing about the attack and did not remember getting up that morning. He had apparently walked about half a mile when he began to become confused and ataxic. Soon after this he collapsed and was taken to his local hospital where he was kept under observation for some hours. He quickly recovered in hospital but it was not until 9 pm that evening that he felt normal.

Table II. The results of a tolbutamide tolerance test and a glucagon stimulation test in Case 2

Investigation	Time (mins)	Glucose (mmol/L)	Insulin (micro-units/ml)
Tolbutamide tolerance test	0	1.6	27
	2	1.6	> 200
	5	—	> 200
	10	—	> 200
	15	—	> 200
	20	0.6	131
	30	0.6	75
	45	0.7	51
	60	0.7	42
	90	0.8	46
Glucagon stimulation test	0	1.6	
	2	—	
	5	2.0	
	10	2.5	
	15	3.0	
	20	2.4	
	30	3.0	
	45	2.1	
	50	1.2	
	90	1.3	
	120	1.6	
	150	1.6	

A second episode of confusion and unsteadiness occurred 2 weeks before admission. This attack once again took place in the morning and on this occasion he had been out late the night before playing basketball. As before, the patient could not recall any details of this episode and could not recall rising that morning. He was found by his family staggering and confused in the hallway of the house. He was immediately admitted to hospital where he gradually recovered over the course of that day.

A random blood sugar level at 8 pm on the evening of admission was 2.5mmol/litre and the following morning was 3.2mmol/litre. A fasting blood sugar was done 4 days after admission and this was 2.2 mmol/litre. It was thought that these episodes were probably hypoglycaemic attacks and a prolonged fast was therefore planned.

His blood sugar level after 12 hours' fasting was 1.4mmol/litre. After fasting for 20 hours he became grossly confused and aggressive; his blood sugar was 0.9mmol/litre. The fast was terminated at this stage and his condition improved rapidly after he had been given a glucose drink. He was then transferred to St. Vincent's Hospital for more detailed investigation. Table II shows the results of a tolbutamide tolerance test and a glucagon stimulation test. Grossly and inappropriately elevated serum insulin levels were recorded during the tolbutamide tolerance test. After 90 minutes, the patient became confused and the test was terminated by an intravenous infusion of 10% dextrose.

It was felt that there was sufficient clinical and laboratory evidence to justify an exploratory laparotomy. At operation 2 islet cell adenomas were removed from the pancreas. A 2cm-diameter tumour was seen on the anterior surface on the body and a 5mm adenoma was felt in the neck. His blood sugar

rose to 14.5mmol/litre in the postoperative period and he required stabilisation with insulin for 4 to 5 days.

No further hypoglycaemic episodes occurred during follow-up, but he was subject to occasional attacks of abdominal pain which were thought to be due to mild chronic relapsing pancreatitis.

Case 3

When first seen, the patient, a woman of 63, gave a 4-year history of occasional episodes of drowsiness, weakness and confusion relieved by food. She had been admitted 12 months previously to her local hospital with an episode of confusion and left hemiparesis which resolved spontaneously. On the day following this admission she had an episode of confusion and unsteadiness, and a plasma glucose reading in that attack was 2.2mmol/litre. Fasting plasma glucose levels taken on 3 occasions during that admission were 1.2mmol/litre; 1.9mmol/litre and 0.8mmol/litre. She refused further investigation at that stage

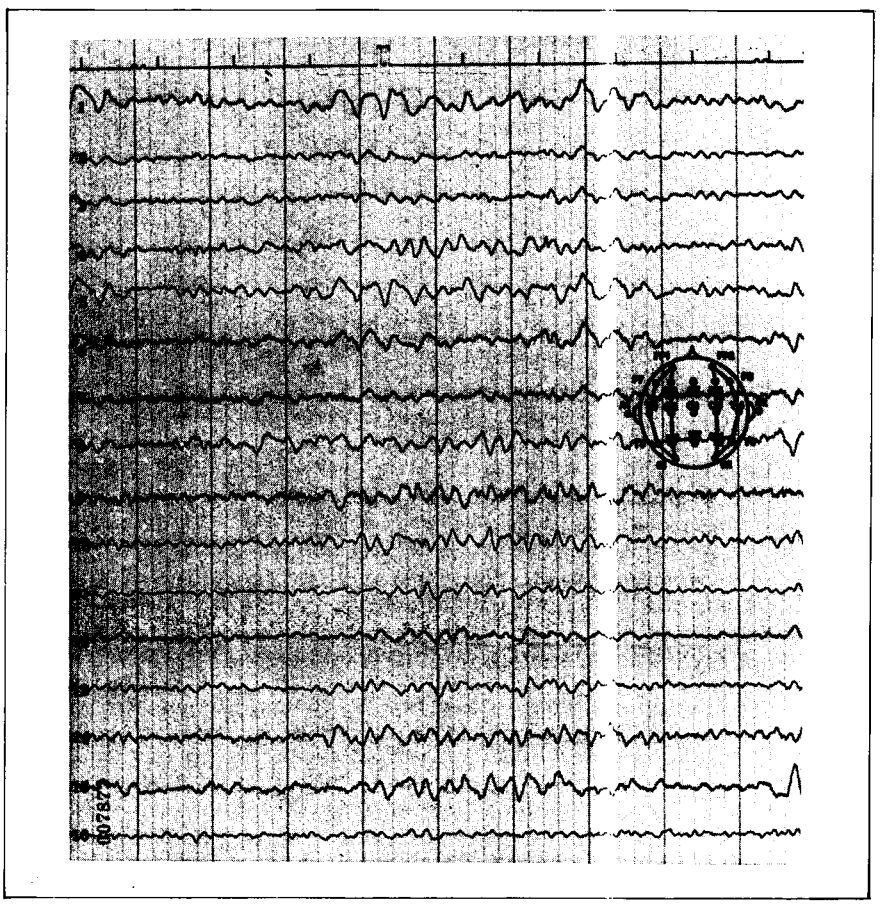

Fig. 1. EEG in Case 4, showing diffuse background slow wave abnormality 10 days after a hypoglycaemic episode.

Table III. Plasma glucose and serum insulin levels in Case 4 after each of a series of overnight fasts

Glucose (mmol/L)	Insulin (micro-units/ml)
2.0	44
2.7	26
2.4	19
2.3	28

Table IV. Serial fasting plasma glucose and serum insulin levels recorded in Case 4

Duration of fast (hrs)	Glucose (mmol/L)	Insulin (micro-units/ml)
15	1.9	19
16	2.0	18
20	2.4	20
27	1.9	12

and was discharged. She found that if she took 6 small meals spread over the day, in the evening and the early hours of the morning, she could prevent most attacks, but if any delay occurred then an episode would develop.

On examination she was found to be anxious, aggressive and rather paranoid but no abnormalities were detected on neurological testing.

A prolonged fast was begun and after 7 hours she became sweaty, confused and aggressive. Plasma glucose level after 6 hours' fasting was 2.1mmol/litre with a serum insulin of 10 micro-units/ml. At the termination of the fast, plasma glucose level was 1.8mmol/litre with a serum insulin level of 9 micro-units/ml. Further investigations were declined by the patient once again and she was discharged on diazoxide 100mg 3 times a day with frequent feeds. She was re-admitted 2 years later because of increasing attacks. At that time episodes were recurring about every 3 weeks. Several attacks occurred in hospital. These consisted of episodes of confused and aggressive behaviour but occasionally grand mal seizures occurred as part of the attack. Her blood sugar level during one such turn was 1.2mmol/litre.

In addition to frequent small feeds, she was treated with prednisone 5mg 3 times a day. An ultrasonic abdominal scan showed no abnormality, but a coeliac and mesenteric angiogram showed the presence of a tumour blush 1 to 2cm in diameter at the junction of the body and tail of the pancreas. At laparotomy a 1cm tumour was located in the tail of the pancreas and a partial pancreatectomy was carried out. Histology disclosed a circumscribed but unencapsulated islet cell adenoma.

Her postoperative course was rather stormy with a Gram-negative septicaemia, right low thoracic pleuritic pain and the development of an upper abdominal mass. Serum amylase levels were persistently raised. Re-exploration was carried out and a large pseudocyst of the pancreas was drained. Her progress after this was uneventful with no further attacks.

Case 4

6 months before admission this man, aged 41, began to experience episodes of confusion and amnesia lasting about 2 hours, usually in the early morning. He often complained of double vision during these episodes. He had also experienced great difficulty in waking in the morning and had arranged for several early morning phone calls to be made in order to rouse him but in spite of these would often go back to sleep for many hours.

He was brought to hospital late one evening by friends who had found him in a vague and confused state. He had apparently had a brief generalised seizure just prior to his arrival. On examination at that time he was confused and disorientated with nystagmus on left lateral gaze and bilateral extensor plantar responses. He then appeared to improve but in the early hours of the morning had an episode of agitated, aggressive and confused behaviour which once again settled spontaneously. However, on examination the following morning he was markedly drowsy. He was noted to have a partial internuclear ophthalmoplegia and in addition made periodic downward tortive movements of both eyes. Both plantar responses were extensor.

A provisional diagnosis of brain stem encephalitis was made at this stage. The patient then had a major seizure but after this spontaneously improved, and although a little slow mentally had no abnormal signs on neurological examination. A random plasma glucose level at this time was 3.1mmol/litre.

A CAT scan and CSF examination gave normal results. The EEG (fig. 1) 3 days after admission showed a generalised excess of slow activity at 3 to 4 Hz which at times had episodic features. This abnormality persisted on subsequent records (7-10 days after admission) and angiography and air encephalography were therefore done in an effort to exclude a mass lesion. Both gave normal results. A hypoglycaemic basis for his attacks was then investigated (tables III and IV).

It was felt that on the basis of these studies, the serum insulin levels were inappropriately elevated in relation to the concurrent blood glucose values and that this was sufficient evidence to warrant pancreatic exploration.

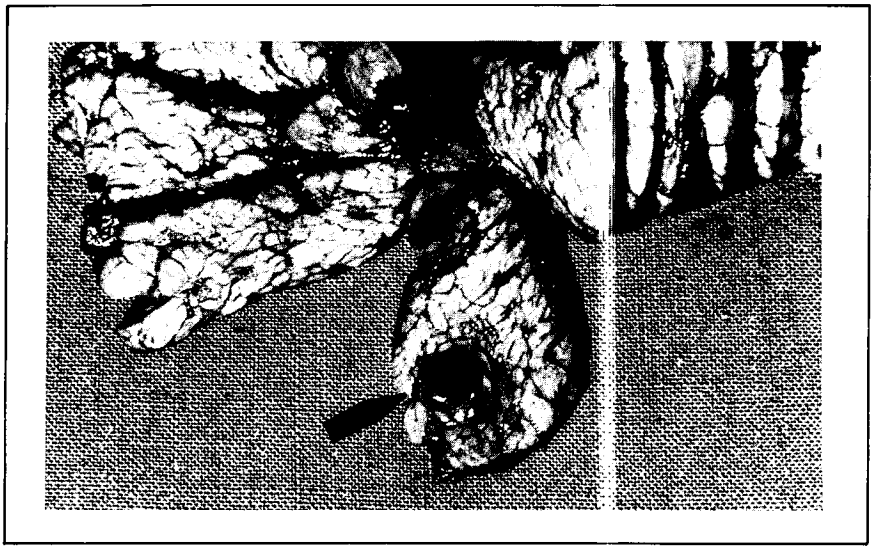

Fig. 2. Case 4. Adenoma discovered by pathologist on sectioning the resected pancreatic tail.

A CAT scan of the pancreas showed no evidence of a tumour mass and an ultrasonic echogram of the pancreas was also normal.

At laparotomy no definite tumour could be detected on palpation of the body of the pancreas and a partial pancreatectomy and splenectomy were therefore performed. On frozen section an ovoid greyish red nodule was seen in the pancreas 50mm from the tail. This nodule measured 10mm × 8mm and microscopically showed the features of a benign islet cell adenoma of the pancreas (fig. 2).

Postoperatively, the patient had a period of hyperglycaemia and also had a markedly elevated platelet count. A pulmonary embolism occurred 10 days postoperatively and was treated with heparin. Following this, the patient's convalescence was uneventful and no further attacks have occurred.

Case 5

This patient, a woman aged 54, had a 6-month history of recurrent strange attacks which would begin with a feeling of vagueness, slowing of speech and sweating. Her speech would become further affected because of difficulty in finding the correct words to express herself. She would then experience distortion of vision, double vision, visual and auditory hallucinations. During these episodes she would often behave in a violent and aggressive manner, screaming obscenities, spitting, shouting and throwing herself around. She did not think that she ever actually lost consciousness at these times. She also complained of recurrent headaches over the previous few months and had noted a deterioration in her memory and concentration.

Examination revealed a mild nominal dysphasia, and tendon reflexes slightly brisker on the right.

A full blood count and ESR were normal. A fasting blood sugar was 2.7mmol/litre. The EEG was normal. Bilateral carotid angiography showed a slight shift of midline structures from left to right but an air encephalogram was normal.

She remained in hospital for 3 weeks and no turns developed during this time. She was discharged on anticonvulsants.

Following discharge she remained well for 2 to 3 months but was then re-admitted to her local hospital after a series of generalised seizures. She was transferred to St. Vincent's Hospital, and on arrival was grossly confused and agitated. She exhibited wild and aggressive behaviour and sat on the floor grunting, refusing to allow anyone near her. However, later that evening she was noted to be alert and cooperative. The following morning however she was found unconscious with head and eyes deviated to the right and a right hemiplegia. Her blood sugar level was immediately measured and was 4mmol/litre. She was started on steroids, and a left carotid angiogram was done which showed a slight deviation of the anterior cerebral artery from left to right. She then improved spontaneously and was able to give a more detailed history, saying that she had been completely well following her first hospital admission up until 1 week before this second admission when her turns began recurring. She found that immediately prior to a turn she would sweat and become weak in the legs. She could occasionally cut an attack short by lying down, but would then often pass into a deep sleep from which it was very difficult for her husband to arouse her.

On neurological examination a mild dysphasia with slight right-sided pyramidal weakness and slightly brisker right tendon reflexes were noted. Her EEG at that stage showed a generalised excess of theta activity, more prominent on the left. Air encephalogram showed some enlargement of the left lateral ventricle and the cortical sulci were prominent, consistent with a cerebral degenerative process.

She was once again discharged on anticonvulsants but re-admitted 2 months later following a further series of attacks. One of these attacks came on during a 5-hour fast and was immediately corrected by intravenous glucose. On this basis she was once again transferred to St. Vincent's Hospital with a clinical diagnosis of hypoglycaemic episodes. A further seizure occurred soon after her arrival and this was immediately corrected by 20ml of 50% glucose intravenously. Following this injection she became alert and was able to converse in a normal manner.

A prolonged fast was therefore begun but terminated after 28 hours because of the development of confusion. Blood sugar levels during the fast are shown in table V. Serum insulin levels were not measured.

Table V. Fasting serial plasma glucose levels recorded in Case 5

Duration of fast (hrs)	Glucose (mmol/L)
12	1.6
24	2.0
28	2.0

Table VI. Results of a glucagon stimulation test performed on Case 5, showing inappropriately raised serum insulin levels

Time (mins)	Glucose (mmol/L)	Insulin (micro-units/ml)
0	2.2	23.5
2	3.0	25.0
5	4.3	55.0
10	4.0	200.0
15	3.6	200.0
20	3.4	200.0
30	1.4	200.0
45	1.1	200.0

It was felt that the clinical history was strongly suggestive of episodes of hypoglycaemia secondary to insulinoma, and on this basis a glucagon stimulation test was carried out (table VI). This showed the presence of hyperinsulinism with insulin readings inappropriately elevated with respect to the blood glucose levels.

At laparotomy a tumour 1.8cm in diameter was located on the posterior surface of the tail of the pancreas. Microscopically this proved to be an encapsulated benign islet cell adenoma.

Postoperative progress was uneventful and no further attacks have occurred.

Discussion

The concept of endogenous hyperinsulinism as a distinct entity was put forward by Harris in 1924. The first case report of islet cell tumour was published by Wilder et al. in 1927. The patient, a physician, had a malignant pancreatic tumour with hepatic metastases, and postoperative survival was only a matter of weeks. In 1929

Howland et al. reported the successful removal of a pancreatic islet cell tumour in a patient with a 6-year history of hypoglycaemic attacks.

Age Group Affected

Although there are many causes of spontaneous hypoglycaemia (table VII), pancreatic islet cell disease with hyperinsulinism is the most important cause in the adult. The condition had been described in patients from infancy to old age but is most com-

Table VII. Causes of hypoglycaemia [modified from Fajans et al. (1975)].

Type of hypoglycaemia	Causes
Organic (recognisable anatomical lesion)	Pancreatic islet cell diseases with hyperinsulinism i) adenoma — single or multiple ii) micro-adenomatosis, with or without macroscopic islet adenomas iii) carcinoma with metastases iv) adenoma or carcinoma associated with adenomas of other endocrine glands (familial multiple endocrine adenomatosis) v) hyperplasia (very rare in adults)
	Non-pancreatic tumours associated with hypoglycaemia Anterior pituitary hypofunction Adrenocortical hypofunction Acquired extensive liver disease Severe congestive cardiac failure Severe renal insufficiency in non-insulin-dependent diabetes
Due to specific hepatic enzyme defects	Glycogen storage diseases Hereditary fructose intolerance
Functional (no recognisable or persistent anatomical lesion)	Reactive functional hypoglycaemia Reactive hypoglycaemia secondary to mild diabetes Alimentary hyperinsulinism Alcohol and poor nutrition Idiopathic hypoglycaemia of infancy and childhood
Due to exogenous causes	Iatrogenic/functional (insulin or sulphonylurea compounds) Other drugs

mon in the 30 to 60-year age group (Fajans et al., 1975). It is of interest that a positive family history of diabetes mellitus has been found in 25 to 30% of patients with this condition (Re Mine et al., 1960; Fajans et al., 1975).

Type of Lesion

80% of patients have a single benign lesion, most commonly of small diameter (less than 2-3cm), found distributed equally throughout the head, body and tail of the pancreas. 10% of patients have multiple adenomata (some have the syndrome of multiple endocrine adenomatosis type 1) and in approximately 10% of patients the lesion is malignant, with liver and regional lymph node metastases (Crain and Thorn, 1949; Service et al., 1976).

In a small number of patients the adenoma is found in ectopic pancreatic tissue: in the wall of the stomach or duodenum, in the hilum of the spleen, or posterior to the pancreas itself [2.5% of cases in the series of Crain and Thorn (1949) and Howard et al (1950)]. Microadenomatosis scattered throughout the gland with or without macroscopic adenomas has been described (Frantz, 1944) but diffuse hyperplasia of the islet cells has not been proved as an entity in the adult (Breidahl, 1955; Fajans et al., 1975).

Although most commonly presenting with hyperinsulinism, benign or malignant functioning islet cell tumours can secrete other hormones either separately from, as well as, or subsequent to, insulin (Broder and Carter, 1973; Schein et al., 1973).

Clinical Recognition

The identification of the patient with pancreatic islet cell adenoma depends on the recognition of the characteristic clinical syndrome. This presupposes that one has been able to obtain a detailed history. The diagnosis is often delayed, and as the condition may imitate a broad spectrum of neurological and psychiatric conditions (Moersch and Kernohan, 1938), it is not surprising that patients may initially be labelled as having such conditions as temporal lobe epilepsy, cerebral tumour, cerebral degeneration, alcoholism or hysteria (Breidahl et al., 1955).

The episodes may initially be quite mild and irregular with months of freedom between attacks. As the condition advances, attacks become more severe and more frequent, possibly owing to increasing activity of the tumour, with release of increasing amounts of insulin (Longmire et al., 1968).

The attacks classically come on in the fasting state and so are most common in the early hours of the morning, before breakfast, or in the late afternoon. As an episode may be provoked by missing a meal, patients soon become aware of the relationship between food and their attacks, and may resort to taking frequent snacks throughout the day and night. Obesity may result although it is uncommon — 18% of patients according to Service et al. (1976).

Exercise is an additional factor tending to provoke attacks, as it leads to an increased uptake of glucose by muscle, thus aggravating the hypoglycaemic tendency (Fajans and Floyd, 1976).

Autonomic phenomena (sweating, palpitation, anxiety, tremor) are often absent in attacks caused by endogenous hyperinsulinism, where the rate of fall of the blood sugar is slow (Longmire et al., 1968; Fajans et al., 1975; Best et al., 1978). In the series of 193 patients analysed by Crain and Thorn (1949) sweating was seen in only 36% of patients.

The clinical picture of the hypoglycaemic episode seen with pancreatic islet cell disease is therefore largely due to the cerebral effects of decreased glucose uptake and utilisation, i.e. a form of 'histotoxic anoxia' (Courville, 1957) or 'neuroglycopenia' (Service et al., 1976). The condition is characterised by the inappropriate and autonomous secretion of insulin by the tumour which continues even in the absence of food ingestion (Longmire et al., 1968). During fasting, and especially during the long hours of sleep, the blood sugar level progressively falls, leading to the production of the major neurological and psychiatric symptoms which characterise an attack and which most typically occur in the early morning before breakfast.

The patient may present with early morning episodes of drowsiness, confusion, headache, irritability and restlessness, double vision, slurring of speech and unsteadiness. The attack may be cut short at this stage by food, with the patient being completely unable to recall the episode. More severe attacks may occur with increasing confusion and bizarre behaviour, leading eventually to stupor or even coma. Epileptic seizures are frequent. Focal neurological signs, such as hemiplegia, visual field defects, cerebellar and brain stem signs and extensor plantar responses may be detected at this stage. Occasionally such attacks have a fatal outcome but more commonly, rapid recovery occurs, whether spontaneously or following glucose administration. However, the patient may complain of mental dullness, or difficulty with memory, for some time, even months, after such an attack (Service et al., 1976). Focal neurological signs commonly resolve rapidly but may persist, although usually only for a short period. Permanent hemiplegia and permanent dementia have been described (Howard et al., 1950; Re Mine et al., 1960; Gautier-Smith, 1965; Fajans et al., 1975).

Pathological Changes

The pathological changes seen in fatal cases of hypoglycaemic coma are those of widespread neuronal loss and degeneration. These changes are maximal in the cortex (often with laminar necrosis) basal ganglia and cerebellum (Lawrence et al., 1942; Courville, 1957). The mode of development of focal neurological signs has aroused speculation and it has been postulated that they may be secondary to some pre-existing anomaly or inefficiency in the cerebral circulation in the area affected (Moorhouse, 1956; Meyer and Portnoy, 1958; Portnoy, 1965; Service et al., 1976).

Confirmation of Clinical Diagnosis

The clinical diagnosis is confirmed by the demonstration that symptomatic episodes produced by fasting are associated with hypoglycaemia (plasma glucose less than 2.5mmol/litre) and are relieved by glucose administration — 'Whipple's triad' (Whipple and Frantz, 1935). In addition, one must demonstrate that concomitant levels of serum insulin recorded during the episodes are inappropriately elevated in relation to the blood glucose levels (Service et al., 1976). This can often be done by recording serum insulin and plasma glucose levels after a series of overnight fasts on consecutive days. More information can be obtained by prolonging the fast to 24, 48 or even 72 hours if necessary, but this must be done in hospital under supervision so that the fast can be terminated immediately should cerebral hypoglycaemic symptoms develop. Serial glucose and insulin levels are recorded throughout the fast, and Fajans et al. (1976) and Samols and Marks (1963) have stressed the importance of frequent sampling, as serum insulin levels can show wide fluctuations from hour to hour. The prolonged fast can be followed if necessary by a period of strenuous exercise, as in patients with insulinoma this will produce a further fall in blood glucose levels with serum insulin either increasing or remaining stationary, whereas in healthy subjects or patients with functional hypoglycaemia exercise will usually provoke a rise in the blood glucose level (Fajans and Floyd, 1976).

The aim of the prolonged fast is to demonstrate that the serum insulin responses are 'inappropriate' with respect to the blood glucose levels, i.e. that serum insulin secretion is autonomous and independent of variations in the blood glucose level. The hyperinsulinaemia may thus be 'absolute' or 'relative' (serum insulin level within the range seen in normoglycaemia but inappropriate in the presence of hypoglycaemia). The upper limit of 'normal' for serum insulin level in the fasting state varies with the sensitivity of the radioimmunoassay, and results from different series are not strictly comparable: '6micro-units/ml in patients with non-insulinogenic hypoglycaemia' (Service et al., 1976); '24 micro-units/ml in fasting normal subjects' (Fajans and Floyd, 1976); '19 micro-units/ml as mean value in fasting normal subjects' (Samols and Marks, 1963). In the present series 8 micro-units/ml has been taken as the upper limit of normal for serum insulin in the presence of hypoglycaemia, and one would expect that patients hypoglycaemic from causes other than hyperinsulinaemia would show little if any detectable insulin activity in their serum (Turner et al., 1971).

Other provocative tests, such as the tolbutamide tolerance test and the glucagon stimulation test, are used much less frequently now than in the past. Such tests have a significant percentage of false negative and occasionally false positive results and carry definite risks of precipitating profound hypoglycaemic reactions. They are probably best reserved for the occasional difficult case where clinical suspicion is high, yet insulin levels recorded during hypoglycaemia persistently remain in the low normal range, so that proof of the autonomy of insulin secretion is lacking (Best et al., 1978).

Measurement of Proinsulin

Proinsulin, the large molecular weight precursor of insulin, can also be measured in the serum. In fasting normal subjects the proinsulin-like component comprises 10 to 30% of the total immuno-reactive insulin level (Gorden et al., 1972). This percentage may be increased in islet cell adenoma and particularly in carcinoma. This measurement may prove a valuable aid to diagnosis in the future, especially in cases where the total immuno-reactive insulin level remains within the normal range (Schein et al., 1973; Fajans and Floyd, 1976; Best et al., 1978).

Identification at Operation

At operation, careful inspection and palpation of the entire pancreas is necessary in the search for single or multiple lesions. This also includes the sites of ectopic pancreatic tissue, especially if no adenoma can be identified within the pancreas. 'Blind' distal pancreatectomy has been favoured in the past when no adenoma can be identified (Re Mine et al., 1960) but this practice has been criticised on the grounds that the concealed adenoma is often buried deep within the mass of tissue of the pancreatic head, rendering re-operation necessary at a later date because of the persistence of symptoms (Longmire et al., 1968). It has been shown that with distal pancreatectomy a lesion is found in only 25% of resected specimens (Mengoli and Le Quesne, 1967). Localisation of the tumour preoperatively would therefore be of immense help to the surgeon. In the series of 361 cases reported by Howard et al. (1950) no adenoma was found in 118 patients at the first operation. Breidahl et al. (1955) found no adenoma at first operation in 27 of 91 patients. In 17 of these 27 patients a blind distal pancreatectomy was done and in 5 of these an adenoma was subsequently identified in the resected specimen.

Role of Other Investigative Procedures

Selective mesenteric and coeliac angiography has been advocated as a preoperative means of localising the lesion. However the success rate has varied from 20 to 70% and not all tumours have been demonstrated in patients with multiple adenomas (Doolas, 1971; Schein et al., 1973; Fajans et al., 1975). The procedure is of value in the preoperative investigation of the patient and an improved yield is possible in the future. The role of ultrasonic echogram and computerised tomographic scanning of the pancreas remains uncertain but was not helpful in the present series.

Medical Treatment

Although surgical resection of the benign adenoma remains the treatment of choice, symptoms can be controlled to a variable degree by medical means. However,

this is applicable mainly to patients with malignant neoplasms. Frequent small meals throughout the day, combined with the use of steroids, growth hormone and glucagon have been used. Diazoxide and phenytoin, both inhibitors of insulin release, can also be used to ameliorate symptoms (Schein et al., 1973). Chemotherapy with antimitotic agents has been used in patients with malignant lesions and reported as resulting in increased survival (Broder et al., 1973; Schein et al., 1973).

Differential Diagnosis of Insulinoma

Although there are many causes of hypoglycaemia in the adult, two important conditions that must be remembered in the differential diagnosis of insulinoma are: functional or reactive hypoglycaemia, and factitious hypoglycaemia secondary to self-administration of insulin or ingestion of sulphonylurea.

With functional hypoglycaemia symptoms do not occur in the fasting state but come on 2 to 4 hours after a meal. The prolonged 5-hour glucose tolerance test is of most use in the investigation of this entity, showing a rebound of the blood glucose level into the normal range after the initial fall. Serum insulin levels are normal to low during a prolonged fast and the blood glucose level rises with the period of exercise at the end of the fast in contrast to the fall with islet cell tumour (Fajans et al., 1976).

With self-administration of insulin, more commonly seen in medical or paramedical personnel or in patients with diabetic relatives, insulin antibodies may be detected in the serum, although these may take 2 months to develop (Fajans et al., 1976). C-Peptide levels can also be measured (the 'connecting peptide' released with cleavage of proinsulin to insulin) and will be low in patients whose hyperinsulinaemia is exogenous (Fajans et al., 1976; Service et al., 1976). With self-administration of tolbutamide it is possible to measure plasma concentration of the drug and a carboxylated excretion product can be detected in the acidified urine (Fajans et al., 1975, 1976).

Persistence of Effects of Hypoglycaemia

It has been mentioned previously that the effects of a particular hypoglycaemic episode may be prolonged and thus outlast the period of hypoglycaemia responsible. This has been demonstrated by Service et al. (1976) who showed that focal and diffuse slow activity on the EEG persisted for several days after treatment of an episode of coma and even after removal of the insulinoma. Similarly a significant impairment of intellectual function persisted in this patient, despite resuscitation and reversal of the episode of coma, and only returned to normal after an interval of 4 months. This situation represents an area of possible diagnostic confusion, especially when one is dealing with a severe hypoglycaemic reaction. The finding of a blood sugar level within the normal range in a patient in coma with focal neurological signs

does not exclude hypoglycaemia as the initiating cause. Similarly the absence of a response to dextrose infusion in a patient in coma does not exclude hypoglycaemia as the cause of that state (Crain and Thorn, 1949; Richardson and Russell, 1952). In these predicaments as in all aspects of this diagnostic problem the availability of a full and detailed history will readily point towards the correct solution.

Summary

The detailed case histories of 5 patients with hypoglycaemic episodes secondary to islet cell adenoma of the pancreas are presented. Clinical recognition of this syndrome remains the major problem but a full and detailed medical history is usually strongly suggestive of the correct diagnosis.

The clinical diagnosis is confirmed by the repeated demonstration that:

1) Symptomatic episodes produced by fasting are in fact due to hypoglycaemia (plasma glucose level less than 2.5mmol/litre)
2) Such episodes are relieved by glucose administration
3) Concomitant hyperinsulinaemia is present (serum insulin greater than 8 micro-units/ml in the fasting state).

Surgical resection of the adenoma produces a complete cure but the identification of the lesion at operation may be difficult and preoperative means of accurate localisation may be needed.

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Idiopathic Communicating Hydrocephalus: The Prognostic Significance of Ventricular Size After Shunting

*K.S. Millingen**

It has been shown by ventriculography in patients with idiopathic communicating hydrocephalus that there is no consistent relationship between clinical improvement after shunting and reduction in ventricular size (Shenkin et al., 1975). A similar conclusion was reached by Jacobs and Kinkel (1976) using computerised axial tomography (CAT) to determine ventricular size. On the other hand Gunasekera and Richardson (1977), using CAT scanning, demonstrated that patients with idiopathic hydrocephalus whose ventricular size did not diminish significantly, showed no improvement.

3 severely affected patients are described who fulfilled the criteria of idiopathic communicating hydrocephalus, who have been investigated by CAT scanning before and after shunting, and who have maintained over a period of 2 years remarkable improvement despite the absence of significant change in ventricular size.

The prediction of the likely success of shunting in this condition is discussed.

Methods

Idiopathic hydrocephalus is defined as that condition in which the patient presents with ataxia, dementia and incontinence, and in whom communicating hydrocephalus is demonstrated in the absence of any clear structural lesion or preceding

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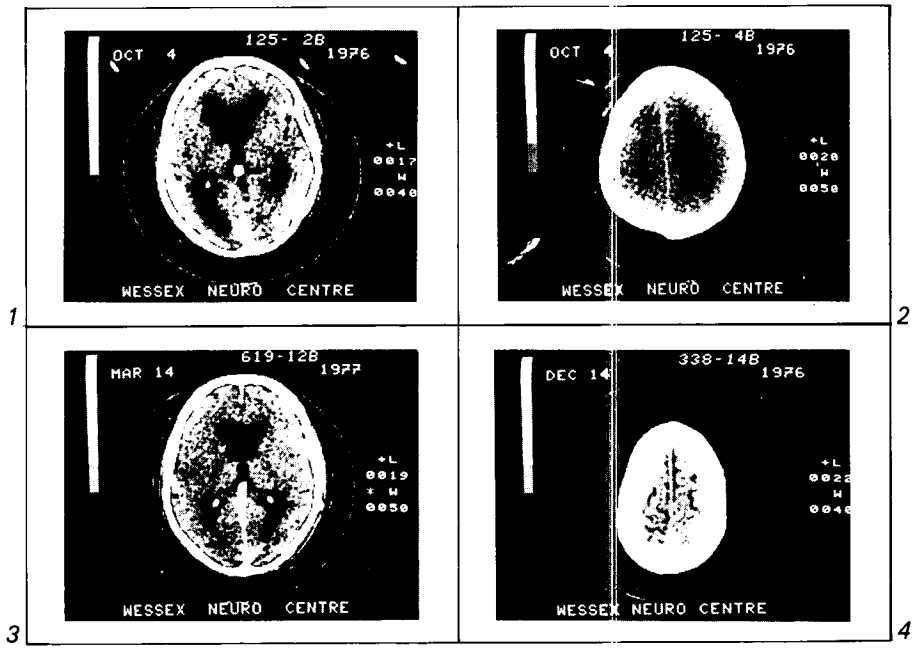

Fig. 1. Case 1. Symmetrical enlargement of lateral and third ventricles. Slight enlargement of quadrigeminal cistern.

Fig. 2. Case 1. Enlarged lateral ventricles and absence of any cortical atrophy.

Fig. 3. Case 1. Insignificant change in ventricular size.

Fig. 4. Case 2. Widening of Sylvian and interhemispheric fissures and cortical sulci.

history of any meningeal lesion such as infection, haemorrhage, trauma or previous operation. The selection of a period of 2 years' follow-up after shunting was adopted in the present study, as presenile and senile dementias should reveal themselves in that period of time and thus be excluded as a cause.

The 3 patients had normal pressure of CSF at lumbar puncture and their CSF constituents were not altered. Skull x-rays were normal, the CAT scan showed communicating hydrocephalus and pneumoencephalography [PEG] (plus positive contrast ventriculography in one) confirmed communicating hydrocephalus and excluded aqueduct stenosis, posterior fossa lesions or anomalies at the foramen magnum. All patients were treated with ventriculo-atrial Spitz Holter valves. All had a psychological assessment and psychometric tests before and after operation. The CAT scan was repeated within 6 months of shunting.

Case Reports

Case 1

A 60-year-old man had a 5-month history of gait disturbance progressing to inability to stand unaided, unconcerned incontinence of urine and faeces, and severe intellectual and memory impairment. Eventually he was unable to move himself to a sitting position in a chair. A CAT scan (fig. 1) showed gross, symmetrical hydrocephalus which included the fourth ventricle. No abnormal widening of the cortical sulci was demonstrated (fig. 2). A PEG confirmed the enlarged ventricles and showed no air over the convexities of the cerebral hemispheres.

A shunt was inserted in November 1976 and by December he had made a remarkable recovery. In March 1977 he was reviewed, when he had returned to complete normality. The CAT scan (fig. 3) showed no significant change in ventricular size. He was reported to be in normal health in January 1979.

Case 2

A 56-year-old accountant and ex-Cambridge classics scholar had a fit in 1972, at which time hypertension was discovered. In 1975 he sustained a left-sided cerebrovascular accident with 2 further fits on the same day. The right hemiplegia improved but some months later he became forgetful and then confused, developing a brief left hemiplegia. Carotid arteriography at that time suggested an expanding lesion of the right thalamus. The PEG was reported as follows:

'Air passed into the ventricular system and over the surface of the brain. The third and fourth ventricles appeared in the midline. There was well marked dilatation of the lateral ventricles, more extensive on the left. There appeared to be a mass in the right thalamic region causing an impression on the posterior end of the third ventricle, stretching the pericallosal sulcus and extending forward to impress the right temporal horn medially. The appearances suggest a right thalamic tumour.'

The EEG showed a continuous spike discharge around the right temporal lobe. The patient recovered to a large extent, only to relapse for a third time some 8 months later, in June 1976. Then ambulation became difficult, he became confused and made mistakes in the date and in simple mathematical calculations although he could still do 'The Times' crossword puzzle. He had a Parkinsonian facies, a positive pout reflex, increased tone in the lower limbs, increased tendon reflexes and equivocal plantar responses. A wheel chair was necessary because of his difficulties in ambulation. Over the next 6 months very gross deterioration occurred. He developed a left hemianopia, left facial weakness, left-sided sensory inattention, bilateral pyramidal tract signs, truncal ataxia, confusion and disorientation, nominal dysphasia, dyspraxia, memory impairment and incontinence. He became ultimately grossly demented. A CAT scan in December 1976 showed marked enlargement of the ventricular system with widening of the Sylvian and interhemispheric fissures and cortical sulci (figs. 4 and 5). The PEG confirmed ventricular dilatation but there was non-filling of the cortical subarachnoid spaces.

A shunt was inserted in January 1977 and he improved rapidly. By March of the same year he was walking unaided, had full control of bladder and bowels and was fully orientated with no dysphasia or dyspraxia. His memory was good and he was interested in his previous pursuits, although his concentration was limited. He had changed his allegiance to the 'Financial Times' crossword which he managed to complete. The CAT scan in March 1977 showed no change in ventricular size (figs. 6 and 7). 2 years later he had maintained his clinical wellbeing.

Case 3

A 69-year-old mildly hypertensive man who had a right upper lobectomy for bronchogenic carcinoma in 1967 presented in July 1976 with a history of headache, giddiness, slurred speech and mental dullness. Examination revealed bilaterial ptosis, tremor and right pyramidal weakness. A ventriculogram and later a CAT scan (fig. 8) showed dilated ventricles with a PEG confirming this, with little air being visualised over the surface of the hemispheres. He was considered to have meningeal carcinomatosis, and was treated with steroids with some improvement. However, a month later he was having difficulty in

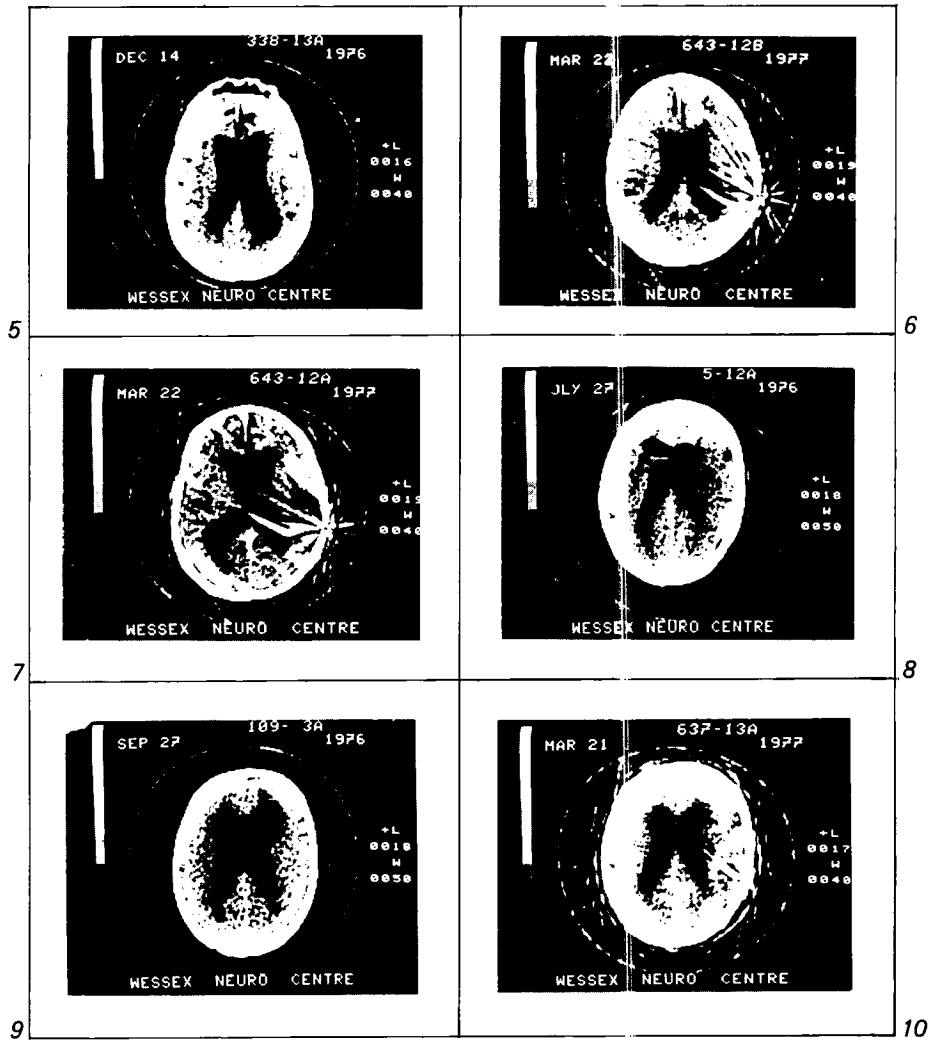

Fig. 5. Case 2. Gross dilatation of lateral ventricles.

Fig. 6. Case 2. Ventricular size unchanged after shunting.

Fig. 7. Case 2. Ventricular size unchanged after shunting.

Fig. 8. Case 3. Dilated lateral ventricles (with residual air from previous ventriculogram).

Fig. 9. Case 3. Low density area at tip of right front horn now showing.

Fig. 10. Case 3. Ventricles remain enlarged after shunting.

walking and was unable to stand without support from his wife. He became aggressive with inappropriate and disinhibited behaviour, defaecating in the garden and urinating in the bedroom. Ultimately he became disorientated in time and space, his memory deteriorated and he was dysphasic. There were bilateral pyramidal signs.

In September 1976 the CAT scan (fig. 9) showed gross symmetrical enlargement of the ventricles and a low density area at the tip of the right frontal horn, possibly a previous infarct. The PEG showed gross dilatation of the ventricular system and failure of gas to pass above the tentorium. A shunt was inserted on 1 October 1976 but for 2 weeks afterward he remained incontinent, dysphasic, disorientated and bedfast. Then in the third week he began to improve so that by March 1977 he was almost normal in every respect. There was only slight impairment of recent memory, his serial subtraction was slow and not completely accurate and his temperament was slightly more labile than previously. He was fully continent but had some urgency. He walked freely although with a mild shuffle and on a slightly wide base. He was totally independent. The CAT scan (fig. 10) in March (almost 6 months later) showed no change in ventricular size. He had maintained this clinical status 2 years later.

Discussion

Case 1 is classical and requires no comment.

Case 2 was at one stage considered to have a thalamic tumour, which explains the delay in surgical management. In retrospect, considering the varying, recurrent, partially transient neurological symptoms and signs, it seems likely he was suffering from multiple lacunar infarcts. The 'right thalamic mass' seen on PEG was probably an infarct. Earnest et al. (1974) reported on the microvascular changes of hypertension with lacunar infarcts as a cause of normal pressure hydrocephalus, and Koto et al. (1977) reported a further similar case of a patient with normal pressure hydrocephalus who improved after a shunting procedure. These lacunes were mainly in the basal ganglia, thalamus and periventricular white matter. It has been proposed that the ventricular enlargement in these cases was due to the effect of increased CSF pulse pressure on a ventricle whose tensile strength had been altered by loss of periventricular tissue. The other interesting feature of this case was the presence of cortical atrophy as revealed by the CAT scan and the failure of the PEG to demonstrate this. Jacobs and Kinkel (1976) described 7 cases in which the CAT scan showed significant cortical atrophy not demonstrated by the PEG. Moreover they found no relationship between the presence or absence of cortical atrophy and the clinical response to ventricular shunting. 6 of their 7 patients with cortical atrophy improved and in 1 the improvement was as dramatic as in the case reported here.

It is likely that the CAT scan alone may provide, with the least harm, the most information concerning ventricular size, the presence and degree of cortical atrophy and the differentiation between obstructive and communicating hydrocephalus (Jacobs et al., 1976). Possibly, although it is too early to be certain, intrathecal 'Amipaque' cisternography combined with the CAT scan (Drayer et al., 1977) may increase the degree of accuracy.

Case 3 was thought to have meningeal carcinomatosis, and so surgical treatment was deferred. The pre-existing hypertension and subsequent dysarthria, tremor,

bilateral ptosis and vertigo suggest a brain stem infarct, followed by bilateral pyramidal signs. Later still the CAT scan suggested a frontal lobe infarct and it is possible that this case too represents the syndrome of idiopathic communicating hydrocephalus associated with multiple infarcts. Hughes et al. (1978) describe 2 of their cases with proven multiple infarcts who improved with shunting.

The duration of symptoms in the 3 cases extended over a period of 5 months to 2 years. Greenberg et al. (1977) showed that there was little difference in the improvement rate between those whose duration of symptoms was less than 12 months and those whose duration of symptoms was from 12 to 60 months.

The lack of relationship between clinical amelioration and reduction of ventricular size after shunting (as well as the lack of relationship between severity of clinical manifestations and the size of the ventricles) may suggest that some other factor than ventricular size *per se* may be involved in the development of symptoms and post-shunting improvement. Indeed it is known that severe communicating hydrocephalus may occur without symptoms. This suggests that parenchymal disease of the brain may be a key factor. Cerebral blood flow is reduced in normal pressure hydrocephalus and cerebral blood flow increases after shunting (Salmon and Timperman, 1971), usually with improvement of neurological symptoms. Dysautoregulation of the cerebral blood flow has been demonstrated in ischaemic cerebrovascular disease, especially with lesions involving the deep structures within the brain (Meyer et al., 1973). These authors showed that cerebral blood flow increased as perfusion pressure to the brain was augmented when CSF pressure was lowered by a shunt. It seems almost certain that lowering of the intraventricular pressure by CSF diversion must explain the improvement in symptoms. Hardmann and Alberti (1977) found that by using CSF pressure monitoring and the intrathecal infusion test it was easier to determine which patients with communicating hydrocephalus should be treated with a shunt operation. However none of their patients was suffering from *idiopathic* communicating hydrocephalus. Moreover Borgesen et al. (1979) concluded that intraventricular pressure measurements were of little help in the selection of patients with normal pressure hydrocephalus who might be expected to improve after shunting therapy. Even Symon and Dorsh (1975) were not able to demonstrate that continuous intracranial pressure monitoring *conclusively* determined those patients with idiopathic communicating hydrocephalus who would benefit by shunting. Perhaps Fisher's (1978) simple test of removing 20 to 30ml of CSF may prove as useful as pressure monitoring as a guide to management, particularly as it may in itself be occasionally helpful as a form of treatment.

Summary

A description is given of the dramatic, sustained recovery of 3 demented and neurologically disabled patients with idiopathic communicating hydrocephalus after they underwent ventriculo-atrial shunting. In these patients there was no significant

change in ventricular size after the ventriculo-atrial shunting. 1 of the patients also had cortical atrophy. Hypertensive vasculopathy and multiple infarcts may be the explanation in 2 of the patients.

Review of the literature results in the following conclusions:

1) The CAT scan alone, perhaps combined with intrathecal 'Amipaque' cisternography, provides the maximum information with the least trauma and may assist in the selection of patients for shunting
2) Test removal of 20 to 30ml of CSF may be as satisfactory as pressure monitoring and infusion techniques in the prediction of successful shunting.

The following *do not* have a reliable predictive value:

a) The presence of cortical atrophy (shunting may sometimes be effective in mild to moderate cortical atrophy)
b) The period of onset of symptoms
c) The ventricular size before shunting and its alteration after shunting.

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Factors Likely to Affect the Development of Multiple Sclerosis in Patients Presenting with Optic Neuritis in a Tropical and Subtropical Area

*P.J. Landy, M. Innis and R. Boyle**

The clinical syndrome of optic neuritis (ON) is defined as the rapid loss of vision associated with a central, paracentral or centrocaecal scotoma, with a good prognosis for the recovery of vision.

The risk of patients with ON later developing multiple sclerosis (MS), as reported in the literature, varies widely. The fact that the findings of series reported from the United States differ from those of European studies suggests that some of the differences may have a geographical basis.

Compston et al. (1978) reviewed (after intervals of between 1 month and 23 years from onset) 146 patients who had presented with ON but without evidence of demyelination elsewhere in the nervous system, and found 40% had developed MS. They identified 3 factors which were significantly associated with the development of MS: positive typing for HLA antigen BT101; winter onset of the initial attack of ON in BT101-positive patients only, and recurrent attacks of ON. They believe recurrent attacks of ON should be given the same significance in the clinical classification of MS as episodes of demyelination occurring elsewhere in the nervous system, in a patient with a previous attack of ON. Bradley and Whitty (1968) found that cases developing MS after ON had declared themselves within 4 years. McAlpine et al. (1965) found that the longer the period of observation, the higher the percentage of cases of ON developing signs of MS. Cohen et al. (1979) prospectively studied 60

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patients with uncomplicated ON to determine the risk of subsequent MS. 21 (35%) developed probable or possible MS over a mean follow-up period of 7.1 years.

Methods

Between 1953 and 1978 one of us (P.J.L.) saw 105 cases of ON in hospital or private practice. In all cases there was no previous evidence of demyelination elsewhere in the central nervous system either from the history or on clinical examination. None of the cases had a history of heavy alcohol intake, heavy smoking or a family history of visual failure. On examination there was no evidence of retinal disease and all had blood pressures of less than 160/100mm Hg.

The cases were followed over a prolonged period to determine how many developed MS and if there were any identifiable risk factors. The following factors were studied: sex, age at onset, the interval to the development of MS, the number of

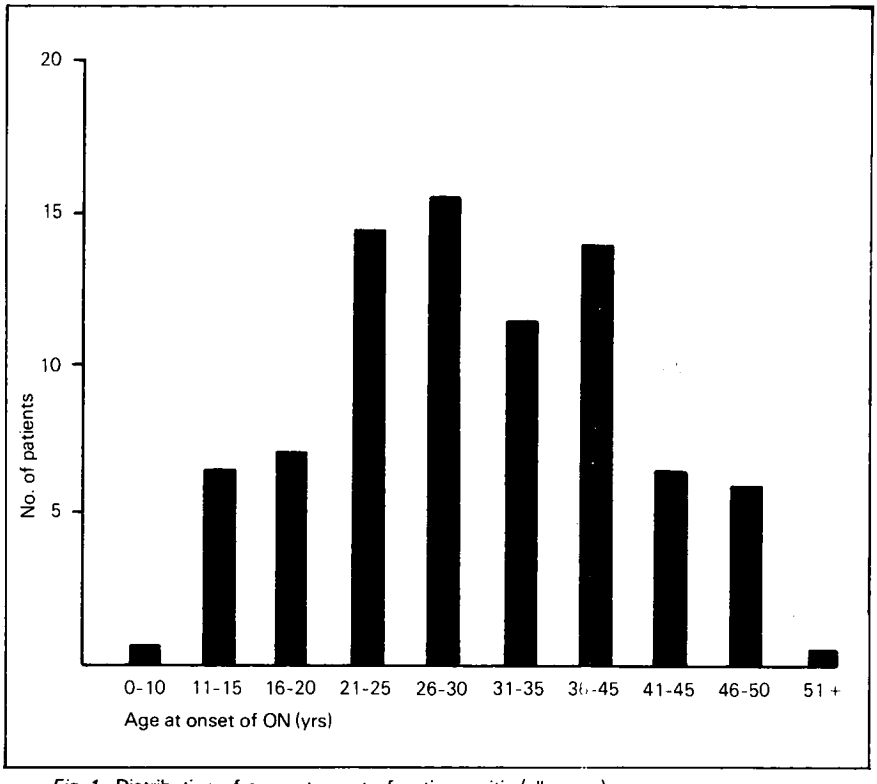

Fig. 1. Distribution of ages at onset of optic neuritis (all cases).

attacks of ON, the side affected, place of birth, place of onset and, recently, the HLA antigens.

The cases were initially reviewed in 1970 (Landy and Ohlrich), again by Boyle in 1977. In 1979 HLA antigens were determined in 49 cases.

Follow-up was by letter and interview. Where letters were returned unclaimed a search of the State electoral rolls was made to see if the patients were still residing in the State, but none were found.

Results

There were 64 females and 41 males in the series and of these 37 (63%) females and 21 (51%) males developed definite MS. The age at onset ranged from 10 to 54 years (fig. 1). The peak grouping was between 21 and 40 years. The age at onset of those developing MS is shown in figure 2. 42 of these patients (72%) were between

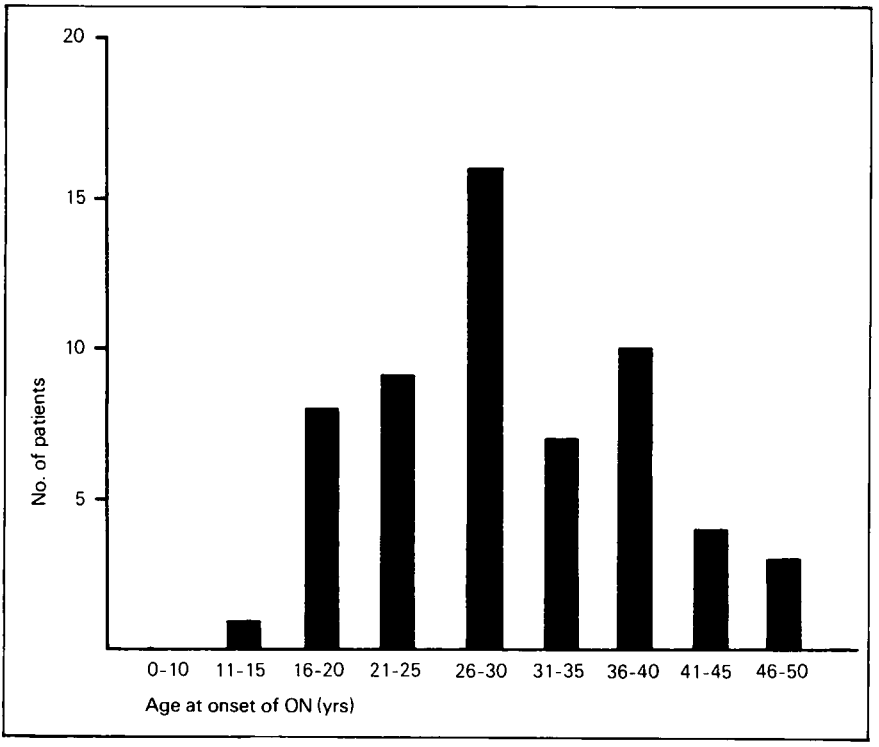

Fig. 2. Distribution of ages at onset of optic neuritis (ON) in cases developing multiple sclerosis.

Fig. 3. Distribution of intervals between occurrence of optic neuritis and development of other manifestations of multiple sclerosis.

21 and 40 years when they had their episodes of ON. The left side was affected in the initial episode in 56 and the right in 49 cases. In 13 cases both sides were affected within 24 hours. Of these, 7 cases (54%) went on to develop evidence of demyelination in areas of the nervous system other than the optic nerves. 25 cases had recurrent episodes of ON, some up to 5 attacks. Of this group 17 (68%) went on to develop evidence of demyelination in other areas of the central nervous system. Of the 8 remaining cases 7 showed no evidence of MS after 1 to 17 years' follow-up. 1 was lost to follow-up.

In all, 38 cases (36%) had recurrent ON or a simultaneous bilateral onset of ON and 24 (63%) of these developed MS, whereas 34 (50%) of cases with a single episode of ON developed MS ($\chi^2 = 1.05$, $p > 0.30$).

Interval to the Development of Multiple Sclerosis

58 (55%) patients developed disseminated lesions of MS over a 9-year period, 48 within 4 years of their episode of ON (fig. 3). Of the cases of ON who had not developed clinical evidence of MS by 1979, 16 could not be contacted by letter, telephone calls or search of the electoral rolls and were presumed to have left the State. Their follow-up had ranged from 1 to 16 years. The length of follow-up of the remaining cases is shown in table I. The place of birth of all patients is indicated in table II, and the place of onset in table III.

Table I. Length of follow-up of 26 patients with optic neuritis who did not subsequently develop clinical evidence of multiple sclerosis

Duration of follow-up (yrs)	No. of patients	Duration of follow-up (yrs)	No. of patients
1	4	12	1
2	1	14	1
4	1	15	1
6	1	16	1
7	2	17	1
8	1	18	1
9	1	22	1
10	4	24	1
11	3		

Table II. Place of birth of the 105 patients with optic neuritis

Place of birth	No. of patients
North of Tropic of Capricorn	13
Tropic of Capricorn to latitude 30°	66
Other areas of NSW below latitude 30°	6
Victoria	4
New Zealand	1
England	4
Scotland	3
Ireland	2
Holland	2
Germany	2
Finland	1
Poland	1

Table III. Place at which onset of optic neuritis occurred in the 105 patients studied

Place of onset	No. of patients
North of Tropic of Capricorn	6
Tropic of Capricorn to latitude 30°	97
Korea	1
Germany	1

Table IV. The Bw4 and Bw6 status of 49 patients with optic neuritis (ON) or with ON progressing to multiple sclerosis (MS) who underwent tissue typing

HLA pattern	Number of patients		
	ON developing MS	ON not developing MS	Total
Bw6 positive Bw4 negative	22	4	26
All other combinations of Bw6 and Bw4	6	17	23
Total	28	21	49

($\chi^2 = 14.76$; $p < 0.001$).

Tissue Typing

49 patients responded to a request to attend for tissue typing; of these, 28 had developed definite MS. 10 antigens on the first sublocus and 18 antigens on the second sublocus were investigated but only Bw4 and Bw6 were found to be significant. The Bw4 and Bw6 status of the 49 patients is given in table IV.

Discussion

60% of the patients with ON were females. Bradley and Whitty (1968) reported that two-thirds of the patients in their series were female. 63% of those developing definite MS were female in the present series. 42 cases (72%) who went on to develop MS had their onset of ON between 21 and 40 years of age. Cohen et al. (1979) also found an increased risk of MS in patients who had their onset of ON between 21 and 40 years. In the present series 48 cases developed MS within 4 years of onset of their first episode of ON. Bradley and Whitty (1968) found that in their cases MS had become evident within 4 years. Hutchinson (1976) predicted on an actuarial analysis that 78% of patients presenting with ON will have developed MS after 15 years. In the present series 58 cases (55%) of ON developed definite MS during their period of follow-up. We found that recurrent episodes and simultaneous bilateral episodes of ON did not statistically significantly increase the probability of progression to MS. The place of birth was consistent with that of the approximate population and migration distribution of the area. Place of onset was related closely to the catchment area of the hospitals involved.

Compston et al. (1978) have shown an increased risk of ON progressing to MS in subjects with the locally defined antigen BT101 (closely related to DRw2). When analysing our results it became apparent that ON in subjects without the 'antigen' Bw4 had a greater propensity to progress to MS than did those with Bw4. In the results of tissue typing, of 26 patients in whom the HLA combination Bw6 positive Bw4 negative was found, 22 (84.6%) progressed to MS, as against 35.3% of patients without this combination who progressed to MS. We conclude that although antisera recognising Bw4 and Bw6 antigens are in fact not monospecific but react to a variety of B locus antigens, nevertheless the combination of Bw6 positivity and Bw4 negativity is a practical way of deciding which subjects with ON are likely and which unlikely to progress to MS.

Conclusion

The age and sex distribution of cases of ON who progressed to MS appears to be similar to that in England and the USA. The prognosis of the condition in a tropical and subtropical area is also similar, with 55% of cases developing clinical evidence of demyelination in more than one site. The majority of cases developed evidence of MS within 4 years of onset of ON. Of those cases with recurrent episodes of ON 68% went on to develop MS. However this figure was not statistically significantly different from the figure for those with single episodes of ON. There is a group of cases who, followed up over a long period, do not develop evidence of MS. Some factor is present which protects these patients from developing MS. HLA Bw4 has been shown in this series to be a prognostic factor in indicating those cases who do not develop MS.

Because of population movements interstate and overseas, a complete follow-up of cases over a prolonged period is difficult.

Summary

The relationship between optic neuritis (ON) and multiple sclerosis (MS) in a subtropical climate is examined. 105 cases of ON were followed for varying periods over 26 years. The factors studied included place of birth, sex, age at onset, presence of recurrent ON, the interval to the onset of MS, and HLA antigen typing. 55% of cases developed evidence of definite MS. The majority of cases who went on to develop MS had their onset of ON between 21 and 40 years of age.

The subtropical climate did not cause any significant variation in incidence. However those cases who had HLA Bw4 appear to be protected from developing MS.

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Antipyrine Half-life as a Measure of Hepatic Enzyme Induction: Clinical Applications in a Chronic Epileptic Population

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Phenytoin and barbiturates have been shown to induce hepatic microsomal enzyme activity in man, resulting in diminished plasma concentration of these and other drugs (Werk et al., 1964; Hansen et al., 1971; Kutt, 1971; Petruch et al., 1974).Microsomal enzyme induction has also been emphasised in the pathogenesis of anticonvulsant-induced osteomalacia (Dent et al., 1970). Quantitation of such enzyme induction in patients with epilepsy may therefore be of value in the investigation of unexplained subtherapeutic drug levels and in identifying patients at risk for metabolic bone disease. Clearance of antipyrine, a pyrazolone compound, is dependent on the activity of similar microsomal enzyme systems to those involved in the metabolism of phenytoin, and this substance can be employed to measure the enzyme induction caused by these drugs (Brodie and Axelrod, 1950; Perrier and Gibaldi, 1974). Salivary antipyrine concentrations accurately reflect the plasma state and a test of antipyrine clearance based on estimation of antipyrine in saliva has been developed (Welch et al., 1975) which obviates the need for frequent venepuncture. We report here results of applying this assay in a population of chronic epileptic patients.

Methods

Data were obtained from 20 healthy unmedicated volunteers (14 males, 6 females, mean age 28 years). The patient group of 31 comprised 6 on phenytoin alone

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(mean duration of epilepsy 14.5 years), 14 treated with phenytoin and a barbiturate (mean duration of epilepsy 20 years), 5 patients with persistently low plasma phenytoin levels on average or high doses (mean duration of epilepsy 14 years) and 6 patients with phenytoin-induced osteomalacia proved by bone biopsy (mean duration of epilepsy 20 years).

The salivary antipyrine test was carried out as described by Harman et al. (1977). The majority of subjects were investigated as outpatients and where medication was taken, it was continued. Antipyrine (10mg/kg) was administered after an overnight fast. Saliva specimens (4ml) were collected before and at 3, 6, 9, 12, 24 and 36 hours after administration. Specimens were stored at — 14°C until antipyrine levels were measured using a gas-liquid chromatographic technique, the values obtained being transformed to a half-life ($t_{1/2}$) using a single compartmental model.

Results

Antipyrine half-life in control subjects varied from 6.5 to 16.2 hours (mean 10.7 hours SD 2.0). In the epileptic group as a whole, half-life ranged from 2.6 to 11.7 hours (mean 5.6 hours SD 2.3), a significantly shorter time than in the control group [$p < 0.05$] (fig. 1, table I). A group of 5 patients suspected of incomplete drug compliance, because of persistently low serum phenytoin levels while being prescribed usually adequate doses, was identified (table II). Antipyrine half-lives in 2 of these patients were short (2.9 and 3.2 hours), which may indicate rapid hepatic breakdown of phenytoin. Further dose increases in these 2 cases produced therapeutic blood levels. By contrast, 2 of the remaining patients, with antipyrine half-lives of 8.0 and 9.5 hours, failed to show a blood level response to dosage increments, which suggests that they may have been poor compliers (table II). The third patient, who had an antipyrine half-life of 7.9 hours, admitted to faulty compliance and has continued to have inadequate serum anticonvulsant levels.

6 patients with phenytoin-induced osteomalacia confirmed by bone biopsy were examined (table III). Antipyrine half-life ranged from 3.1 to 11.7 hours (mean 6.7 hours) and statistical analysis failed to demonstrate any difference between this subgroup and the epileptic group as a whole (table I). It is interesting to note that a patient who had an antipyrine $t_{1/2}$ of 11.7 hours belonged to this category of drug-induced osteomalacia.

6 patients on phenytoin alone were investigated (table IV). Antipyrine half-life in this group ranged from 3.0 to 7.9 hours (mean 4.9 hours). 14 patients investigated were being treated with a combination of phenytoin and another drug, usually a barbiturate (table V). In this group, antipyrine half-life ranged from 2.6 to 11.7 hours (mean 6.0 hours). Comparison of the results obtained in these 2 subgroups is shown in figure 1 and table I.

Table I. Comparison, by unidirectional analysis of variance, of the antipyrine half-lives in control and epileptic subjects

Groups compared	Probability
Control *vs* all epileptic patients	$p < 0.05$ (S)
Osteomalacia *vs* other epileptic patients	$p > 0.05$ (NS)
Phenytoin alone *vs* polytherapy	$p > 0.05$ (NS)

Table II. Antipyrine half-lives in 5 patients suspected of poor drug compliance because of persistently low plasma levels

Patient	Phenytoin dose (mg)	Duration of epilepsy (yrs)	Other treatment	Phenytoin level (μmol/L)	Antipyrine half-life (hrs)
1	500	18	Primidone	28	2.9
2	460	3	Carbamazepine	30	3.2
3	300	23	—	18	7.9
4	400	6	Primidone	25	9.5
5	500	20	Carbamazepine Valproate	24	8.0

Table III. Antipyrine half-lives in 6 patients with phenytoin-induced osteomalacia

Patient	Phenytoin dose (mg)	Duration of epilepsy (yrs)	Other treatment	Phenytoin level (μmol/L)	Antipyrine half-life (hrs)
1	230	20	Carbamazepine	40	5.3
2	200	21	Primidone	60	8.4
3	400	30	Primidone	40	5.2
4	300	19	Ethotoin Carbamazepine	34	6.8
5	400	—	Primidone Carbamazepine	76	11.7
6	300	10	—	22	3.1

In the epileptic group as a whole, no significant correlation was found, using Spearman rank correlation, between antipyrine half-life and phenytoin dose ($r_s = 0.34$ $p > 0.05$) or between half-life and plasma phenytoin levels ($r_s = 0.12$ $p > 0.05$).

Discussion

The reduction of mean salivary antipyrine half-life in the epileptic population as a whole compared to the control group indicated significant microsomal enzyme induction, confirming previous reports of such induction derived from serum antipyrine studies (Petruch et al., 1974) and D-glucaric acid kinetics (Hunter et al., 1971). The epileptic population however was homogenous with respect to antipyrine $t_{1/2}$ and there were no significant differences between the subgroups identified clinically in this study.

In particular, no statistically significant difference in antipyrine $t_{1/2}$ was seen in the osteomalacia group when compared to patients without known bone disease. Antipyrine $t_{1/2}$ was however significantly lower in the bone disease subgroup than in the controls and it is probable that enzyme induction is one factor in producing borderline vitamin D levels, although another factor, dietary or environmental, may be a prerequisite for the development of frank osteomalacia. From these results, it does

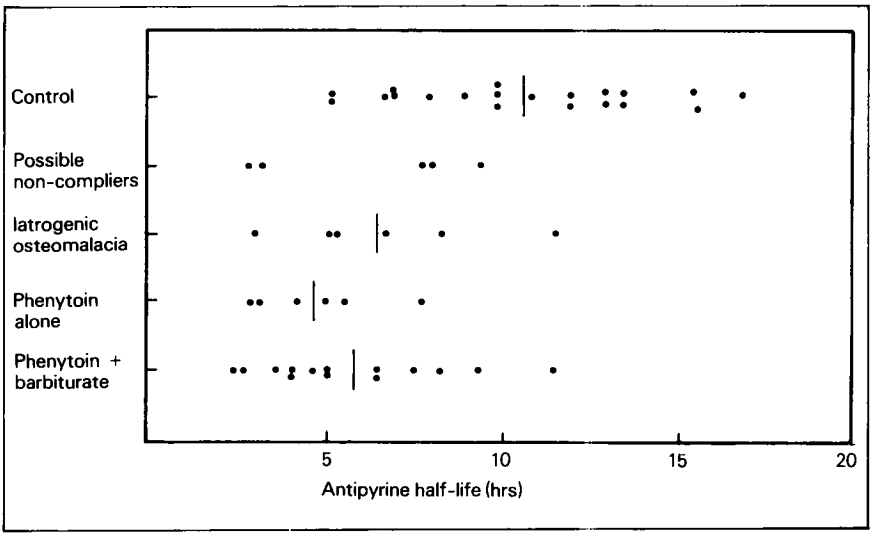

Fig. 1. Diagrammatic representation of the antipyrine half-lives in the various groups that were examined.

Table IV. Antipyrine half-lives in 6 patients on phenytoin alone

Patient	Phenytoin dose (mg)	Duration of epilepsy (yrs)	Phenytoin level (μmol/L)	Antipyrine half-life (hrs)
1	450	23	36	5.8
2	600	11	91	5.1
3	300	18	50	3.0
4	300	10	22	3.1
5	300	20	108	4.3
6	300	4	17	7.9
Mean	375	14.5	60	4.9

not seem that antipyrine clearance can be employed to aid early identification of high risk patients for bone disease.

Patients on seemingly adequate dosage yet with low serum phenytoin levels may be divided into 2 broad groups (Kutt et al., 1966). In the first, low serum levels may reflect inadequate intake, poor compliance or very rarely malabsorption from the gut. The second group comprises those patients in whom unusually rapid hepatic breakdown of administered phenytoin occurs. Differentiation between these 2 groups is of practical importance as, while increase of dosage is likely to increase blood levels in the first group (malabsorption excepted), alteration of prescribed dosage will be ineffective in poor compliers. In this study, 5 patients with persistently low phenytoin levels were investigated. These patients were suspected of poor compliance. It was possible to identify 2 cases with very short antipyrine half-lives suggesting that rapid hepatic breakdown of phenytoin was responsible for high dose requirements. Both responded to an increase in phenytoin dosage. By contrast, the remaining 3 cases had antipyrine half-lives ranging from 7.9 to 9.5 hours, which may suggest that the clinical impression of faulty compliance was correct. Antipyrine kinetics may have a limited place in assessing drug compliance in cases in which there is clinical doubt.

In some reports, phenobarbitone has been shown to lower plasma phenytoin levels (Buchanan et al., 1969) and *in vitro* studies have demonstrated increased phenytoin breakdown in isolated hepatic microsomes after pretreatment with a barbiturate (Kutt et al., 1969). In other clinical studies however the effect of barbiturates on phenytoin levels has been noted to be indefinite or variable (Kristensen et al., 1969; Kutt et al., 1969). Kutt (1971) suggested that maximum enzyme induction with phenytoin alone, or a genetically determined inability to increase microsomal enzyme activity with addition of a barbiturate, may account for this disparity. In this study, the antipyrine half-lives in patients treated with phenytoin and a barbiturate were not significantly different from those taking phenytoin alone. Mean phenytoin dosage and plasma levels were comparable in the 2 groups, confirming the apparent lack of an additional induction due to barbiturates in the group as a whole.

Table V. Antipyrine half-lives in 14 patients who were treated with a combination of phenytoin and another anticonvulsant

Patient	Phenytoin dose (mg)	Duration of epilepsy (yrs)	Other treatment	Phenytoin level (μmol/L)	Antipyrine half-life (hrs)
1	200	21	Primidone	60	8.4
2	400	30	Primidone	40	5.2
3	400	—	Primidone Carbamazepine	76	11.7
4	500	18	Primidone	14	2.9
5	400	20	Primidone	25	9.5
6	330	24	Phenobarbitone Carbamazepine	58	4.2
7	460	25	Primidone Sulthiame	41	6.7
8	330	29	Primidone Sulthiame	58	4.9
9	200	26	Primidone	74	3.8
10	400	20	Phenobarbitone	69	4.3
11	400	11	Primidone	43	7.7
12	300	25	Phenobarbitone Carbamazepine	64	5.3
13	200	6	Ethosuximide Primidone	83	2.6
14	200	18	Primidone	17	6.8
Mean	330	≃20		51	6.0

The present study suggests that there is a limited role for the measurement of antipyrine half-life in the clinical management of some epileptic patients. While this measure is not an ultimate predictor of therapeutic dosage and has not proved useful in distinguishing patients with osteomalacia from other epileptics, it has aided in the differentiation of patients with unusually rapid hepatic breakdown of administered drug from patients with inadequate compliance.

Summary

Quantitation of hepatic microsomal enzyme induction in epilepsy has a theoretical role in identifying patients at risk of metabolic bone disease, in assessing drug

compliance and in predicting anticonvulsant dose/serum level relationships. The clinical usefulness of antipyrine half-life as a measure of enzyme induction in chronic epilepsy has been explored in this study. Mean antipyrine half-life in a control group (mean 10.7 hours SD 2.0) was significantly longer than in an epileptic group (mean 5.6 hours SD 2.3). Antipyrine $t_{1/2}$ did not distinguish epileptics with osteomalacia from other epileptic patients and half-lives were similar in patients treated with phenytoin and a barbiturate to those in patients on phenytoin alone. No significant correlation was found between antipyrine half-life and phenytoin dose or between half-life and phenytoin level. In 5 patients with low serum levels of anticonvulsant, antipyrine kinetics suggested poor compliance in 3 and rapid hepatic phenytoin degradation in 2. This study suggests that measurement of antipyrine half-life may be useful in assessing drug compliance, but is not useful in predicting the onset of osteomalacia or dose/serum level relationships.

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Urticaria Pigmentosa — Change in Conscious State Associated with Rise in Plasma Histamine Levels

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Urticaria pigmentosa is an uncommon disease which was first described by Nettleship in 1869. It is characterised by excessive accumulation of mast cells in pigmented skin lesions. Systemic mastocytosis is an extension of this dermatological syndrome with abnormal mast cell accumulation in bone (Sagher and Shorr, 1956), viscera (Havard and Bodley Scott, 1959) and the entire reticuloendothelial system (Gonnella, 1967). Symptoms in systemic mastocytosis are considered to be due to excessive release of histamine and include fever, weight loss, flushing, pounding headaches, extreme thirst, bronchospasm, hypotension, diarrhoea, rhinorrhea, palpitation and dyspnoea. We describe a case of urticaria pigmentosa with systemic mastocytosis where profound depression of conscious state for 20 minutes on 2 occasions was associated with faecal and urinary incontinence. A milder form of this change in conscious state was reproduced under controlled conditions and was associated with a rise in plasma histamine levels.

Case Report

A 42-year-old tradesman had an afternoon swim in a river on 23 December 1977. Shortly afterwards he experienced an episode of diarrhoea and at 9.30 pm there was a sudden onset of severe frontal headache, nasal stuffiness and tachycardia. His wife witnessed him fall back onto his stretcher deeply unconscious and not responding to painful stimuli. While being carried to the car he became incontinent of faeces but upon arrival at the local hospital, 20 minutes later, he was beginning to regain consciousness.

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Examination at that time revealed no abnormalities; in particular his cardiovascular and neurological system were within normal limits. He was observed overnight and discharged the following morning. The next evening after a further vigorous swim in the river that afternoon he was awakened from his sleep by troublesome tachycardia and nasal stuffiness with headache. He was able to call for help before losing consciousness. Once again while being taken to the local hospital he became incontinent of urine and faeces. 20 minutes from the onset he was rousable and orientated. He was admitted to the Austin Hospital, Melbourne, on 14 February 1978 for further investigation.

From the age of 9 years he had suffered from a skin condition, diagnosed as urticaria pigmentosa by a dermatologist, which had been steadily progressing. He suffered from no other allergic phenomena and had no other relevant personal or family history; in particular he had no history of migraine.

Examination revealed an intelligent, slightly anxious man with no abnormal neurological signs. His blood pressure was 140/80mm Hg lying and standing. There was no clinical evidence of systemic mastocytosis in terms of hepatosplenomegaly, lymphadenopathy, bony tenderness, anaemia or jaundice. A rash of a pigmented maculopapular type with dense truncal concentration of lesions, diminishing peripherally, was seen. The face was not involved. Mild dermatographia was present.

Investigations

The haemoglobin was 16.3g/litre and the white cell count was 4,900/mm^3 with no mast cells seen and no excess of basophils. The sedimentation rate was 2mm in the first hour and the glucose tolerance test was normal. Liver function tests, serum alkaline phosphatase, liver-spleen scan and bone scan were all within normal limits. A skeletal survey showed areas of increased radiological density in the right humerus, right femur and left femur, consistent with mast cell infiltration. A skin biopsy showed infiltration with mast cells consistent with urticaria pigmentosa. Bone trephine biopsy also showed infiltration with mast cells consistent with urticaria pigmentosa or systemic mastocytosis. The CSF protein was 0.6g/litre (globulin normal) and the CSF contained 1 red cell only. Both cerebral CAT scan and EEG were normal.

Experimental Studies

The patient was admitted to the intensive care unit where cardiac, temperature, blood pressure and respiratory monitoring was undertaken. A blood sample (5ml) was taken from the antecubal vein for establishing the basal plasma histamine level. The subject's right hand was immersed in ice-water for a period of 2 minutes and then a blood sample was immediately obtained. Further blood samples were obtained at intervals after withdrawal of the hand. No change in conscious state of the patient occurred during this time although there was a moderate erythematous change in the immersed region of the hand.

The patient then exercised strenuously by repeated squatting for a period of 5 minutes. After 2 minutes, the patient became extremely unwell and found difficulty in performing the exercise. He became very flushed and perspired excessively. His conscious state then became depressed but at all times he obeyed verbal commands, though with difficulty. There was no faecal or urinary incontinence. After a period of 20 minutes the patient had recovered from his state of semi-coma. The symptoms he described were headache and extreme thirst.

Blood samples (5ml) were taken at intervals throughout this period and placed on ice in heparin tubes. Blood samples were centrifuged at 2,500g for 15 minutes at 4°C immediately at the conclusion of the experiment. Plasma was removed and frozen at — 20°C overnight. Plasma histamine levels were then measured using 0.1ml aliquots of plasma by the radioenzymatic assay of Kobayashi and Maudsley (1972).

An age- and sex-matched control was then subjected to the same procedure and his plasma histamine levels were measured by the same method.

Results

The resting plasma histamine level in both the patient and the control was approximately 1.8ng/ml. After immersion of the hand of each subject in ice-cold water there were no pronounced changes in plasma histamine levels for as long as 15 to 20 minutes after removal of the hand from ice-water (fig. 1a). However, following exercise, there was a dramatic rise in the patient's plasma histamine concentration to 4.3ng/ml by 7 minutes after exercise. This elevated plasma concentration was maintained for at least 13 minutes (fig. 1b). This represented the period of depressed conscious state, mild headache, flushing and extreme thirst. Blood pressure during this period did not alter significantly (140/80mm Hg) but pulse rate increased from 60 to 100 beats per minute. No significant change in plasma histamine concentrations was seen in the control subject over the same time interval (fig. 1b).

Discussion

The neurological complications of urticaria pigmentosa are rare and their description is singularly lacking in reviews of the subject (Caplan, 1962). The condition has not previously been discussed in the neurological literature. Direct mast cell infiltration of the central nervous system was thought to be the mechanism of production of pyramidal signs and perhaps, by an indirect effect (such as is seen in malignant disease), of the neuromyopathic signs in a recently reported case (Hancock et al. 1976). The indirect effects of histamine release from mast cells are responsible for the symptoms of headache by virtue of its effect on vascular smooth muscle (Demis,

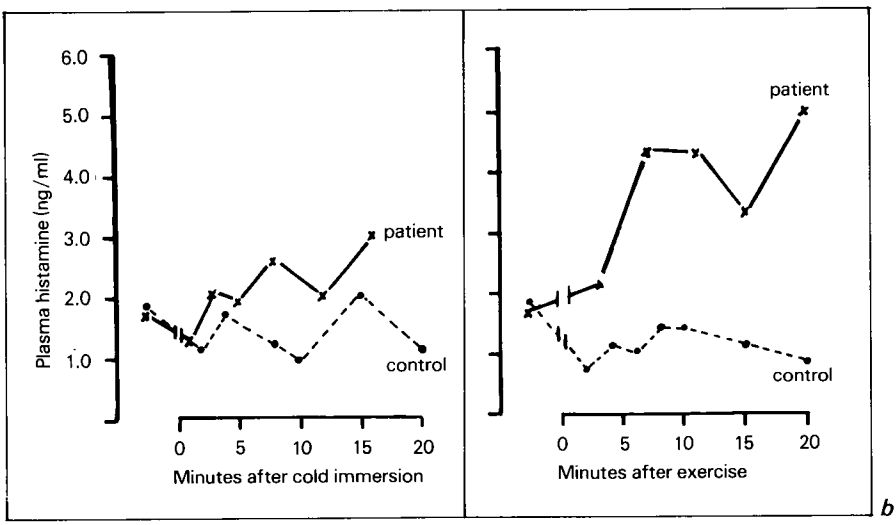

Fig. 1. a) Plasma histamine levels of the patient and an age- and sex-matched control after cold immersion of an upper limb. b) Changes in plasma histamine levels after strenuous exercise in both subjects.

1963). A similar vascular effect may result in hypotension, syncope and even convulsions (Havard and Bodley Scott, 1959).

Symptoms of histamine release in systemic mastocytosis have been correlated with histamine appearance in the urine (Demis, 1963). Rises in plasma levels of histamine after exercise, cold immersion, and arm vibration in other allergic conditions such as cold urticaria (Kaplan et al., 1975) and hereditary vibratory angioedema (Metzger et al., 1976), with demonstrated hypotension, have been more recently reported. A change in conscious state in cases of systemic mastocytosis associated with a rise in plasma histamine level has not previously been documented. Various stimuli such as cold, trauma, infection and alcohol have long been recognised as precursors of symptoms of histamine release in systemic mastocytosis (Szweda et al., 1962). Since our subject had exercised by swimming in the cold river prior to his episodes of loss of consciousness, the combination of hand immersion in ice and strenuous exercise as stimuli was employed in our experiment.

The role of histamine in producing states of prolonged coma with loss of reflex control in our subject was substantiated by reproduction of similar, but milder, symptoms under controlled conditions. This was parallelled by a rise in plasma histamine levels, whereas an age- and sex-matched control showed no such rise. The production of headache, palpitation, facial flushing and extreme thirst are characteristic of histamine release from mast cells (Demis, 1963). The rise in plasma histamine demonstrated in our subject was associated with some depression of conscious state, while blood pressure was seen to drop only slightly. This may reflect a primary central nervous system effect of histamine on conscious state rather than one mediated via decreased cerebral perfusion associated with extreme hypotension.

This case draws attention to the role of histamine as a mediator in the change in conscious state in patients suffering from urticaria pigmentosa with systemic mastocytosis. Prophylactic treatment of these patients with antihistamines has been found useful (Caplan, 1965) and symptoms of diarrhoea have been improved by the use of oral disodium cromoglycate (Dolovich et al., 1974), which suggests that this substance may also be beneficial in ameliorating other symptoms of histamine release.

Summary

The case is described of a 42-year-old man with urticaria pigmentosa and documented systemic mastocytosis who had 2 episodes of loss of consciousness, headache, nasal stuffiness and faecal incontinence, following a swim in a river. Under controlled conditions the patient was subjected to immersion of the right hand in ice-water for a period of 2 minutes, followed by 2 minutes of strenuous exercise. Similar symptoms involving change in conscious state were evoked with accompanying rises in plasma histamine levels. These findings suggest that histamine is at least one of the

major mediators of the change in conscious state that is reported rarely in these patients and draws attention to the neurological facets of this rare disorder.

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Oscillations in Performance in Levodopa-treated Parkinsonians: Treatment with Bromocriptine and L-Deprenyl

*C.M. Lander, A. Lees and G. Stern**

Levodopa is the most effective available treatment for patients with idiopathic Parkinson's disease. It improves the quality of life and prolongs life expectancy in the majority of sufferers but after a static period of about 2 years deterioration occurs and disabling fluctuations in performance, not seen before the advent of levodopa, become increasingly apparent.

Two major patterns of bradykinetic oscillation are seen in levodopa-treated patients. End-of-dose deterioration (the wearing-off effect) is the commonest disturbance, occurring in at least 50% of patients after 6 years of levodopa treatment. It is characterised by a progressive reduction in the duration of benefit derived from each dose of levodopa and is relatively predictable. In contrast, the rarer 'on-off' phenomenon is unpredictable and includes periods of akinesia with hypotonia and rapid oscillating cycles of relative mobility and bradykinetic incapacity over several minutes (the yo-yo effect) [table I]. Levodopa-induced abnormal involuntary movements are independent clinical variants and may be subdivided into those occuring at peak plasma dopa levels, those occurring at the onset and at the end of the interdose period (biphasic dyskinesias) and early morning dystonia (Lees et al., 1977a). Freezing episodes also cause increasing disability resulting in falls and postural instability.

Two recently introduced drugs have been reported to be of value in such patients. Bromocriptine, a dopaminergic agonist with pre- and postsynaptic effects, is an effective anti-Parkinsonian drug comparable in potency to levodopa (Calne et al., 1974;

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Table I. Incidence of Parkinsonian oscillations in 91 patients after 6 years of continuous treatment with high dose levodopa (adapted from Lees, 1978)

Akinetic disabilities	Patients affected (%)	Dyskinetic disabilities	Patients affected (%)
End-of-dose deterioration (including early morning akinesia, nocturnal akinesia)	50	Abnormal involuntary movements a) peak dose b) biphasic	 80 10
On-off effect (rapid oscillations, yo-yo effect, hypotonic freezing)	15	Early morning dystonia	10
Freezing phenomena	63		

Lees et al., 1978). Because the plasma half-life of bromocriptine is 3 to 4 times that of levodopa it has been suggested that bromocriptine might be helpful in smoothing out the fluctuations in patients who are disabled by severe oscillations. Several trials have described improvement of 'on-off' effects by partial substitution of bromocriptine for levodopa (Kartzinel and Calne, 1976; Parkes et al., 1976). Bateman et al. (1978) also, have recently reported that the addition of low dose bromocriptine to levodopa therapy is of some use in the 'on-off' syndrome.

L-Deprenyl is a selective Type B monoamine oxidase inhibitor without 'cheese effect' (Stern et al., 1978) which probably acts primarily on the intact nigrostriatal neurones and may increase intraneuronal storage of dopamine (Knoll, 1978). When given in addition to levodopa, L-deprenyl has been reported to benefit akinesia and certain Parkinsonian oscillations (Birkmayer et al., 1977; Lees et al., 1977b).

We report here experience with these two drugs in Parkinsonian patients with oscillations in performance, studied at University College Hospital, London.

Patients and Methods

Patients with idiopathic Parkinson's disease and disabled by marked fluctuations in performance were selected because they were known to be observant individuals capable of completing self-scoring diaries in their homes. All were taking optimum doses of levodopa, alone or with a decarboxylase inhibitor. The dose and interdose interval of levodopa had been adjusted to give the smoothest possible daily response. If oscillations remained disabling, after informed consent the patient was included in the trial. Patients were initially observed in hospital for a day to assess the degree of disability and the type, severity and frequency of oscillations. Separate akinesia and dyskinesia scores were recorded hourly on a 7-point scale, and the patients were in-

Table II. Clinical features of 74 Parkinsonian patients taking levodopa who were treated with either bromocriptine or L-deprenyl

Added drug	No. of pts	Sex	Mean age (yrs)	Mean duration of disease (yrs)	Mean stage (Yahr classification)
Bromocriptine	14	9M 5F	60	10	3
L-Deprenyl	60	33M 27F	59	11	3.5

structed in the use of a self-scoring diary. A baseline outpatient assessment was then made using patients' diaries with hourly observations. Details of the 74 patients studied are shown in table II.

1. Bromocriptine Study

14 patients were first given 2.5mg bromocriptine a day and the dose was gradually increased while reducing the dose of levodopa (with carbidopa). A substitution of 10mg bromocriptine for 100mg levodopa plus carbidopa was first attempted and this ratio was adjusted by trial and error to find the best possible combination for each patient.

Self-scoring diary assessments were completed by the patient at home for at least 1 week when the best possible drug regimen had been achieved and then 2 consecutive day assessments were performed in hospital. In a double-blind study active bromocriptine for the equivalent levodopa-carbidopa dose (contained within otherwise empty bromocriptine capsules) was given for each day. Throughout both day assessments the patient and the assessor completed hourly diaries. At the end of the 2-day hospital assessment both patient and assessor expressed an opinion as to the day on which the patient had benefited most.

After a variable interval during the next month, the patient was given 'placebo' bromocriptine (i.e. capsules containing the equivalent levodopa-carbidopa dose) for 2 weeks, in a single-blind study.

2. L-Deprenyl Study

After assessment, patients with disabling fluctuations of performance were given L-deprenyl 5mg twice daily in addition to levodopa (with or without a dopa decarb-

Table III. The effects of partial bromocriptine substitution for levodopa on Parkinsonian oscillations in 14 patients

Akinetic disabilities	No. of pts	No. of pts improved	Dyskinetic disabilities	No. of pts	No. of pts improved
End-of-dose effect	9	0	Abnormal involuntary movements	14	0
On-off effect	5	0	Early morning dystonia	6	4
Freezing phenomena	8	0			

oxylase inhibitor). They were seen at 2-weekly intervals. After 4 weeks' treatment the patients was re-assessed for 1 day in hospital with self-scoring diaries. At varying intervals in the next month, placebo was substituted at a time unknown to the patients or assessor and continued for 4 weeks before active treatment was recommenced. A further day assessment in hospital was then performed as outlined above.

At the end of the trials mean disability scores were calculated for the baseline, active therapy and placebo phases during hospital and outpatient observations.

Results

1. Bromocriptine Study

18 patients began bromocriptine, but 4 could not continue either because of side effects (2) or because of increased disability when the initial substitution was made (2). In the remaining 14 patients a mean dose of 40mg daily of bromocriptine was substituted for a mean dose reduction of 300mg of levodopa with carbidopa. Table III shows the number of patients with each type of oscillation and the response to bromocriptine substitution. These results were calculated by means of the physician's assessment during the hospital admission days and also from self-scoring diaries. 4 of the 6 patients with early morning dystonia benefited to some degree with bromocriptine, but there was no convincing improvement in any of the other types of oscillation.

1 patient developed an increase in tremor when active bromocriptine was replaced by 'placebo' bromocriptine during the 2-week single-blind study; another patient noted increased akinesia during the same phase. In both patients the problems were overcome by increasing the dose of levodopa.

Table IV. The effects of L-deprenyl on Parkinsonian oscillations in 60 patients taking levodopa

Akinetic disabilities	No. of pts	No. of pts improved	Dyskinetic disabilities	No. of pts	No. of pts improved
End-of-dose effect	39	19	Abnormal involuntary movements	59	0
On-off effects	10	1	Early morning dystonia	10	0
Freezing phenomena	22	0			

2. L-Deprenyl Study

60 patients have been studied during the last 2 years. Table IV shows the responses in those treated with the addition of L-deprenyl to optimum doses of levodopa. 19 of 39 patients (48 %) with end-of-dose deterioration showed definite and sustained improvement with this treatment. A levodopa 'sparing' effect (mean dose reduction of 200mg per day levodopa) was also observed. Abnormal involuntary movements were frequently exacerbated by the addition of L-deprenyl, but could usually be reduced when the dose of levodopa was lowered.

Discussion

Assessment of Parkinsonian patients with oscillations in performance is difficult. Swings can be so rapid and so variable that a single conventional examination frequently bears little relationship to overall functional capacity. Furthermore the frequency of short term memory impairment, defects of concentration and perseverative errors in Parkinsonians frequently prevents them from providing an accurate account of their fluctuations. Despite obvious limitations, 7-point self-scoring diaries completed each hour of the waking day are a useful system, even allowing that the selected patients need to be observant and without substantial cognitive impairment.

The use of an inpatient day assessment allows the assessor to check the patient's accuracy in the self-scoring method, but may underestimate disability since the patient is often more relaxed and secure while in hospital. Therefore the more realistic score, when possible, is obtained when the patient is undertaking his usual daily routine at home or at work.

In this study the results of partial substitution of bromocriptine for levodopa preparations were disappointing. The process of substituting bromocriptine is lengthy, time-consuming and requires frequent attendances. Our results indicate that there is no clearly defined place for partial bromocriptine therapy in the management of the

more common Parkinsonian oscillations, namely, end-of-dose deterioration, peak dose abnormal involuntary movements and the on-off phenomenon. However small doses (e.g. 5-10mg) of bromocriptine at night help some patients with early morning dystonia. On discontinuing bromocriptine 2 patients deteriorated to a degree of disability greater than that before bromocriptine was given and both of these made a gradual improvement to baseline levels over the ensuing 2 weeks. This observation has been made previously by Bateman et al. (1978). It is suggested that this is the result of alteration in receptor sensitivity in the basal ganglia after bromocriptine therapy.

The use of L-deprenyl was more encouraging. Almost 50% of those patients who suffered end-of-dose deterioration gained worthwhile improvement, but those with other patterns of oscillation were rarely helped. L-Deprenyl frequently aggravated levodopa-induced involuntary movements and did not help early morning dystonia.

The patients in this study had all been treated with high dose levodopa for at least 5 years. There is some evidence to suggest however that the use of submaximum doses of levodopa from the outset of therapy may help in reducing the incidence of Parkinsonian oscillations (Birkmayer, 1976). Furthermore, Shaw et al. (1978) have noted the absence of 'on-off' effects in 18 previously untreated patients who had taken bromocriptine alone for more than 1 year, and 8 treated for more than 3 years. Such means of 'prevention' of Parkinsonian oscillations offer more encouragement in the management of this difficult problem than do attempts to suppress established complications.

Summary

Fluctuations in performance in levodopa-treated Parkinsonians pose frequent and difficult problems of management. Controlled trials with two recently introduced drugs, bromocriptine and L-deprenyl, have been performed in an attempt to clarify their use in Parkinsonian oscillations. Bromocriptine, partially substituted for levodopa, was helpful in 4 of 6 patients with early morning dystonia, but did not benefit 9 patients with end-of-dose deterioration and 5 patients with 'on-off' changes. L-Deprenyl 10mg daily gave substantial benefit to 19 of 39 patients with end-of-dose deterioration, but to only 1 of 10 patients with 'on-off' phenomena. Neither L-deprenyl nor bromocriptine helped patients disabled by freezing episodes or levodopa-induced involuntary movements.

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Ischaemic Optic Neuropathy

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Ischaemic optic neuropathy refers to sudden painless visual loss in one or both eyes, which in the acute phase is associated with a pale swollen disc, often with peripapillary haemorrhages, and arcuate scotomata or altitudinal hemianopia. In the late stages the field changes remain and the optic disc is atrophic. Although cranial arteritis is an important and treatable cause, the majority of patients do not have clinical or laboratory evidence of arteritis.

Recent work by McLeod et al. (1977; 1978) has shown that experimental occlusion of the posterior ciliary artery supply to the optic nerve head causes infarction of the immediate retro-laminar myelinated optic nerve. The consequent complete obstruction of rapid orthograde axoplasmic transport at the lamina cribrosa is thought to be the fundamental cause of opaque prelaminar swelling that characterises acute ischaemic optic neuropathy. The disc swelling is equivalent to a 'cotton wool spot' of the optic nerve head and is due to an accumulation of axoplasmic debris adjacent to the infarction.

The typical field defects, long known as arcuate or Bjerrum scotomata, are due to a loss of retinal nerve fibres following infarction of fibre bundles as they pass through the optic nerve head. Originally arcuate defects were believed to be synonymous with glaucoma, but Harrington (1959) showed that transient scotomata could be produced in glaucomatous patients by lowering systemic blood pressure, thus indicating the vascular basis of such defects.

Hayreh (1970) showed that centripetal vessels in the anterior optic nerve and disc are radial and have a segmental area of supply arising from the posterior ciliary

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arteries. Thus the nerve fibre bundles are involved in a sectoral fashion with posterior ciliary artery occlusion.

Apart from cranial arteritis, the major causes of posterior ciliary artery occlusion and therefore ischaemic optic neuropathy are arteriosclerotic disease (Francois et al., 1968), diabetes, hypertension (Miller and Smith, 1966; Cullen, 1967; Sanders, 1971; Boghen and Glaser, 1975; Ellenberger et al., 1973), migraine (McDonald and Sanders, 1971), syphilis (Sanders, 1971) and polyarteritis (King, 1935; Kimbrell and Wheliss, 1967). Pathological studies showing the infarction of the optic nerve within and behind the lamina cribrosa in both cranial arteritis (Henkind et al., 1970) and in non-arteritic cases (Knox and Duke, 1971) have been limited.

Methods

Over a 3.5-year period, 22 patients have been seen in whom a diagnosis of ischaemic optic neuropathy has been made. In all patients the presence of glaucoma was excluded by tonometry, often on numerous occasions. In the patients with the classical presentation of sudden painless visual loss with a pale swollen disc and altitudinal field defects, investigations were directed at identifying an underlying cause. In some patients in whom acute demyelinating optic neuritis was considered, a search for other evidence of demyelination was made. Differentiation between ischaemic optic neuropathy and demyelinating optic neuritis is sometimes an insoluble problem. Both may show swelling of the disc, dilitation of papillary vessels and leakage of the dye on fluorescein angiography. The absence of pain and early pallor of the disc favour ischaemia. A central scotoma suggests optic neuritis whereas an altitudinal hemianopia suggests an ischaemic optic neuropathy. The patient with demyelinating optic neuritis usually makes a good recovery in terms of visual acuity, although this may happen with an ischaemic lesion. In this study patients in whom there was diagnostic doubt were excluded.

In patients where the visual loss had occurred acutely in the past and disc oedema was not observed, a strenuous effort to exclude optic nerve compression was made. In most of these cases a lengthy period had elapsed without evidence of progression. However, it is realised that a lesion of the optic nerve as far back as the chiasm may present as a pale disc and arcuate scotoma. Hoyt (1962) and Harrington (1964) have reported meningiomas of the posterior end of the optic canal and dorsum sella and pituitary adenomas presenting with arcuate scotomata and optic atrophy.

Investigations in all patients included medical, neurological and ophthalmological examination, fundal photography, Bjerrum perimetry and, in some instances, fluorescein angiography. Routine full blood examination, ESR, blood viscosity, fasting blood sugar, cholesterol and triglycerides, VDRL, ECG, lumbar puncture, skull, optic canal and chest x-rays were performed and, in some patients, visual evoked responses, computerised axial tomography (CAT) of the brain and orbits and superficial temporal artery biopsy were also undertaken.

Results

There were 22 patients, 11 males and 11 females with 32 affected eyes. They fell into 5 subgroups:

1) Cranial arteritis (1 case)
2) Vascular disease (8 cases)
3) Trauma (2 cases)
4) Migraine (4 cases)
5) Idiopathic (7 cases)

Cranial Arteritis

Only 1 patient fell clearly into this group.

Case 1

An 83-year-old lady presented with a 3-week history of sudden loss of vision in the right eye. She had vague shoulder pain for 4 months but no scalp or temple discomfort. The VAR was 6/60 and VAL 6/18 with visual fields showing an altitudinal hemianopia in the right eye and multiple arcuate defects in the left eye (fig. 1). Her fundi both revealed pale swollen discs with peripapillary haemorrhages (fig. 2). The ESR was 38 and 55mm/hour on two occasions and a superficial temporal artery biopsy confirmed the diagnosis.

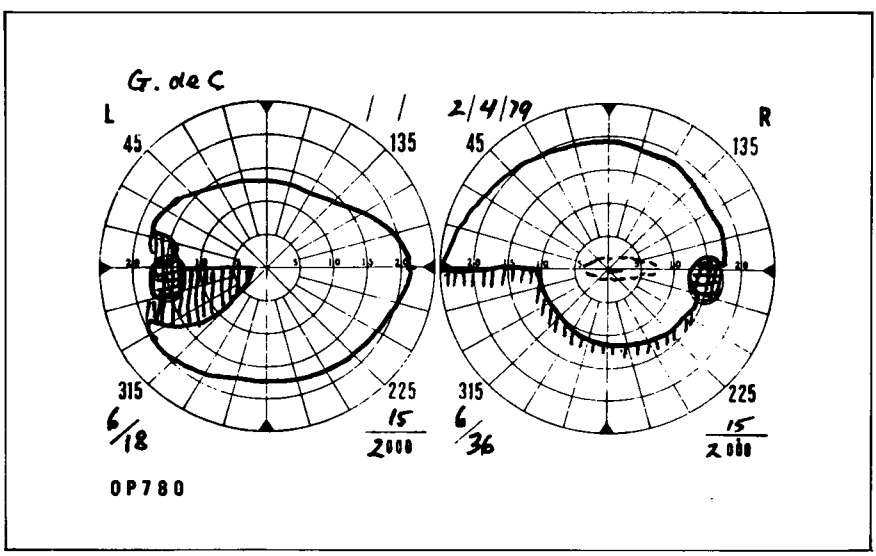

Fig. 1. Case 1. Visual fields (using Bjerrum screen with 15mm target at 2 metres) with ischaemic optic neuropathy secondary to cranial arteritis.

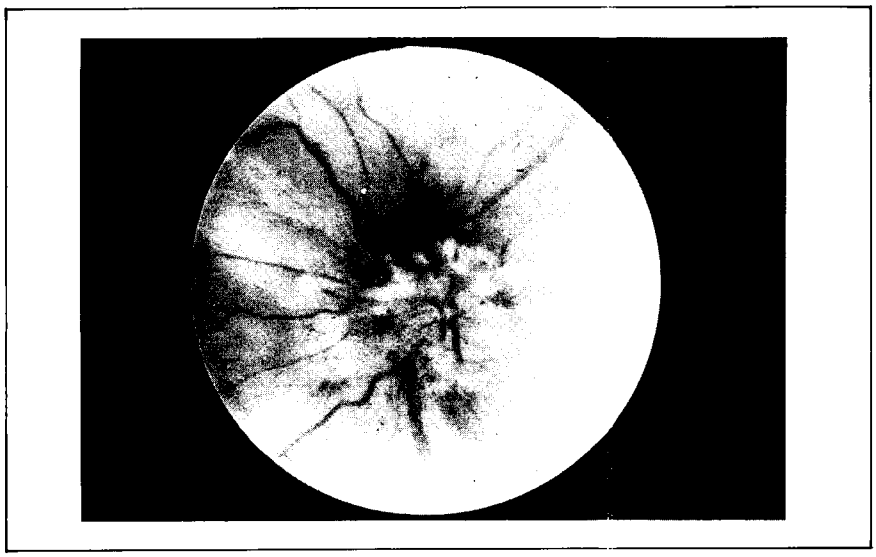

Fig. 2. Case 1. Fundal photograph showing ischaemic papillopathy. The right optic disc is pale and swollen with peripapillary haemorrhages.

Vascular Disease

There were 8 patients with objective evidence of vascular disease; 5 had hypertension, 1 had a previous myocardial infarction, and 2 had intracranial aneurysms with demonstrated cerebrovascular disease on angiography. This result almost certainly underestimates the importance of vascular disease, especially in the older patients, who were not included unless they had overt features of arterial disease.

Case 2

A 42-year-old hypertensive woman awoke one morning with painless blurred vision in the left eye. She was unaware of any abnormality in the right eye. Her VAR was 6/5 and VAL 6/18. The visual fields (fig. 3.) showed an extensive lower field loss in the left eye with a large nerve fibre bundle defect in the lower half of the right eye. The left disc was pale and swollen in its upper half and the right disc was only slightly pale. Routine investigations were all normal and she was considered to have essential hypertension.

The other 4 patients with hypertension were older, aged 55, 62, 65 and 72 years, respectively. One had an associated empty sella syndrome. The 50-year-old man with a past history of myocardial infarction had a family history of diabetes and had presented for investigation of cough headaches and unilateral visual impairment. 2 elderly patients with known intracranial aneurysms, 1 of whom also had hypertension, had extensive extracranial vascular disease shown angiographically. It was considered that their visual impairment was not directly related to the aneurysms.

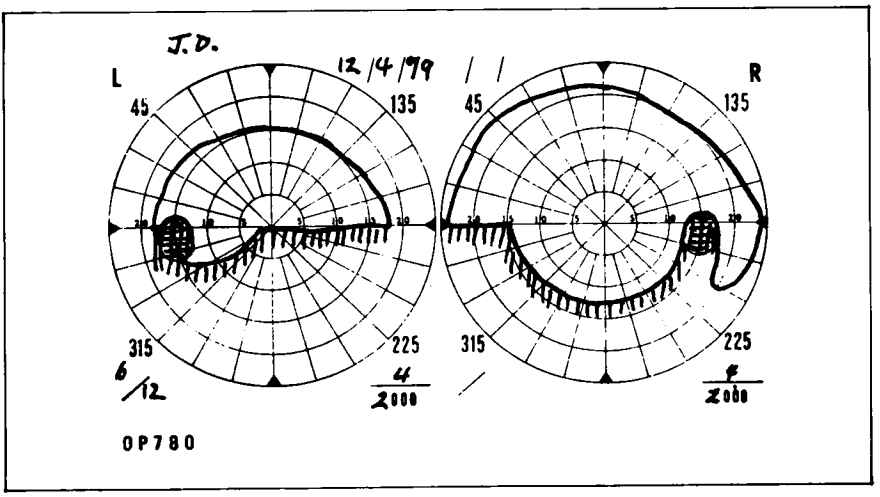

Fig. 3. Case 2. Visual fields using the Bjerrum screen with a 4mm white target at 2 metres. They show an altitudinal hemianopia in the symptomatic left eye and a large arcuate scotoma in the lower field of the right eye.

Trauma

There were 2 cases in whom trauma was considered to have played a role in the production of an ischaemic optic nerve lesion.

Case 3

A 55-year-old man was struck in the right eye by an overhanging branch and thereafter noticed poor vision in the eye. 10 years before the incident he had suffered an injury to the left eye and was aware of a small loss of vision in that eye. Examination after the second injury showed VAR 6/60 and VAL 6/6, and in the right eye he had nerve fibre bundle defects involving fixation. The left visual field showed multiple arcuate defects with extensive field loss (fig. 4). The right fundus, 4 weeks after the accident, showed a macular star, which became more obvious at 7 weeks (fig. 5) and then regressed to leave a pale atrophic disc.

The macular star is believed to be due to degenerating axons and the pattern of retinal involvement corresponded with the field defect in the right eye. The role of trauma has medico-legal overtones and is controversial, but in this patient the complaint of visual loss was made immediately after the accident and the subsequent development of the macular star supported a temporal relationship.

The other patient in whom trauma apparently precipitated an ischaemic optic nerve lesion noticed the unilateral visual loss immediately after a head injury sustained in a motor car accident.

Migraine

4 patients suffered from moderately severe migraine and in 2 instances the permanent visual loss occurred during an attack.

Case 4

A 20-year-old female clerk, not taking the oral contraceptive, gave a 2-year history of attacks of bifrontal and retro-orbital headache, with nausea, lasting up to 48 hours. There had been no visual disturbance associated with the attacks until 3 weeks before presentation, when she awoke with blurred vision in the left eye after 2 days of typical headache. Her visual acuity was 6/5 in both eyes but she had a superior arcuate defect in the left visual field (fig. 6) and a pale swollen segment of the left disc and peripapillary region in the 5 o'clock position. Her routine investigations were all normal and in particular there was no evidence of arteritis.

Case 5

A 58-year-old business executive with intractable migraine complained of permanent visual loss in the right eye during an attack of migraine. Over the preceding 12 months he had had 3 episodes of transient blindness in the right eye during severe migraine. Examination showed a VAR of 6/18 and VAL of 6/6. The right visual field had multiple arcuate defects and the right fundus showed a pale atrophic disc. Carotid angiography revealed only ectatic atheromatous vessels.

In 2 other cases, migraine was a prominent illness in patients with stable unilateral ischaemic optic nerve lesions of 8 and 11 years duration respectively.

Idiopathic

7 remaining patients did not fall into any of the groups above. However, one may presume that some of the patients probably had vascular disease. 4 patients were aged between 60 and 69 years, 2 in the 50 to 59 year age group and 1 patient was 40

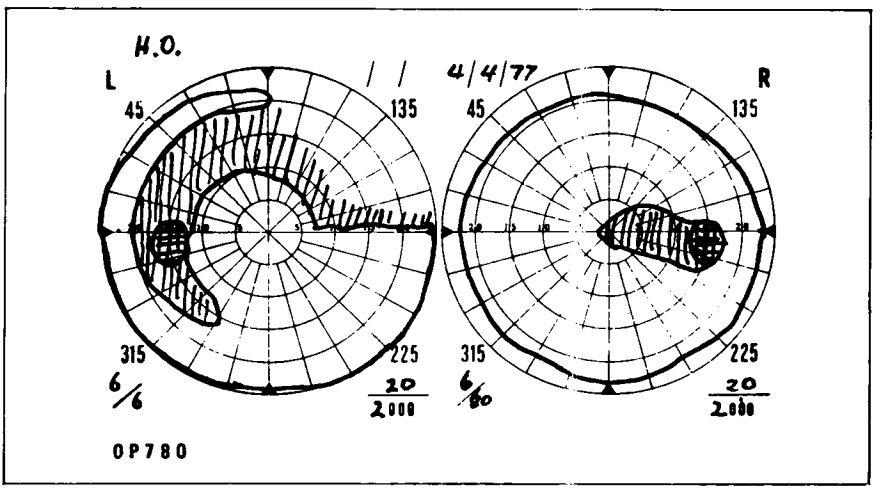

Fig. 4. Case 3. Visual fields using a Bjerrum screen with 20 mm white target at 2 metres. The symptomatic right eye has a field loss involving papillo-macular fibres and the left visual field shows multiple arcuate defects.

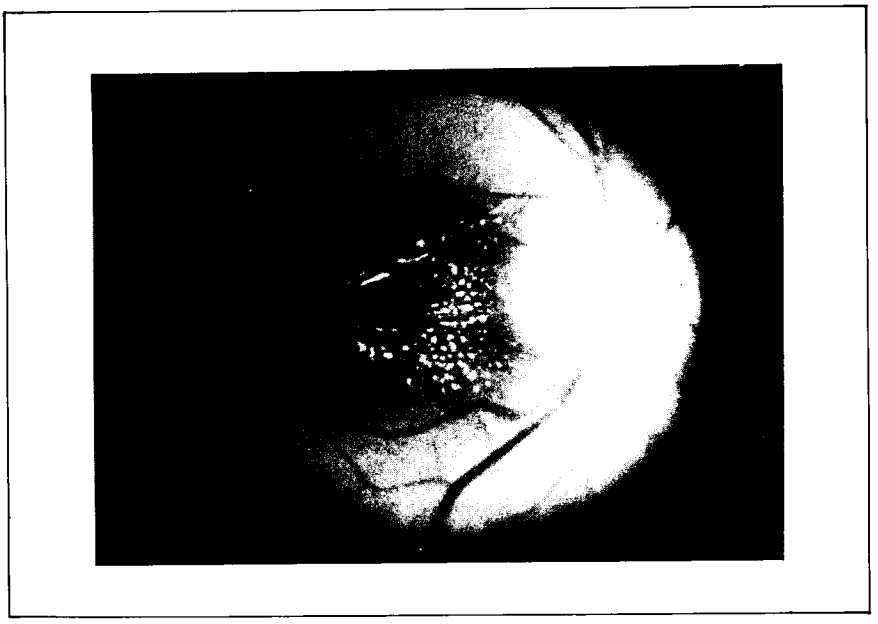

Fig. 5. Case 3. Fundal photograph of right eye showing macular star 4 weeks after sudden onset of visual loss.

years of age. The following conditions were present in the 7 patients: diverticulosis, coeliac disease, gout and thalassaemia minor.

Overall there were 10 patients with bilateral ischaemic optic neuropathy and 12 with unilateral disease. In only 2 patients was there documented progression of the visual loss, 1 proceeding to complete blindness in the affected eye in 3 distinct episodes.

Of the routine investigations the full blood examinations were all normal with 2 exceptions. One patient was anaemic and subsequently found to have adult coeliac disease and another had thalassaemia minor. There were no cases of polycythaemia. The blood viscosity was mildly elevated in 3 patients and no patient had markedly abnormal lipid levels. The VDRL was negative in all 22 cases and there were no diabetics. Apart from the patient with cranial arteritis, the ESR in all the other patients was less than 40mm/hour. It is noted that Boghen and Glaser (1975) considered that 35 to 40mm/hour was an acceptable upper limit of the ESR in the elderly.

It is not possible in this study to make any assessment of the value of treatment. The place of steroids in cranial arteritis is well established; in non-arteritic ischaemic optic neuropathy they may have a place although this has not been proven (Eagling et al., 1974).

Discussion

Ischaemic optic nerve lesions are not uncommon and if seen early, the characteristic pale, swollen disc with peripapillary haemorrhages and an arcuate or altitudinal field defect make the diagnosis relatively easy. The degree of visual loss is quite unlike that in papilloedema, by definition due to raised intracranial pressure, and these days raised intracranial pressure can readily be excluded by CAT scan followed by lumbar puncture. In the patient presenting with an acute disc swelling in one eye and optic atrophy in the other eye, the so-called Foster-Kennedy syndrome, the most likely cause, especially if there is any visual loss, is bilateral ischaemic optic neuropathy.

As mentioned, differentiation between ischaemic optic neuropathy and demyelinating optic neuritis is sometimes difficult although the latter condition is usually painful, with a central scotoma and no altitudinal features and is generally confined to the younger age group. Carcinomatous optic neuropathy presents diagnostic difficulties in the absence of signs of diffuse malignancy. Both eyes are usually involved and progression of the visual loss is the rule. However, the diagnosis in the early stages may depend on finding neoplastic cells in the CSF using a Millipore filter (Susac et al., 1973).

Leber's optic atrophy may present acutely in the absence of a family history and one needs to look for the pathognomonic features, namely circumpapillary telangiectasis, swelling of the nerve fibre layer around the disc and absence of staining on fluorescein angiography (Smith, et al., 1973).

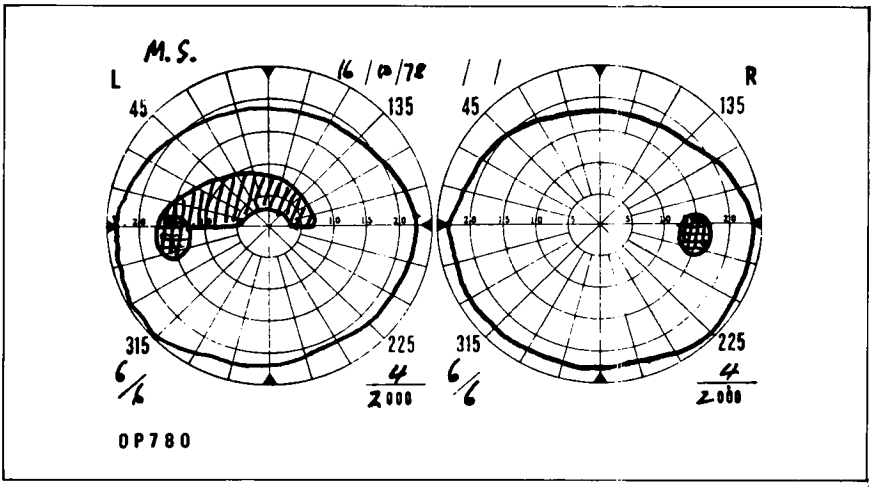

Fig. 6. Case 4. Superior arcuate defect in left visual field using a 4mm white target at 2 metres with a Bjerrum screen.

If the patient with an ischaemic optic nerve lesion is seen after the disc swelling has subsided, the possibility of optic nerve compression must seriously be considered. Arcuate defects may be produced by lesions of nerve fibre bundles as far posteriorly as the chiasm (Hoyt, 1962) and therefore investigations must include skull and optic canal x-rays, CAT scan and regular follow-up. The diagnosis of purely retrobulbar ischaemic optic neuritis is fraught with danger.

In a patient with typical ischaemic optic neuropathy, the initial step must be to identify the cases due to arteritis, principally cranial arteritis, since early treatment with steroids may save the other eye. No longer can one rely on cranial arteritis confining itself to patients over 60 years of age with a very high ESR and a positive temporal artery biopsy. In the single patient in this study with cranial arteritis, the presentation was typical although the ESR was not particularly high. Cullen (1963) reported the occurrence of cranial arteritis with a normal ESR and Eagling et al. (1974) had 2 similar cases. A biopsy-proven case of cranial arteritis in a 35-year-old was reported by Bethlenfalvay (1964).

In cranial arteritis, the posterior ciliary arteries, together with the superficial temporal, vertebral and ophthalmic arteries are the most constantly and severely involved vessels (Wilkinson and Russell, 1972). The same authors found that the central retinal artery, once it entered the optic nerve was rarely involved and never involved inside the globe. Thus there is a pathological basis for sudden visual loss in cranial arteritis being due to acute ischaemic optic neuropathy rather than central retinal artery occlusion. Clinically the distinction is easy in that in ischaemic optic neuropathy, the optic disc is pale and swollen, whereas in central retinal artery occlusion, the retina is pale and opaque and the optic disc relatively normal.

In this study as in others (Millller and Smith, 1966; Cullen, 1967; Ellenberger et al., 1973; Eagling et al., 1974; Boghan and Glaser, 1975) hypertension has been common in the non-arteritic group of patients with ischaemic optic neuropathy. In view of the similar clinical presentation, the patients with arteriosclerosis are usually grouped with the hypertensives and, as mentioned, the age of the majority of patients in the idiopathic group in this study makes the presence of arteriosclerosis likely.

The studies of Hayreh (1970) in monkeys have shown that the prelaminar, laminar and retrolaminar parts of the distal optic nerve are supplied by the short ciliary arteries and although the prelaminar portion may anastamose with central retinal artery branches, the retrolaminar region is solely dependent on the ciliary circulation. Sanders (1971) has suggested that the microcirculation of the optic nerve must be a rèlatively high pressure capillary system to compensate for the intra-ocular pressure and that there must be a water-shed area between the retinal and ciliary circulations. These factors contribute to a special susceptibility to infarction in the retrolaminar region which is aggravated by oedematous swelling within the rigid confines of the scleral canal.

The limited pathological studies reported and the work by McLeod et al. (1978) indicate that infarction of the retrolaminar optic nerve may be produced by posterior

ciliary occlusion and that the swelling of the disc is due to prelaminar intra-axonal accumulation of axoplasmic debris.

In patients with vascular disease, infarction in a water-shed area will occur if perfusion is further impaired. Systemic hypotension and severe anaemia due to any cause, carotid occlusive disease, progression of small vessel disease, e.g. in hypertensives or diabetics, and increased resistance to blood flow as in polycythaemia and hyperlipidaemia, may be relevant. In the distal optic nerve a further factor is raised intraocular pressure. Although Hayreh (1974) has suggested emboli to the posterior ciliary circulation, there is no histological confirmation of this happening in contrast to the retinal circulation. This has given rise to doubt as to whether carotid angiography is indicated in cases of ischaemic optic neuropathy. However, it seems possible that cholesterol or fibrin-platelet emboli could lodge in posterior ciliary arteries and produce sectoral infarction of the retrolaminar nerve. Boghen and Glaser (1975) found no significant association with extracranial carotid occlusive disease.

The patients in whom an ischaemic optic nerve lesion occurred after head trauma are interesting. In one case there may have been transient elevation of intraocular pressure, and in the other the visual loss was noted immediately after a minor head injury. One can only surmise that the minor trauma produced a slight fall in perfusion in individuals already susceptible to ischaemic optic neuropathy.

The relationship between migraine and ischaemic optic neuropathy has been reported by McDonald and Saunders (1971). In Case 4, it is unlikely that there was an element of underlying vascular disease, whereas in Case 5, migrainous vasospasm was superimposed upon angiographically demonstrated underlying vascular disease. The mechanism of ischaemic optic neuropathy in migraine is presumably spasm of posterior ciliary vessels although the frequent involvement of retinal vessels suggests that the spasm may also involve the ophthalmic artery.

The prognosis for recovery of vision after an acute attack is improved by the use of steroids in both the arteritic and non-arteritic forms of ischaemic optic neuropathy (Hayreh, 1974). Burde (1973) is less optimistic about the value of steroids and found phenytoin to be of no value. He felt that the prognosis for the recovery of useful vision was good and although the disease tended to be bilateral, second attacks in an already involved eye were very rare (Burde, 1976). In this limited study only 2 of 22 patients had subsequent attacks in the same eye.

This study has confirmed earlier reports on ischaemic optic neuropathy which is now well documented as a cause of sudden visual loss, particularly in the elderly. The syndrome is not uncommon and should be readily recognised on clinical grounds. Once diagnosed, the next step must be to identify the patients suffering from occult arteritis and to start treatment with high-dosage corticosteroids. The remainder with non-arteritic ischaemic optic neuropathy should not be subjected to unnecessary neuro-radiological procedures, but investigated to determine whether any of the specific underlying disorders are present.

Summary

Ischaemic optic neuropathy is a well recognised cause of sudden visual loss in middle and late life. It is characterised by painless visual impairment, pale swelling of the optic disc and nerve fibre bundle field defects. Although some cases are due to cranial arteritis, the majority of patients suffer from non-arteritic diseases, particularly hypertension.

The present study consists of a review of 22 cases of ischaemic optic neuropathy. Apart from cranial arteritis and vascular disease, migraine and trauma appear to have a causal relationship to the disorder.

Acknowledgements

I would like to thank my many colleagues who referred their patients for this study, particularly Dr Peter Ebeling, Dr Robert Hjorth, Mr J.E.K. Galbraith, Mr B.A. Crawford and Mr D. Kaufman, of the Royal Melbourne Hospital. My thanks are also extended to Mr Arthur Wigley for his photographic assistance.

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Clinical Application of the Patterned Light Visual Evoked Response (VER)

*J.I. Manson, P.F. Weston and R.G. Beran**

In 1972 Halliday et al. reported the use of the visual cortical response evoked by pattern reversal (VER) as a clinical tool in the diagnosis of optic neuritis. In 1973 Halliday et al. described their experience with the VER in the diagnosis of multiple sclerosis, and subsequently (Halliday et al., 1976) in the diagnosis of visual pathway compression. A number of publications have appeared, describing the application of this procedure to various clinical situations (Asselman et al., 1975; Lowitzsch et al., 1976; Mastaglia et al., 1976; Hennerici et al., 1977; Zeese, 1977; Shahrokhi et al., 1978; Holder, 1978; Ashworth et al., 1978).

We have examined the VER as a clinical tool in the assessment of the visual pathways in both children and adults, and in this paper report our experience over a 2-year period.

Methods

We based our technique on that of Halliday et al. (1972), using a commercially available black-and-white checkerboard pattern generator. The generator consisted of a slide projector, a mirror mounted on a galvanometer, and a screen. The black-and-white pattern was projected from a photographic transparency mounted in the slide projector onto the mirror, and reflected on the screen. The movement of the mirror was adjusted to give an impression of pattern reversal of the image on the screen, at a

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rate of 2 reversals per second. The subject sat at a distance of 1 metre from the screen, which subtended an angle of 17° at the eye, and which contained individual black-and-white squares measuring 38' of arc. The subject was asked to fixate on a small red dot in the centre of the screen, and at least 2 runs of 128 responses were performed for each eye. The procedure was carried out under dim light conditions. Evoked responses were recorded from a mid-occipital electrode placed 3cm above the inion, and right and left occipital electrodes were placed 5cm from the midline electrode. A common reference electrode was situated at the vertex. The signal was amplified by a routine electroencephalograph, averaged by a signal averager, and displayed on an oscilloscope. The responses were stored on tape, and subsequently written out on an X-Y plotter.

2 groups of subjects were examined: a control group, and a group of patients with neurological disease for investigation. The control group consisted of 45 subjects, and could be divided into 2 sub-groups. The first group consisted of 18 paediatric cardiac patients who were having a comprehensive neurological assessment, including EEC examination and VER, as part of a preoperative assessment for major cardiac surgery. The second group consisted of 27 adult volunteers, with no history of eye disease or neurological impairment. The mean age of the paediatric group was 6.3 years (range 4 years to 10 years, with a standard deviation of 2 years). The mean age of the adult group was 26.6 years (range 12 years to 56 years, with a standard deviation of 8 years).

Previous investigations (Celesia and Dayly, 1977a,b), have shown that the most consistently occurring components of the normal VER are the initial negative wave (N1), and the subsequent primary positive wave (P1). We recorded the latencies of N1 and P1, and the amplitude of the peak to peak N1-P1 complex, as obtained from the mid-occipital electrode, from each eye separately. The mid-occipitally recorded inter-ocular latency differences for N1 and P1 were recorded. For each eye the inter-occipital latency differences for N1 and P1 were recorded. We made an inter-ocular comparison of the N1-P1 responses in each subject by expressing the ratio of the amplitude of the smaller response to the amplitude of the larger response as a percentage. The amplitudes of the right and left occipital responses, as obtained from each eye tested, were compared similarly by expressing their ratio as a percentage. From the entire group of control patients we derived the mean value, range, and standard deviation for each of the above mentioned parameters. We also compared the results in the paediatric group with those for the adult group. We did this by deriving the mean values, ranges, and standard deviations, for certain selected parameters in each group. The parameters selected for the purpose of this comparison were the latencies of N1 and P1, and the amplitude of the N1-P1 complex, as recorded at the mid-occipital electrode. We used Student's t test for statistical analysis, where appropriate.

The clinical patient population studied consisted of both adults and children. The children were referred from various departments of The Adelaide Children's Hospital, predominantly the Departments of Neurology, Neurosurgery, and Oph-

Table I. VER latency and amplitude data from the 90 eyes of 45 control subjects

Measurement	Mean	Range	SD	Mean + 3 SD
Latency N1[1] (msec)	70.8	59-75	5.2	86.4
Latency P1 (msec)	100.2	93-110	5.3	116.0
Amplitude N1P1 (μV)	18.5	3-47	10.8	—

1 Mean for 89 eyes (N1 absent in one eye).

Table II. Mean inter-ocular differences of VER latency and amplitude, recorded in the mid-occipital region, in the 90 eyes of the 45 control subjects

Measurement	Mean	Range	SD	Mean + 3 SD
Latency difference N1[1] (msec)	2.0	0-8	1.6	6.8
Latency difference P1 (msec)	1.7	0-7	1.6	6.5
Amplitude ratio[2] (%)	86.9	68-100	9.3	—

1 Mean for 44 subjects (N1 depressed or absent in one patient)

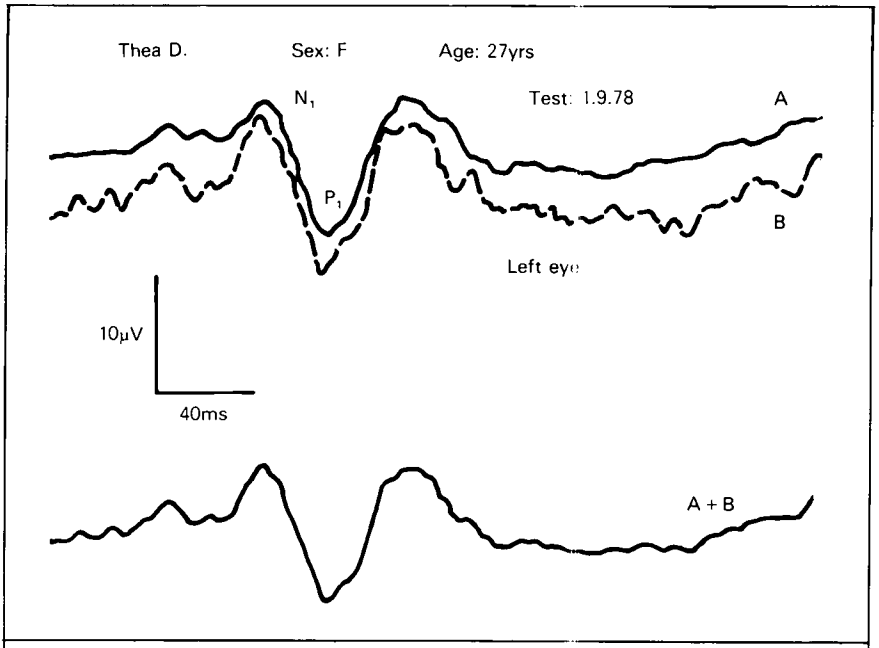
2 Amplitude ratio (%) $= \frac{\text{smaller N1P1}}{\text{larger N1P1}} \times \frac{100}{1}$

thalmology. Adult patients were referred by neurologists, neurosurgeons, and ophthalmologists practising outside The Children's Hospital. Patients were grouped into diagnostic categories (shown in table IV) on the basis of their clinical and laboratory history, by one of us (J.I.M. or R.B.). However, for a diagnosis of definite or probable multiple sclerosis, the patients were classified on the basis of a retrospective questionaire sent to the referring neurologist.

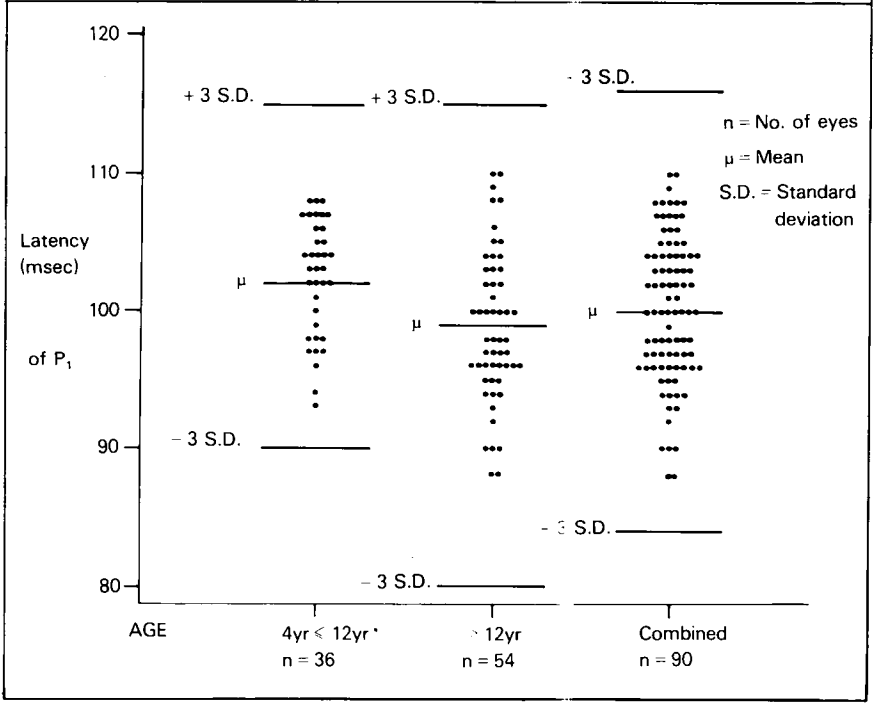
Results

Control Group

Figure 1 shows a typical normal young adult response. Table I shows the latency and amplitude data for the mid-occipital response. In agreement with the work of other authors, the latency of P1 had a narrow normal range and a low standard devia-


Thea D.
Sex: F
Age: 27yrs
Test: 1.9.78
N1
P1
A
B
Left eye
10μV
40ms
A + B

1


120
110
100
90
80
Latency (msec) of P1
+ 3 S.D.
+ 3 S.D.
- 3 S.D.
n = No. of eyes
μ = Mean
S.D. = Standard deviation
μ
μ
μ
- 3 S.D.
- 3 S.D.
- 3 S.D.
AGE
4yr ≤ 12yr
n = 36
> 12yr
n = 54
Combined
n = 90

2

Table III. Mean inter-occipital differences of VER latency and amplitude, in the 90 eyes of the 45 control subjects

Measurement	Mean	Range	SD	Mean + 3 SD
Latency difference N1 (msec) n[1] = 82	2.4	0-12	2.3	9.3
Latency difference P1 (msec) n = 85	3.2	0-15	3.2	12.8
Amplitude ratio[2] (%) n = 87	76.1	33-100	18.4	—

1 n = number of eyes with clear responses recorded

2 Amplitude ratio (%) $= \frac{\text{smaller N1P1}}{\text{larger N1P1}} \times \frac{100}{1}$

tion. It was calculated that 99.77% of controls would have P1 latencies falling inside the limit set by 3 standard deviations about the mean (i.e. 84 to 116msec). By contrast, the amplitude of the primary negative-positive complex was highly variable, with a range of 3 to 47 microvolts.

Figure 2 shows that the mean latency for P1 was not significantly different in the younger group of patient controls and in the older control group. By contrast the mean amplitude of the N1-P1 complex was higher in the younger group compared with older group (fig. 3). The Student's t test confirmed the significance of this impression for the males ($t = 4.96$; $p < 0.001$), as well as for females ($t = 10.3$; $p < 0.001$).

Table II shows mean inter-ocular differences in the control group for latencies of N1 and P1, and the amplitude of the N1-P1 complex, as recorded at the mid-occipital region.

Table III shows the inter-occipital differences for N1 and P1 latency, and N1-P1 amplitude, as recorded for individual eyes. The wave forms tended to be more variable for the right and left occipital responses, as compared with the mid-occipital response. In a small number of cases, N1 or P1 were not readily identifiable in the right or left occipital regions. In 1 patient the right and left occipital responses were not recorded.

Fig. 1. Pattern VER of a normal control subject. Each result consists of the summated response of 2 consecutive runs.

Fig. 2. Comparison of latencies (msec) for the primary positive component (P1) in individual eyes of young and adult control groups.

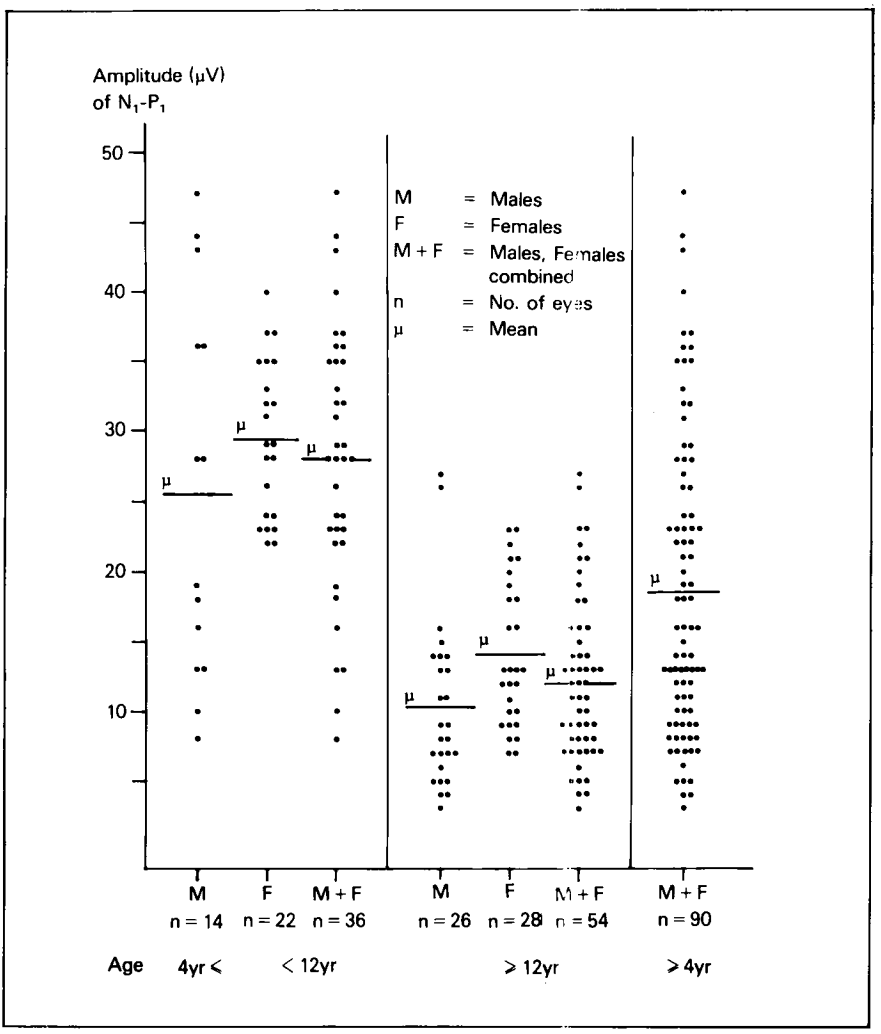


Fig. 3. Comparison of amplitudes (μV) for the combined primary negative-positive complex (NI-PI) in individual eyes of the control group, classified by age and sex.

Patient Group

On the basis of the information available from the control data, the following criteria for abnormality were adopted:

1) Latency of P1 exceeding 3SD

Table IV. Incidence of abnormal VER in 201 patients, according to diagnosis

Clinical diagnosis	No. of patients	No. with normal VER	No. with abnormal VER (%)
Definite multiple sclerosis	22	5	17 (77)
Probable multiple sclerosis	17	9	8 (47)
Optic neuritis without probable or definite MS	14	3	11 (79)
Miscellaneous with optic neuropathy	32	7	25 (78)
Compressive optic neuropathy	5	2	3 (60)
Papilloedema (generalised raised intracranial pressure)	15	13	2 (13)
Undiagnosed	33	29	4 (12)
Miscellaneous without optic neuropathy	63	58	5 (8)
Total	201	126	75

2) Complete absence of the N1-P1 complex, as recorded from the mid-occipital electrode
3) Abnormal configuration of the N1-P1 complex, such that P1, recorded from the mid-occiput, could not be identified
4) Inter-ocular P1 latency difference greater than 3SD
5) Inter-occipital P1 latency difference greater than 15msec.

The criteria for abnormality were set so that no person in the control group had any parameter which could be classified as 'abnormal.'

Table IV shows the incidence of normal and abnormal VER's in the various diagnostic groups. The prevalence of various types of abnormal VER's is shown in Table V. Figure 4 shows the scatter of latencies of P1 in the 2 groups of multiple sclerosis patients, compared with the controls. Table VI shows the relation between VER results and clinical signs of optic neuropathy in the definite and probable multiple sclerosis groups.

Case Reports

Some examples of individual cases where the pattern reversal VER has been of value are presented on page 225.

Table V. Types of VER abnormality (based on mid-occipital P1 response) in 75 patients, according to the diagnosis

Clinical diagnosis	No. with abnormal VER	Interocular latency difference only	Bilateral latency delay	Unilateral delay only	Unilateral delay, contra-lateral absence	Bilateral absence	Unilateral absence only	Abnor-mal config-uration
Definite multiple sclerosis	17	2	7	5	2	—	—	1
Probable multiple sclerosis	8	1	5	1	—	—	1	—
Optic neuritis without probable or definite MS	11	4	2	3	2	—	—	—
Miscellaneous with optic neuropathy	25	4	8	4	1	4	4	—
Compressive optic neuropathy	3	—	—	—	—	2	1	—
Papilloedema (generalised raised intracranial pressure)	2	—	—	—	2	—	—	—
Undiagnosed	4	—	—	3	—	—	—	1
Miscellaneous without optic neuropathy	5	—	—	1	—	1	2	1
Total	75	11	22	17	7	7	8	3

Table VI. The relationship of abnormal VER to the presence of clinical optic neuropathy in 22 patients with definite and 17 patients with probable multiple sclerosis

Multiple sclerosis	VER	
	normal	abnormal
Definite		
+ clinical signs of optic neuropathy	1[1]	10
no clinical signs of optic neuropathy	4	7
Probable		
+ clinical signs of optic neuropathy	2[2]	8
no clinical signs of optic neuropathy	7	0

1 VER questionably abnormal.
2 Questionable optic disc pallor.

Case 1

This 43-year-old woman complained of malaise, anorexia and nausea. She reported blurred vision, and corrected visual acuities were shown to be N5 in the right eye and N6 in the left eye. On examination her fundi were thought to be normal, with questionable temporal disc pallor. There was an 'incomplete internuclear ophthalmoplegia.' VER's (fig. 5) were abnormal with responses for the left eye delayed by 10msec compared with those for the right eye (although considered independently, neither response was in itself significantly delayed). This finding strongly suggested previously left optic nerve demyelination.

Case 2

This 34-year-old woman complained of variable dysaesthesiae on the left side of her body. She had had an episode of 'blurred vision' involving her right eye during her high-school years. Examination revealed an 'hysterical' personality with visual acuities 6/6 on the right, and 6/6-1 on the left. There was a suspicion of pallor in the left optic disc. Pattern VER's were requested and these demonstrated moderately delayed responses bilaterally, with greater delay on the right (fig. 6), confirming the presence of bilateral optic nerve demyelination.

Case 3

VER's were performed on this 8-year-old boy, with papilloedema due to posterior fossa medulloblastoma. Preoperative visual acuities were normal. Responses were found to be severely delayed in the right eye, and of borderline latency in the left eye. Postoperatively the child was found to be blind in the right eye, whilst normal vision was preserved in the left eye. At that time, VER's were absent in the right eye, and were present, although moderately delayed in latency, in the left eye (fig. 7). This case suggests the potential value of the VER in prediciting the impact of papilloedema on visual function.

Case 4

This 7-year-old girl with Stage 4 neuroblastoma presented with sudden loss of visual acuity in the right eye. Her visual acuity in her left eye was 6/6. There was mild bilateral disc swelling and mild proptosis in the right eye. VER's were performed, and no responses could be recorded for her right eye, whilst responses for her left eye were within normal limits (fig. 8). The findings were interpreted as right optic nerve compression by secondary neuroblastoma in the posterior orbit, and further appropriate investigations and treatment were undertaken.

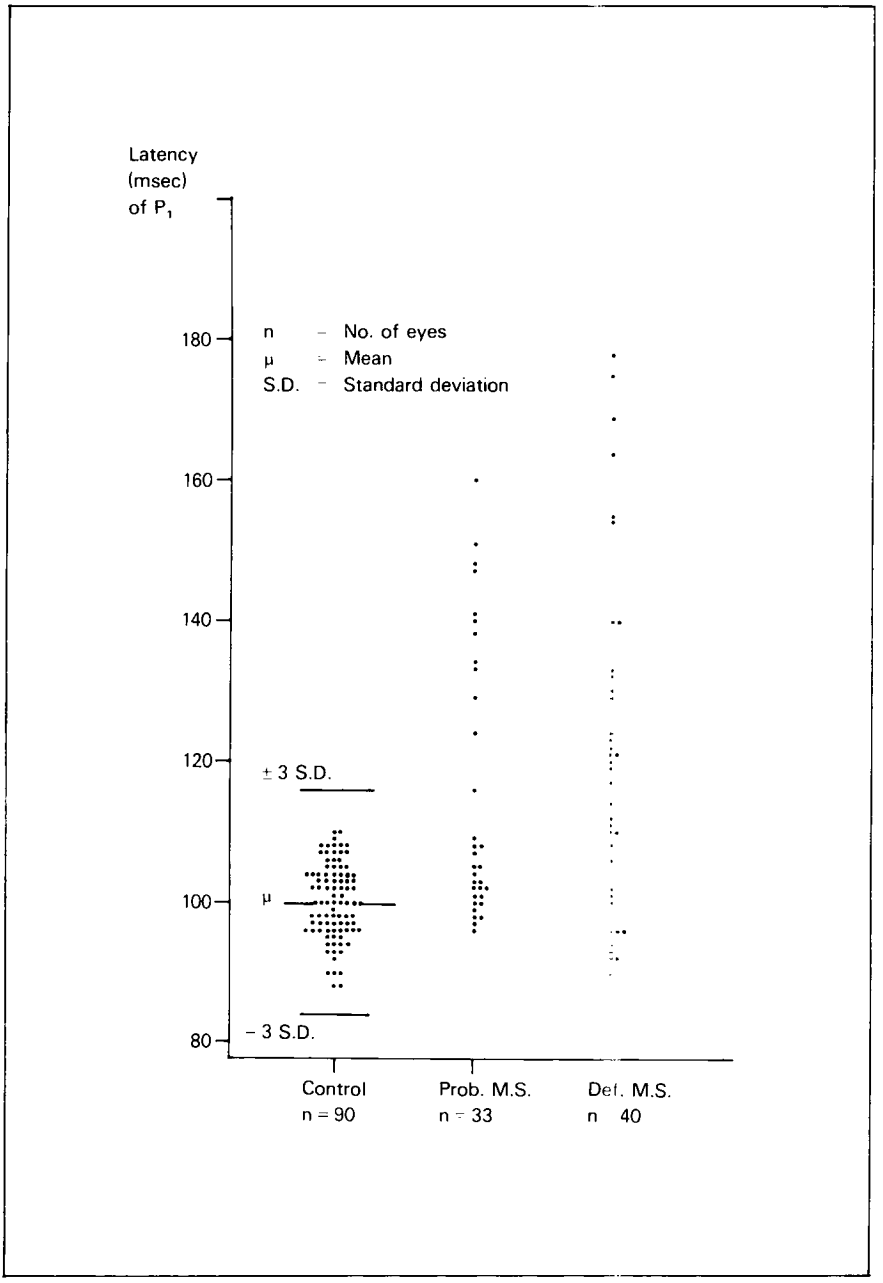


Fig. 4. Comparison of mean latencies (msec) for the primary positive component (P1) in individual eyes of definite multiple sclerosis, probable multiple sclerosis and control groups.

Case 5

This middle-aged housewife presented with progressive headaches over several months, then rapid onset of severe bilateral visual impairment. Bilateral disc swelling was present. Pattern VER's were of grossly abnormal configuration (fig. 9). CAT scan suggested an extensive butterfly glioma involving both optic radiations. Surgical exploration revealed a massive cystic ependymoma.

Case 6

This 7-year-old had an episode of bilateral optic neuritis 2 years previously. She presented with sudden onset of left cerebellar ataxia. CAT scan showed large demyelinating lesions in the white matter of the left cerebellar and left cerebral hemispheres. EEG showed a delta focus in the left anterior regions. Her VER's showed an abnormal configuration, and there was also a striking asymmetry between the right and left occipital responses, with delay and depression of the left occipital response (fig. 10).

Discussion

This study shows that certain parameters of the VER, especially P1 latency, have a well-defined and narrow range in normal controls. Since it is possible to exclude retinal disease by ophthalmoscopy and electroretinography (Starr et al., 1978), and the latencies are stable in the presence of marked refractive errors (Goff et al., 1978), the latency of the VER is a potentially sensitive index of function of the neurological visual pathways. Although Celesia and Dayly (1977a) have reported changes

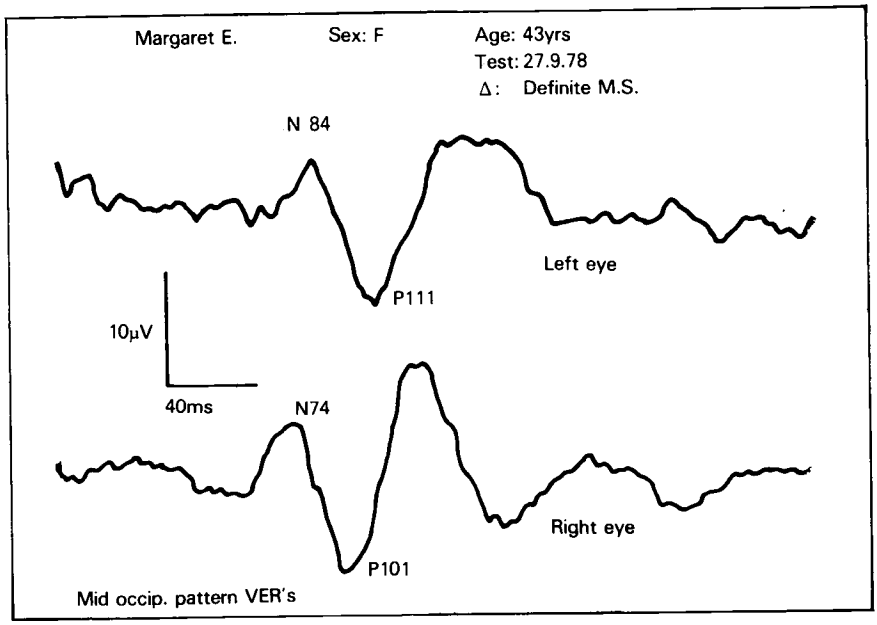


Fig. 5. Case 1. VER's.

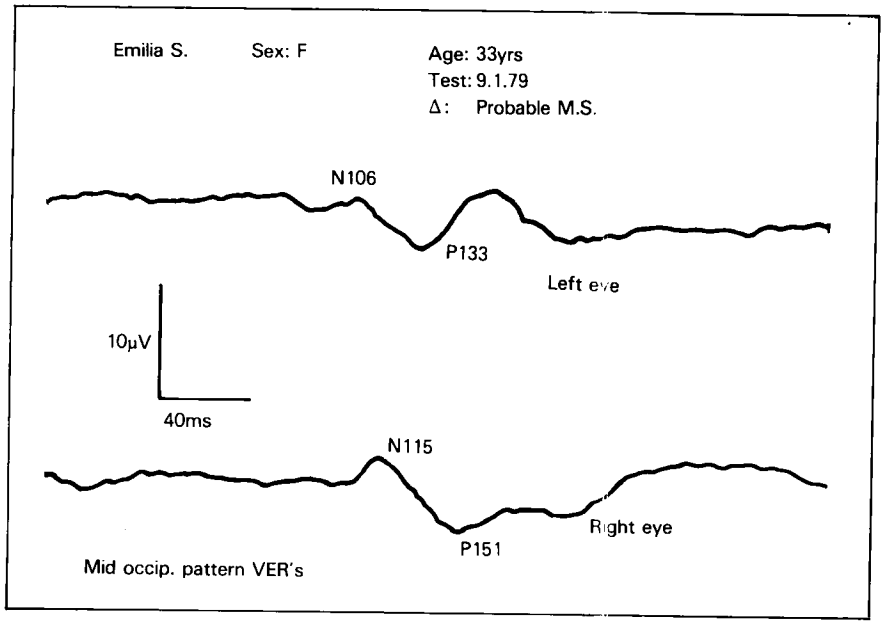


Fig. 6. Case 2. VER's.

in the latency of the pattern reversal VER, which could be correlated with advancing years, we were unable to detect such a trend in our results. This may have reflected insufficient numbers of geriatric subjects in our control group. In order to allow for non-pathological factors which might have affected the latency of the VER, we adopted a conservative level of 3SD as our upper limit of normality.

Whilst the latency of the VER falls within a well-defined range, the finding that the amplitude was highly variable between subjects, concurs with the findings of previous authors (Hoeppener and Lolas, 1978; Shahroki et al., 1978). In addition, peripheral factors such as refractive errors, vitreous opacities, and the degree of fixation on the patterned screen, are known to influence the amplitude (Shahroki et al., 1978; Starr et al., 1978). Thus in practice the amplitude of the VER is an unreliable index of optic neuropathy, unless these peripheral factors have been excluded. Nonetheless it was clear that an absent P1 response or a distorted configuration of the response to such an extent that P1 was unrecognisable, constituted an abnormal response, as these findings did not occur in any of our control subjects with mid-occipital recording.

In contrast to the absence of age-related changes in the latency of the VER, we found evidence of significant age-related changes in the amplitude of the VER. We are unaware of any other report of amplitude changes with age for pattern reversal VER's in children and young adults. Klorman et al. (1978) cite the studies of

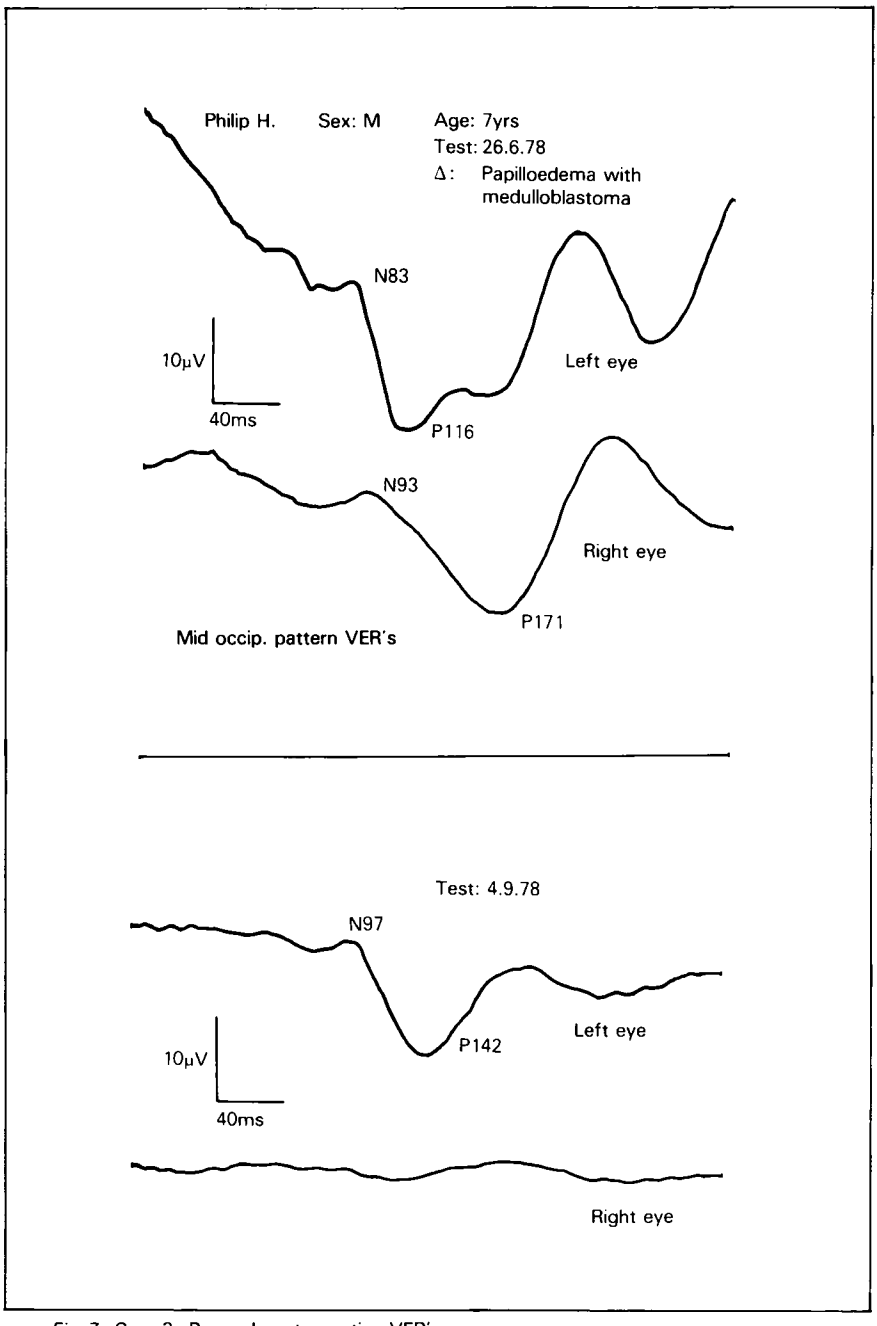


Fig. 7. Case 3. Pre and postoperative VER's.

Schenkenberg, who reported that after early adolescence there was a reduction in the amplitude of the flash evoked response components occurring between latencies of 100 and 175msec; this observation parallels our experience with the pattern evoked response. Our criteria for abnormality have proved reasonably successful in detecting visual pathway disease. The 77% (17 out of 22) of abnormal VER's in the definite multiple sclerosis group was comparable with percentages reported by previous authors — 81% (Hennerici et al., 1977) — 97% (Halliday et al., 1973). When the definite and probable multiple sclerosis patients were considered together, the level of abnormality, 64% (25 out of 39) in the total multiple sclerosis population was compatible with that reported previously — 50% (Mastaglia et al., 1973) — 96% (Halliday et al., 1973). In the definite multiple sclerosis group, the VER was of particular clinical value in 7 cases where abnormal responses were recorded in the absence of clinical signs of optic neuropathy. The absence of success in detecting clinically silent lesions in the probable multiple sclerosis group may possibly be attributable to the influence of the VER result on the referring doctor's retrospective classification. The 39% (7 out of 18) level of detection of clinically silent optic nerve lesions in our combined definite and probable multiple sclerosis population was similar to that reported by Shahrokhi (1978). The more common form of abnormal response in the multiple

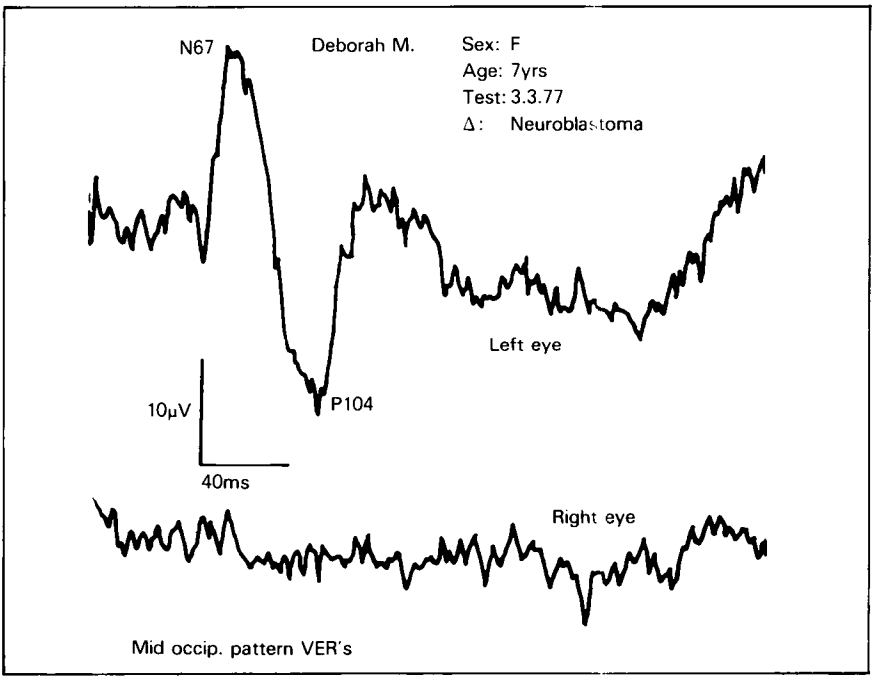


Fig. 8. Case 4. VER's.

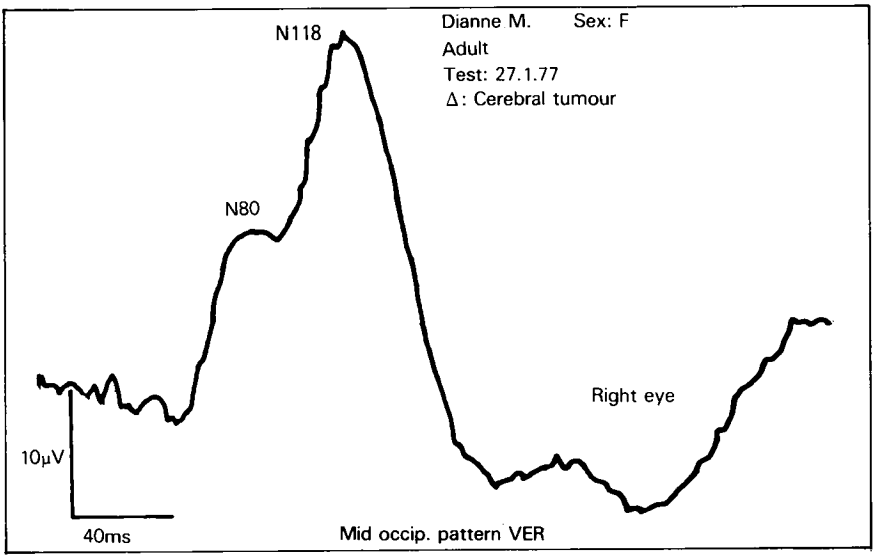


Fig. 9. Case 5. VER.

sclerosis population was found to be delay in the latency of P1 for either one eye or both eyes. The occasional occurrence of interocular latency difference as a sole abnormality, in the absence of an absolute latency delay, emphasises the importance of comparing VER's recorded for each eye separately.

There were similar yields of abnormal VER's in the definite multiple sclerosis group, the clinically pure optic neuritis group, and in miscellaneous diagnoses with clinical signs of optic neuropathy, which included optic atrophy associated with toxic, congenital and degenerative causes. The prevalence of absent VER's among the compressive optic neuropathy patients would be compatible with the severely reduced visual acuities in these cases. Abnormal VER's were generally not observed with papilloedema due to raised intracranial pressure, except in 2 cases with deteriorating vision. In Case 3 the delayed VER appeared to anticipate the loss of vision in the right eye subsequent to posterior fossa decompression. Another patient with papilloedema due to posterior fossa medulloblastoma did not have objective visual impairment, but experienced transient visual obscurations. This patient had P1 latencies approaching our upper limit of normal.

As might be expected, in the group of miscellaneous diagnoses (without clinical optic neuropathy), the number of abnormal VER's was low, and the VER was mainly of value in tending to exclude optic nerve disease. If the VER is abnormal, according to the criteria we have outlined, there is an extremely high probability, almost a certainty, that there is a disease process involving the neurological visual pathways. However, if the VER is normal, it is not possible completely to exclude optic

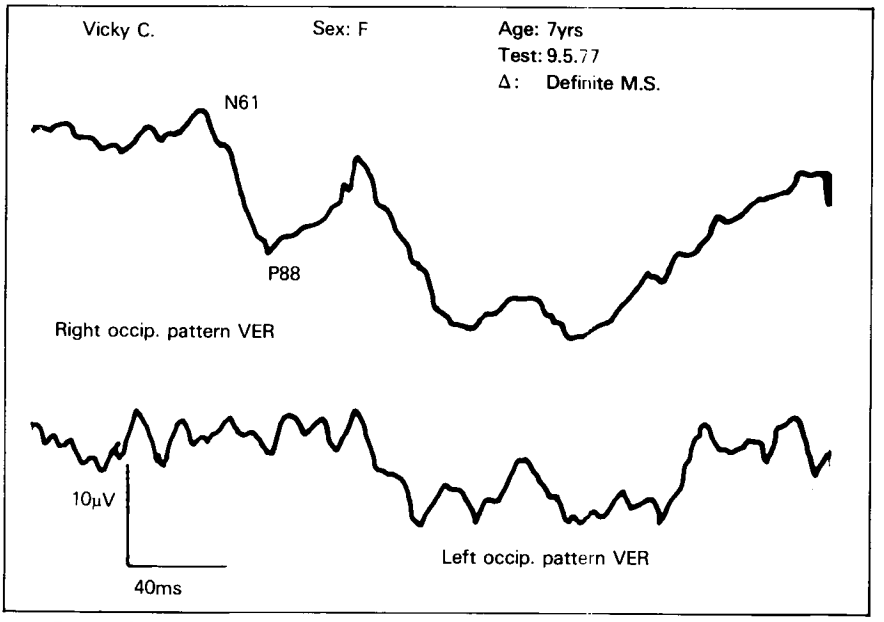


Fig. 10. Case 6. VER's.

neuropathy, as can be seen by the presence of normal VER's in a small number of cases of optic neuropathy of miscellaneous types.

We believe that the pattern VER has the potential for a wider application than the diagnosis of multiple sclerosis alone. We have found it more useful to regard the entire VER as an extension of the clinical neurological examination, similar to the routine EEG. Different patterns of abnormality may arise in the VER in various clinical situations. Although not often of pathognomonic diagnostic value, the procedure provides a valuable addition to the sum of localising 'signs' available to the clinical neurologist, thus enhancing his ability to formulate a diagnosis and a plan of management.

Acknowledgements

We wish to acknowledge: the cooperation of Dr Elton Goldblatt of the Department of Cardiology at The Adelaide Children's Hospital, who has made his patients available for study as part of preoperative assessment; the expertise of members of the Electronics Department of The Adelaide Children's Hospital, in particular Messrs D. Lloyd, D. Pfeiffer and K.B. Gassmanis, whose skill has been responsible for the trouble-free operation of electronic equipment; and Mrs C.M. Lloyd and Miss J.F. Brown of the Department of Photography at The Adelaide Children's Hospital for preparing the tables and illustrations for this presentation. We also wish to express our appreciation to the various clinicians who have been most cooperative in providing detailed follow-up clinical information about the patients referred for study; and to the EEG technicians — Mr Herbert Theodore, Mesdames M. Turner and V. Clark for the excellent technical work.

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Observations on Voluntary Nystagmus

*A. Fisher, H. Davies and S. Wallis**

The ability to jiggle the eyes (otherwise known as voluntary nystagmus) has been regarded as an amusing trick most often displayed at convivial gatherings. On occasions the phenomenon has been used by the subject to deceive, annoy or confound unwary medical examiners. Although voluntary nystagmus was first described in 1866 (Duke Elder, 1949) it is probable that difficulties with recording or lack of sophistication in apparatus were responsible for the absence of analytical studies of the condition until 1962 (Goldberg and Jampel).

The features of voluntary nystagmus studied in 5 unrelated adults form the basis of the present report.

Method

4 females and 1 male with age range from 21 to 45 years were studied. Between the ages of 6 and 8 years all these individuals became aware of their ability to produce the movements at will. A familial occurrence of the phenomen was noted in 2. In all respects the subjects were healthy and were not taking any medication. All individuals were submitted to a clinical survey. Electro-oculography was undertaken under varying conditions (see below) using silver-silver chloride electrodes in standard placement to permit independent and simultaneous recording of movements of each eye. The potentials derived were subjected to pre-amplification in a specially

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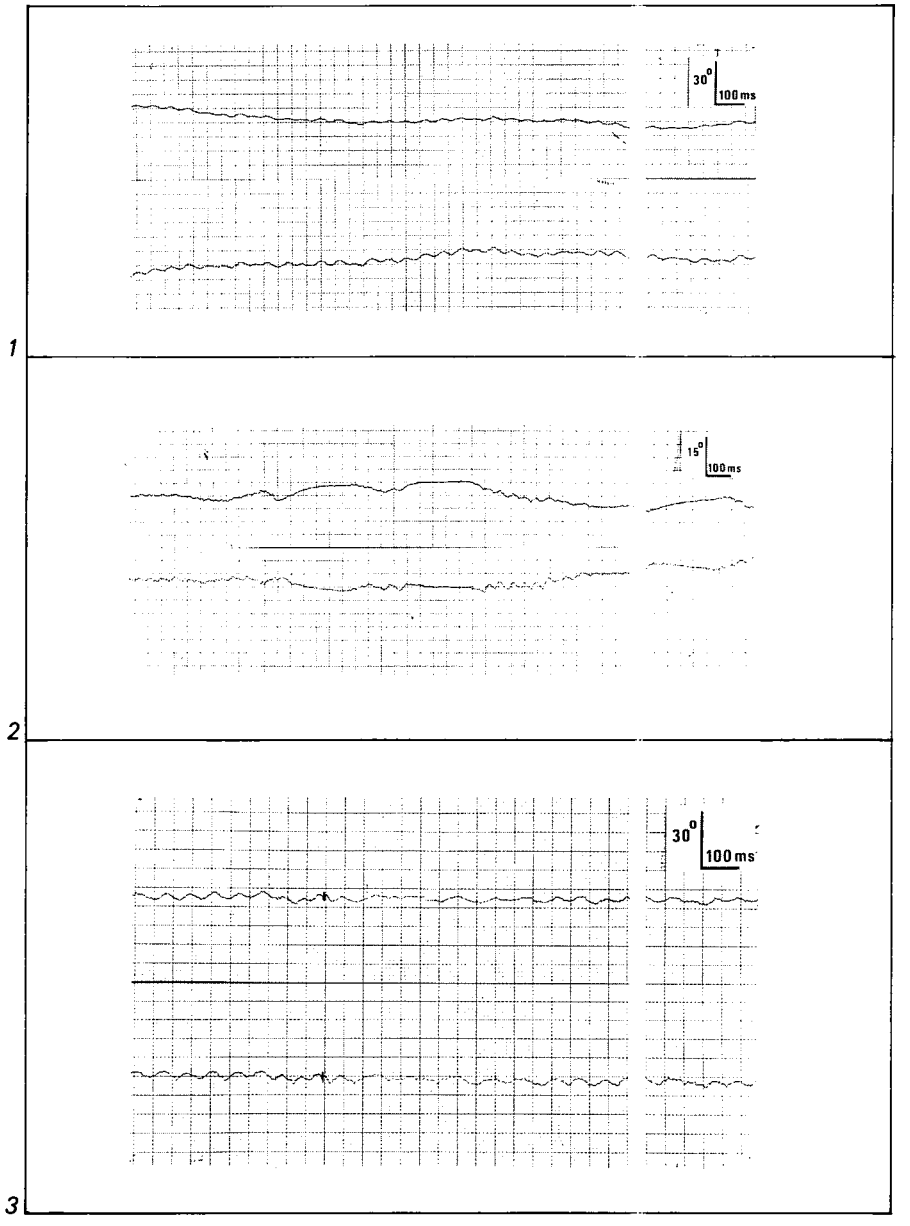

Fig. 1. Voluntary nystagmus under conditions of full illumination.

Fig. 2. Fatigue pattern of voluntary nystagmus showing bursts of activity.

Fig. 3. Voluntary nystagmus in total darkness.

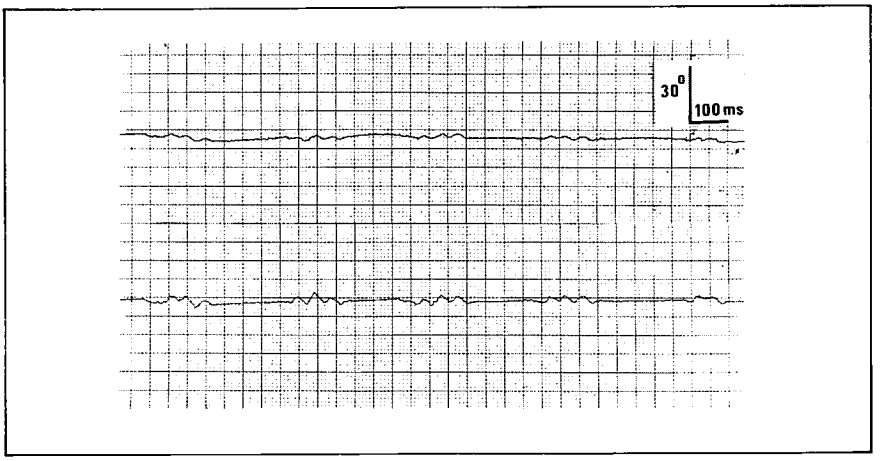

Fig. 4. Bursts of voluntary nystagmus in total darkness.

designed unit using DC coupled amplifiers with low drift, low noise (5μV), high gain (up to 5000 X), high common rejection ratio (100 dB) and high input impedance (100 G Ω). The upper frequency roll-off of 80 Hz band width was determined by the characteristics of the pen recorders. Recordings were made using a Devices polygraph driven by the pre-amplifier output. During the recording, the subject was seated comfortably without head restraint, and the study was conducted under the following conditions:

1) With full illumination
   a) eyes in the primary position
   b) eyes diverted horizontally to a target 30 degrees to the right and left of the midline
   c) eyes moved to a target 30 degrees to the right and left after the nystagmus had been initiated
2) Eyes closed
3) Eyes open in complete darkness.

Results

In all instances the nystagmus was conjugate, pendular, and horizontal. The amplitude of the movement varied between 2 and 5 degrees from subject to subject, while the frequency was recorded between 15 and 23Hz (fig. 1). The duration was averaged over 5 estimations and varied between 2 and 16 seconds from subject to subject.

As some of the subjects tired, short bursts of nystagmus replaced a previously continuous movement (fig. 2) and the subjects reported a sense of ocular strain. Convergence was sometimes observed. Movements of the eyes to the right and left to reach a defined target after the nystagmus had been initiated resulted in 2 subjects continuing to execute the nystagmic movements during the additional eye movement and when they reached the target, while 1 continued nystagmic movements only during laevoversion and when the eyes came to rest. In the remaining subjects the voluntary nystagmus ceased during version but recommenced when the eyes came to rest and were directed at the eccentric target.

Eye closure resulted in convergence of the eyes with continuation of the voluntary nystagmus in 3, while 1 subject continued without alteration of the visual axes and the other ceased the voluntary nystagmus altogether.

In the darkness with eyes open 1 subject showed no change (fig. 3), 1 continued the voluntary nystagmus with the eyes converged, 1 continued with only a reduction in amplitude, 1 showed discontinuous bursts of voluntary nystagmus with a normal amplitude (fig. 4) and the fifth subject had discontinuous bursts of nystagmus with reduced amplitude.

Discussion

All workers have accepted that the eye movements of voluntary nystagmus are physiological. If so, it is difficult to decide where voluntary nystagmus should be placed in the taxonomy of ocular movements. The usual manifestations of fixation such as tremor, drift, and microsaccades would seem to be excluded on grounds of their respective frequencies and the fact that fixation is unnecessary for the initiation of voluntary nystagmus. Ocular flutter, opsoclonus and convergence tremor are close to the frequency range of voluntary nystagmus but the first is discontinuous, the second is pathological and the third requires convergence for its production. The latter movement is usually unnecessary for the production of voluntary nystagmus (table I).

Because of its wave form, Zahn (1978) has suggested that voluntary nystagmus is analogous to pendular nystagmus. Admitting this point, the differing frequencies may make it difficult to accept identity of the two movements. Recollection that congenital pendular nystagmus is initiated by fixation and abolished by eye closure and darkness and inverted by optokinetic stimulation would seem to exclude this condition. Likewise acquired pendular nystagmus is also abolished by eye closure though is unaccompanied by optokinetic inversion.

During the past 10 years, the theory that the cerebellar nuclei and their connections with the brain stem are involved in continuous regulation of steady voluntary eye position has been advanced (Kornhuber, 1971). It has been argued that a defect of

Table I. The frequencies of some ocular movements

Type of movement	Frequency (Hz)
Tremor	30-80
Drift	2-5
Microsaccades	*Irregular*
Acquired pendular nystagmus	2-4
Convergence tremor	16-17
Flutter and opsoclonus	13

this holding mechanism is responsible for the acquired pendular nystagmus seen in some 4% of patients with multiple sclerosis (Aschoff et al., 1974).

Although we have not undertaken any specific analysis of the wave forms in voluntary nystagmus and acquired pendular nystagmus, if there is similarity in the form, it is not unduly facile to suggest that voluntary nystagmus appears in an individual who is capable of inhibiting the cerebellar holding mechanism. Whether this represents a newly developing ability in man which has some useful purpose or indicates the persistence of an atavistic attribute is clearly conjectural.

There are now a number of reports of familial inheritance of the tendency, (Goldberg and Jampel, 1962; Aschoff et al., 1976). Rettelbach has traced this tendency through 5 generations in his family and suggests that it is carried as an autosomal dominant gene with incomplete penetrance. Nevertheless others have recorded subjects admitting that they learned the activity from an older sibling (Bruckner, 1917), or as a result of gazing in a concentrated fashion at the railway track alongside a speeding train (Friedenwald, 1926). In a recently reported group of subjects, 79% admitted that someone in their family could produce voluntary nystagmus (Zahn 1978). No-one can yet resolve whether voluntary nystagmus is learned or innate.

Finally it should be noted that in our subjects, voluntary control of this phenomenon was restricted to its initiation and duration; the frequency and amplitude could not be influenced. Therefore the fact that no change occurred in the movements in some subjects executing another voluntary eye movement, namely version, should not surprise us.

Until recently, when an incidence of the condition was recorded in 8% of a college-age population in the USA, previously reported estimates of the incidence of voluntary nystagmus were non-quantitative, Duke Elder using the phase 'high incidence' and Aschoff and his colleagues 'considerable rarity'. A study designed to estimate the incidence of the condition in this country is now in progress and will be the subject of an extended report elsewhere.

Summary

Until recent times, reports concerning voluntary nystagmus have been dismissive, most observers regarding the phenomenon as a form of ocular acrobatics or an amusing party trick. The introduction of sophisticated recording apparatus coupled with renewed interest in ocular kinetics has resulted in a more analytical approach. Clinical and electro-oculographic study of the condition in 5 subjects was undertaken in an attempt to relate voluntary nystagmus to the known mechanisms of ocular movement control. The frequency of the movement varied from 15 to 23Hz and amplitude from 2 to 5 degrees. The wave form was similar to that seen in acquired pendular nystagmus. It was concluded that, despite differences in frequency, the similarity in form of the movements of voluntary nystagmus and acquired pendular nystagmus suggested a possible identity in the mechanisms of the movements.

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Motor Fibre Refractory Period and Motor Conduction Velocity Range

*J. Vernea**

The study of the refractory period in peripheral nerves is a useful method of assessing peripheral nerve disease (McLeod, 1977). Gilliat and Willison (1963) were the first to measure the refractory periods in man. Their study and most of the subsequent studies (Buchthal and Rosenfalck, 1966; Lowitzsch and Hopf, 1972; Hopf et al., 1974; Tackmann and Lehmann, 1974; Betts et al., 1976; Hopf et al., 1976) were performed on sensory and mixed fibres. The examination of the refractory periods of motor fibres was prevented by the fact that two successive motor action potentials elicited by paired stimulation could not be measured adequately.

This difficulty has been overcome recently by an elaborate computerised subtraction technique (Kopec et al., 1978), capable of separating two successive motor action potentials. Kimura (1976) and Kimura et al. (1978) used a collision technique, which they applied in normal subjects.

We employed this technique to study the refractory periods in normal and diseased nerves and also as a correction factor in the calculation of the range of motor conduction velocity of the nerves examined.

Methods

The populations studied consisted of 25 patients and 25 normal controls. 20 patients had diabetic peripheral neuropathy; they were aged between 38 and 69 years. The neuropathy was slight in 12 patients (who had abolished ankle jerks only) and

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moderate to severe in 8 patients. 2 further patients had a slight alcoholic neuropathy, 1 had a moderate carcinomatous neuropathy and the remaining 2 patients had motor neurone disease.

A Medelec electromyograph, model MS6, with two interconnected stimulators (NT6 and NS6) was used. The NS6 stimulator is capable of delivering successive stimuli at intervals adjustable by 0.1msec. The median, ulnar, common peroneal (lateral popliteal) and posterior tibial nerves were stimulated by 0.02msec duration pulses which were just supramaximal (175 to 200V). The proximal stimulation points for the median and ulnar nerves were at the elbow or slightly above, and the distal points were at the wrist. The points of stimulation for the common peroneal and posterior tibial nerves were the same as in the conventional method for the study of motor conduction velocity. Paired stimuli at various intervals (usually between 0.5 and 5msec) were applied proximately by increasing the interval stepwise by 0.1msec. The recordings were performed with surface electrodes over the corresponding distal muscle as in the conventional method for testing motor conduction velocity. The first proximal stimulus was always blocked by the antidromic impulse from the distal stimulus which was delivered simultaneously, whereas the distal stimulus always had a motor effect. The second proximal stimulus had a motor effect only if the interval from the first proximal stimulus was longer than the absolute refractory period (fig. 1). This collision method allows a clear recording of the action potential elicited by the second proximal stimulus, by avoiding superimposition and interference with the action potential due to the first proximal stimulus.

The same position of the stimulating and recording electrodes was used to determine the range of motor conduction velocity of the nerves studied (Thomas et al., 1959; Hopf, 1963). Simple (non-paired) pulses of the same characteristics as used for the study of the refractory periods were applied first at the distal and then at the prox-

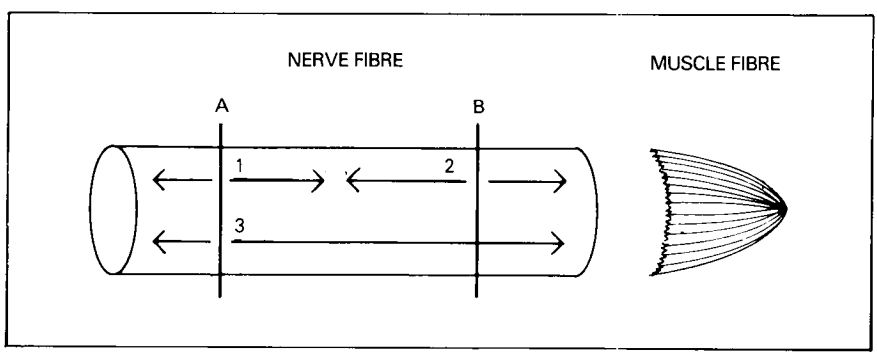

Fig. 1. The collision technique for studying motor fibre refractory periods. The stimuli 1 and 2 are simultaneously applied. Stimulus 2 will always have a motor effect whereas stimulus 1 will be always blocked. The effect of stimulus 3, which is the test stimulus for the study of the refractory periods will never be superimposed over the effect of stimulus 1, which is always blocked.

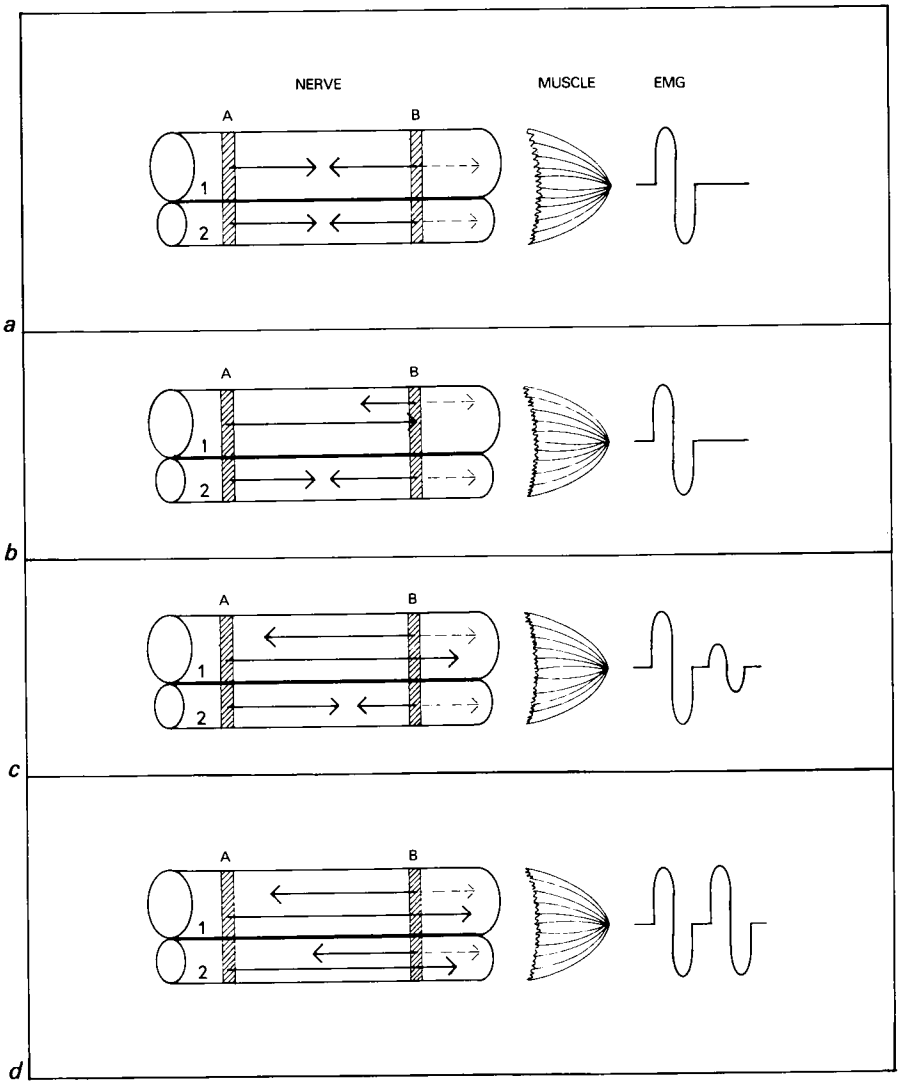

Fig. 2. The collision technique for studying the range of motor conduction velocity. Fibres 1 are of larger diameter (faster conducting) than fibres 2. The stimulation is applied first at A and then at B. There will always be a first action potential from stimulation at B (dotted arrows). The shaded areas at A and B represent the refractory periods caused by stimulation at these points.

In (a), the stimulus interval is short so that the response from A is blocked by collision in both fibres 1 and 2. In (b), the stimulus interval is marginally longer than the minimum conduction time of fibres 1 but no second response occurs, since the stimulus in fibres 1 falls within the refractory period at B. In (c), the stimulus interval slightly exceeds the minimum conduction time so that a small second response through fibres 1 occurs. In (d), the stimulus interval exceeds the maximum conduction time (of fibres 2), so that no collision occurs and the second response is identical to the first.

imal stimulation point. The interval between the stimuli was increased stepwise (by 0.1msec steps) from 3msec upwards (fig. 2). As long as the stimulation interval was below the minimum conduction time between the stimulated points, it was possible to record only the action potential elicited by the distal stimulus since the proximal stimulus was blocked by the antidromic effects of the distal stimulus. When the interval between the stimuli slightly exceeded the minimum conduction item, the fastest conducting fibres could be stimulated, without this being blocked by collision, as the proximal impulse had already passed the distal stimulating point. In this situation a small second action potential was recorded (fig. 2c). As the interval between the stimuli increased the stimulation of slower and slower fibres became effective (not blocked), so that the second action potential increased gradually. When the interval between the stimuli reached the same value as the conduction time of the slowest fibres, the second action potential reached its maximum and no longer increased in amplitude when the interval between the stimuli was further increased. Having obtained the maximum and minimum conduction times by this method, it was easy to calculate the minimum and maximum motor velocities, since one knew the distance between the stimulating points.

However, in order to have more accurate estimates of these velocities, it was necessary to subtract the refractory period from the conduction time thus obtained (the absolute refractory period from the maximum conduction time and the relative refractory period from the minimum conduction time). Indeed, the stimulus interval corresponding to the initial small action potential also included the refractory period of the fastest conducting fibres (fig. 2b). A similar situation applied to the minimum conduction velocity.

A phenomenon encountered in moderate and especially in severe neuropathies was failure of the action potential due to proximal stimulus to be completely suppressed by the distal stimulus.

In such cases there was always a small second wave It was the variation in amplitude of this wave (over which the effect of the second proximal stimulus was superimposed) that was used for assessing the refractory periods or the motor conduction times.

The motor conduction velocities of the nerves studies were examined by the conventional method as well for comparison.

Results

The values of the absolute and relative refractory periods in normal subjects are presented in table I.

The data obtained in normal subjects for the maximum and minimum conduction velocities, studied by the collision method and corrected by subtracting the refractory period from the conduction times, are set in table II, which shows the finding in the popliteal nerves (15 nerves examined).

Table I. Values of the absolute and relative refractory periods in 25 normal subjects

Nerve	Absolute refractory period (msec)			Relative refractory period (msec)		
	range	mean	standard deviation	range	mean	standard deviation
Median (110 studies)	0.8-1.3	1.13	0.16	1.0-1.9	1.55	0.25
Ulnar (5 studies)	0.8-1.2	0.94	0.17	1.2-2.0	1.48	0.27
Lateral popliteal (15 studies)	0.6-1.1	0.90	0.12	1.0-1.5	1.24	0.14
Posterior tibial (5 studies)	0.8-1.0	0.92	0.08	1.0-1.4	1.25	0.11

Table II. Conduction velocities and their ranges (in m/sec) in the lateral popliteal nerve of 15 normal subjects

Measurement	Range	Mean	Standard deviation
1. Maximum conduction velocity (collision method)	41-63	51.2	3.0
2. Maximum conduction velocity (conventional method)	41-62	51.0	3.81
3. Minimum conduction velocity (collision method)	38-54	47.4	3.42
4. Range of conduction velocities (difference between 1 and 3)	2-11	3.8	2.3

Table III. Refractory periods (msec) and motor conduction velocities (in m/sec) in the lateral popliteal nerves of 20 patients with diabetic neuropathy

Measurement	Range	Mean	Standard deviation
1. Absolute refractory period	1.1-2.4	1.48	0.33
2. Relative refractory period	1.2-3.0	1.81	0.56
3. Maximum conduction velocity (collision method)	26-41	36.08	4.1
4. Maximum conduction velocity (conventional method)	27-40	35.95	3.86
5. Minimum conduction velocity (collision method)	24-38	32.83	4.66
6. Range of conduction velocities (difference between 3 and 5).	1-7	3.25	1.48

The difference between the maximum conduction velocity calculated by the conventional method and the collision method in no instance exceeded 3.5m/sec. There was no tendency for one of these methods to give higher figures than the other.

Table III shows the refractory periods and motor conduction velocities in the lateral popliteal nerves of 20 patients suffering from diabetic neuropathy.

In 1 patient with mild alcoholic peripheral neuropathy, the refractory periods were at the upper limits of normal, whereas the conduction velocities were reduced.

In the other case, the refractory periods were increased and the conduction velocities only marginally reduced.

In 2 patients with amyotrophic lateral sclerosis, the median nerve showed virtually normal conduction velocities and refractory periods. The range of conduction velocities however, was reduced (below 1 m/sec in both cases). The patient with carcinomatous peripheral neuropathy showed reduced conduction velocities and prolonged refractory periods.

Discussion

The normal absolute refractory periods found in this study are longer than those found in animals: 0.5msec according to Gasser and Grundfest (1936). Gilliat et al. (1963) interpreted their higher figures in human median nerves as due partially to lower intensity stimulation but mainly to the fact that the human median nerve contains thinner fibres. Betts et al. (1976) explain their higher figures as being caused by a lower stimulus intensity. In the collision method used in this study, another factor may operate. The second proximal stimulus, if delivered shortly after the end of the absolute refractory period, may reach the point of collision between the first proximal stimulus and the distal stimulus during the local relative refractory period. The second proximal stimulus, being itself elicited in the relative refractory period, may thus be incapable of propagating through a nerve segment in the refractory period. This gives the impression of a prolonged refractory period. Low temperature can also be a contributory factor in the prolongation of the refractory period, a phenomenon studied extensively by Low and McLeod (1977). However, it is unlikely that in our investigation temperature played any significant part, since the temperature was maintained constant. The relative refractory period obtained with the collison method represents in fact the range of the absolute refractory periods of various diameter fibres, as shown by Kimura (1976).

The results in tables I, II and III show that both maximum and minimum conduction velocities are significantly reduced in diabetic neuropathy. The normal range of conduction velocity, which we found to be 2 to 11 m/sec, differs from that given by other authors: 4 to 7m/sec according to Hopf (1963), 7 to 12m/sec according to Miglietta (1968) and Chaco (1970), 11 to 22msec according to Blackstock et al. (1972). These authors did not correct their calculation by subtracting the refractory periods from the conduction times. Moreover, they did not study diabetic neuropathies.

The relative refractory periods given by some authors (Lowitzsch et al., 1972; Betts et al., 1976) are longer than ours. It is difficult to explain this descrepancy. It is however worth mentioning that their figures, when subtracted from the conduction times as a corrective factor in the calculation of the maximum and minimum conduction velocities gave illogical results (Betts et al., 1976). As shown above we could use

the values obtained by us for these calculations. This is confirmed by the close results obtained for the maximum motor conduction velocity with the collision and the conventional methods.

In some cases of peripheral neuropathy, there is a failure of the proximal stimulus to be totally suppressed by the distal stimulus. This is very likely explained by two factors:

a) The stimulation threshold increases so that supramaximal stimulation becomes painful and cannot be applied;

b) Fibre degeneration and reinnervation cause the proximal and distal regions of the nerve to contain, apart from identical fibres, a contingent of non-identical fibres.

The following conclusions can be drawn from our study:

1) The collision technique for studying motor refractory periods and maximum and minimum motor conduction velocities can be applied to all main nerves of the limbs.

2) The refractory periods can be used to correct the calculation of the conduction velocities. The maximum conduction velocities calculated with this method correspond closely with those obtained by conventional methods.

3) The refractory periods are prolonged in peripheral neuropathies, especially those of segmental demyelination type. Both maximum and minimum conduction velocities are reduced in such peripheral neuropathies but the range of conduction velocities is not necessarily increased.

4) The failure to suppress fully by collision the effect of a proximal stimulus by a distal stimulus is a phenomenon found in peripheral neuropathy.

Summary

The absolute and relative motor refractory periods and the range of motor conduction velocity were investigated in 25 normal subjects and in 25 patients suffering from peripheral neuropathy.

The refractory periods were examined by a collision method, which eliminates the effect of the first of the paired stimuli, thus allowing the effect of the second stimulus to be clearly recorded. The range of conduction velocity was also examined by a collision method, and the conduction times were corrected by subtracting the absolute and relative refractory periods from the figures given by this method. The maximum motor conduction velocities obtained with this technique closely corresponded with those found using conventional methods. The results show that the refractory periods are prolonged and the conduction velocities are reduced in peripheral neuropathies, especially of segmental demyelination type, but the range of conduction velocity is not necessarily increased. The failure to suppress fully the effect of the proximal stimulus by a distal stimulus is a phenomenon found in peripheral neuropathies.

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Troxidone (Trimethadione) Embryopathy: Case Report with Review of the Literature

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There has been an increasing number of reports of an association between the taking of anticonvulsant drugs and the birth of defective babies. Wilson (1977) was able to list some 35 reports covering 1700 births to women given drug therapy to control seizures during all, or most of, pregnancy. The authors of several surveys have concluded that the malformation rate among births to epileptic women is at least twice that expected in comparable non-epileptic women. Lowe (1973) in Wales found 111 epileptic mothers not on anticonvulsants during pregnancy produced no more defective babies (2.7%) than did non-epileptic controls, whereas 6.7% of the infants of a group of epileptic mothers on anticonvulsants were malformed. Monson et al. (1973) quoted a malformation rate for offspring of epileptic mothers on phenytoin throughout pregnancy of 6.1% (in contrast to the malformation rate in children of non-epileptic women of 2.5%). Rat, mouse and primate studies all have shown dysmorphogenic effects of phenytoin at plasma levels 2 or 3 times therapeutic ones.

Troxidone (trimethadione) and paramethadione have also been reported as having teratogenic effects in man. German et al. (1970) reported cardiac defects in 4 of 14 infants whose mothers had received troxidone in the first trimester of pregnancy. 8 of the 14 had facial abnormalities and there were 3 spontaneous abortions and 3 healthy offspring. In 1 mother after cessation of troxidone the 5th and 6th pregnancies resulted in healthy children, 3 earlier babies having died in infancy of major development defects, and 1 having survived despite defects. In another family a 6th baby, conceived after withdrawal of paramethadione, was the only normal child.

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Nichols (1973) reported facial, abdominal, cardiac and spinal defects in an infant whose mother had taken troxidone for several years. Tsun Yu and Stiles (1975) described a persistent 5th aortic arch in the child of a woman on troxidone. Zachai et al. (1975) reported 7 offspring of 3 mothers taking troxidone during most of their pregnancies and postulated a 'fetal trimethadione' syndrome; this was said to consist of mild mental retardation, speech difficulties, V-shaped eyebrows, low-set ears, palatal anomalies and abnormal teeth, with or without growth retardation, congenital heart disease, microcephaly and ocular anomalies.

The problem of aetiology is bedevilled by the facts that many of the mothers had been taking additional anticonvulsants as well as troxidone and that the clinical syndrome described has been thought by many authors to merge into those described in the offspring of mothers treated with phenytoin and/or barbiturates.

Wilson (1977) reported 1 instance of malformation and 2 abortions in the offspring of 16 pregnant rhesus monkeys treated with 2 to 3 times normal adult human doses of troxidone in contrast to his finding of only 6 normal fetuses amongst the offspring of 17 phenytoin-treated pregnant rhesus monkeys. Poswillo (1972) failed to produce malformations in the offspring of 6 cynomolgus monkeys, *Macacas Irus,* treated in early pregnancy with troxidone or paramethadione, although 2 animals became very drowsy and ataxic and pregnancy ceased, the embryo being resorbed in both. Pashayan et al. (1971) reported the normal younger sibling of an affected child conceived while the mother was taking phenytoin. The second child was born normal despite the mother taking troxidone throughout the pregnancy, suggesting that the dysmorphogenicity risk of troxidone was less than that of phenytoin.

Feldman et al. (1977) reported a family where 7 pregnancies during which the mother was taking troxidone, barbiturates and acetazolamine resulted in 4 children with multiple congenital anomalies and 3 spontaneous abortions. After withdrawal of all medication, including troxidone, 2 normal children were born. There was no increase of fit frequency during these last 2 pregnancies. 2 of the infants had died within hours of birth with patent ductus combined with septal defects and in 1 there was a hypoplastic aorta with stenosed thoracic aorta. A third also had a patent ductus, but survived for 8 months. 3 had tracheo-oesophageal defects. These authors reviewed reports of 53 pregnancies where conception occurred with the mother taking troxidone alone (8 cases) or with other medication. 13 pregnancies aborted, while 33 of the 40 survivors (86%) had at least one major congenital anomaly, leading to 14 deaths. Only 7 (17%) had no apparent major congenital defect. There was a tendency to intrauterine growth retardation, to malformed or low-set ears, cleft lip or palate, tracheo-oesophageal defects, and to complex congenital heart defects (frequently with patent ductus arteriosus, septal defects and aortic arch anomalies). It should be borne in mind that, as far as the cases of Feldman et al. (1977) are concerned, acetazolamide is itself a known teratogen, although characteristically it produces its effects on the forelimb rather than in the face and heart, as occurred in the cases these workers reported.

Case History

Mrs J.B. was a third child, born rather precipitately, in 1951. She was slow to speak, but her motor milestones were normal. Self-induced photic epilepsy with repetitive blinking began at the age of 8 years, and occasional major convulsions began at 11. One such episode ushered in by self-induced spells at the age of 15 years lead to falling with loss of consciousness which lasted for 20 minutes. EEG showed generalised bursts of chiefly 3Hz spike and slow wave complexes with occasional phase reversals in the left temporal region. Ethosuximide made her dizzy and troxidone was therefore given combined with phenytoin sodium. There was reduction but not abolition of the self-induced attacks. Paramethadione and carbamazepine (800mg daily) were therefore substituted with increased alertness, but after 2 further major convulsions, both clearly preceded by poor compliance, 1500mg troxidone daily was substituted for the paramethadione.

Albuminuria was detected at the age of 17 years and confirmed on subsequent occasions, an elevated blood pressure being detected at the age of 20, mild mesangial proliferative glomerulonephritis being detected on renal biopsy 2 years later. Propranolol 30mg 3 times a day was started in March, 1975, with later dose increases to 80mg thrice daily.

Some spells continued on rare occasions, often precipitated by overtiredness. Some were characterised by post-ictal automatisms or expressive speech difficulties. A further major episode in October, 1977 led to arrangements being made to substitute sodium valproate for the troxidone, but the patient demurred. In August, 1978 the patient reported herself as 4.5 months pregnant and continuing to have occasional minor blinking spells, which had culminated in a major convulsion ushered in by an expressive dysphasia. This had precipitated her return for review. Fetal retardation and falling oestriol levels led to elective Caesarian section 7 weeks before term. The baby's birth weight was 1.270kg with an Apgar score of 6, 7. The baby required bag and mask resuscitation at birth. The baby was dysmorphic with facial asymmetry and small misshapen ears with a down-folded upper helix (figs. 1 and 2). At 2 weeks of age cardiac failure led to investigation of a suspected congenital heart lesion. There was cardiomegaly with gross pulmonary congestion, an enlarged right ventricular outflow tract and a loud pulmonary second sound. Cardiac catheterisation showed pulmonary hypertension, a patent ductus arteriosus, a large aorto-pulmonary window and an interrupted aortic arch, the left subclavian artery arising proximally with no continuity with the descending thoracic aorta which itself was continuous with the left pulmonary artery. There was a moderate amount of aortic regurgitation and a dilated ascending aorta with a large aorto-pulmonary window producing a left to right shunt and filling of an enlarged pulmonary artery with pulmonary plethora, and rapid filling of the descending aorta through a patent ductus arteriosus.

After several episodes of pulmonary oedema, on 26 February 1979 a clip reducing the size of the aorto-pulmonary window was inserted when the patent ductus was tied and the left subclavian artery was anastomosed to the thoracic aorta.

Discussion

The patient's first child shows defects which resemble in many respects those described by German et al. (1970) and more recently by Feldman et al. (1977) in the offspring of mothers who have received either troxidone or paramethadione. It should be noted however, that in the series of Feldman et al. (1977) as well as phenobarbitone, acetazolamide, itself a teratogen, was being taken. However reports would suggest that the principal effect of acetazolamide is usually on forelimb development. The case here reported was a hypertensive of some standing, with known renal damange, and had been taking propranolol for 3.5 years and car-

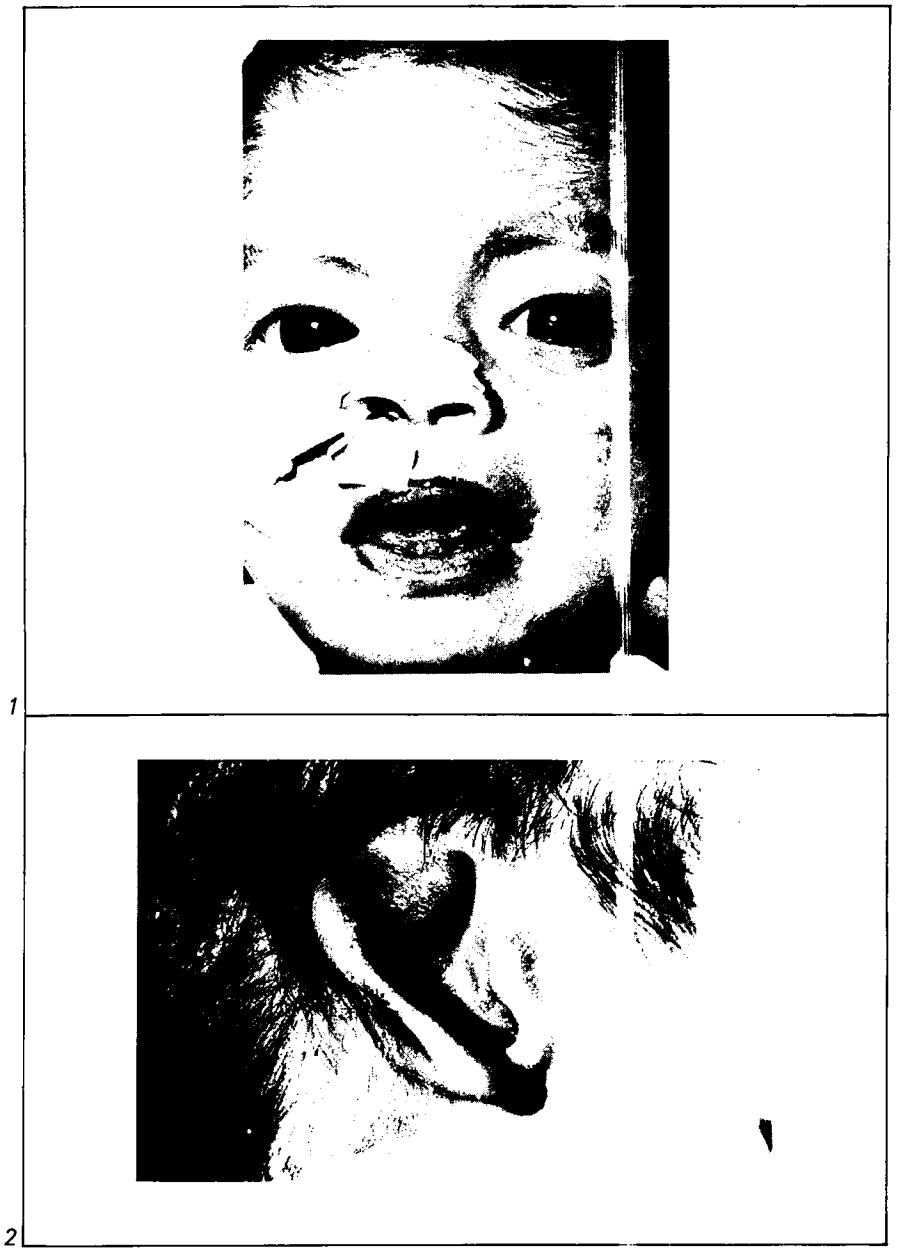

Fig. 1. Baby B. Full face view.

Fig. 2. Baby B. Lateral view of face to show lowslung deformed ears.

bamazepine for a decade, both drugs being continued during the pregnancy. Despite these possibly relevant facts and complicating circumstances, and despite Poswillow's (1972) failure to demonstrate teratogenicity from troxidone in monkeys, the presumption that the embryopathy in the present case is the consequence of the continued use of troxidone in the first trimester of pregnancy seems almost certainly to be correct.

It is a matter for speculation whether the substitution of sodium valproate for troxidone, which was suggested to the patient some 6 months before conception occurred, would have led to a happier outcome. Jeavons (personal communication, 1979) has knowledge of some 16 pregnancies successfully concluded whilst the mother continued to take sodium valproate, but so far the evidence for the non-teratogenicity of sodium valproate in pregnancy remains largely anecdotal.

Summary

It has long been known or suspected that phenytoin and probably phenobarbitone prescribed in pregnancy may lead to fetal malformations.

The use of troxidone for epileptic women during pregnancy was reported in 1970 to lead to malformations. Over 50 instances of pregnancy in women taking troxidone have since been reported. In 8 of these the drug was used alone. 13 pregnancies resulted in abortion and 33 of the 40 survivors had a major congenital anomaly, leading to death in 14. Complex congenital heart lesions with patent ductus, septal defects and aortic hypoplasia were apparent in half the survivors. Malformed or low-set ears were seen in nearly half the cases, palatal deformities were less common and evidence of intrauterine growth retardation was frequently present.

A 29-year-old mother taking troxidone and carbamazepine, and with a history of hypertension and proteinuria dating back to adolescence, delivered her first child prematurely. The child was small, showed deformed ears, displayed feeding problems and was found to be in cardiac failure with a systolic murmur and absent femoral pulses. Postnatal growth was retarded and after further cyanotic attacks a cardiac catheter study was performed. This showed a hypoplastic aortic arch with an anomolous origin of the left subclavian artery and patent ductus arteriosus, findings similar to those previously reported in neonates following maternal use of troxidone.

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Two-dimensional Echoencephalography in Paediatric Neurology

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Two-dimensional ultrasonography is a rapidly expanding area of medicine, resulting from the application of advances in computer technology. Echoencephalography as a diagnostic tool has proved somewhat disappointing in adult neurological practice, as the thickness of the skull acts as a barrier to the passage of ultrasound. However, in infancy, the thin skull permits sufficient passage of ultrasound to delineate major tissue interfaces within the skull. Two-dimensional echoencephalography in infancy permits the delineation of interfaces between brain tissue and fluid e.g. ventricular walls, cyst walls, major cerebral fissures, etc. Maximal reflection of echoes take place when the tissue interface is at right angles to the direction of the ultrasonic beam, which is the situation in hydrocephalus.

Two-dimensional echoencephalography has been in use for a number of years in the diagnosis of hydrocephalus and congenital structural malformations of infancy. Lombroso et al. (1968), Valkeakari (1973), and Garrett et al. (1974), have made significant contributions in this field in recent years.

The Adelaide Children's Hospital acquired a Unirad two-dimensional echo-scanner in 1976, and this paper reports our experience with this instrument, over a period of 18 months, in the investigation of infants and young children with suspected congenital malformations of the central nervous system.

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Methods

The Unirad contact scanner is used with a transducer of 13mm diameter, which generates ultrasound at a frequency of 3.5MHz. Optimal focus is achieved between 4 and 8cm from the transducer, a distance which approximates the midline to far-side of the infant's skull. Scanning is performed with the infant in a lighly sedated state, and is carried out initially from the left side of the head, and then from the right side. The operator technician moves the transducer in a compounded linear and arc motion across the head surface, which is covered with coupling gel to reduce the air-tissue interface at the head of the transducer. The transducer sweeps in a series of horizontal and coronal planes, using the external auditory meatus as a reference (fig. 1). The transducer also functions as a receiver of reflected echoes and the pattern of echoes received is fed into a computer, which portrays the result of each sweep as a two-dimensional pattern on an oscilloscope screen. The pattern thus displayed is photographed on polaroid film to provide a permanent record.

For purposes of comparison with previous or subsequent studies, certain measurements are routinely made on the two-dimensional pictures. First, we measure the width of the bodies of the lateral ventricles, just anterior to their point of lateral divergence at the atria (X), and secondly measure the width of the cerebral hemisphere at that point (Y) [fig. 2]. We express the ratio of X to Y as the lateral ventricular index. We also measure the width of the third ventricle. The position of the third ventricle mid-line echo is determined where possible by A-scan technique.

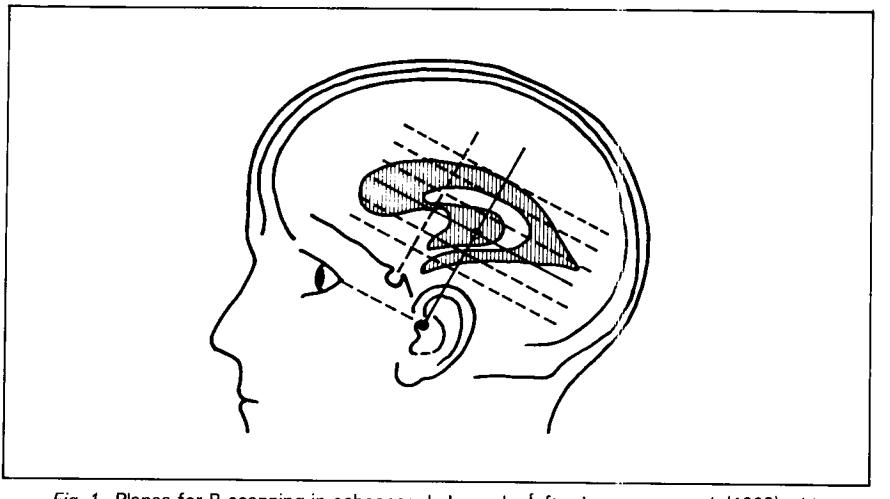


Fig. 1. Planes for B scanning in echoencephalography [after Lombroso et al. (1968) with permission of the editor].

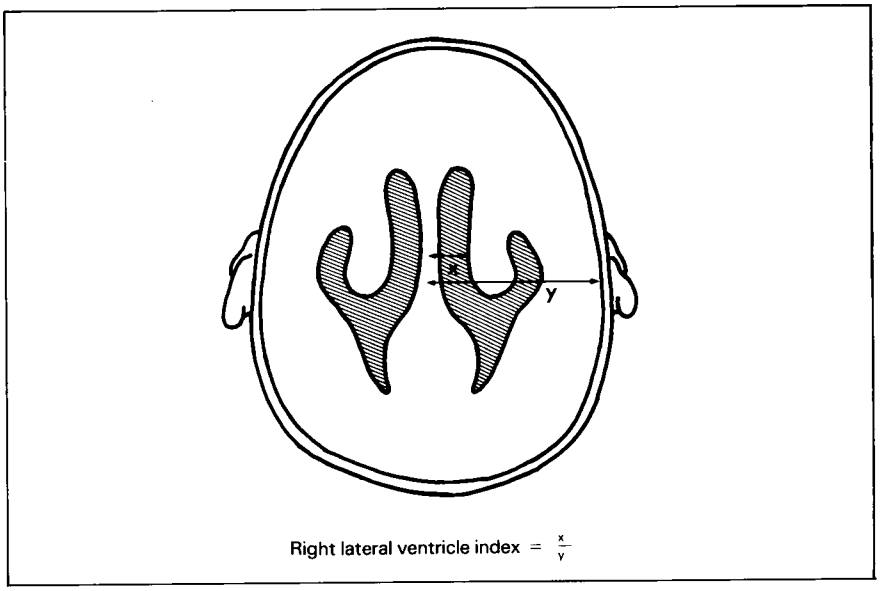


Fig. 2. Method of calculating the lateral ventricular index.

Results

Table I shows the results of the first 100 scans. Table II shows the breakdown of diagnoses in the miscellaneous group.

We tested the validity of the procedure in the diagnosis of hydrocephalus by selecting those hydrocephalic patients, and patients suspected of hydrocephalus, in whom both the two-dimensional echoencephalogram and a more definitive neuroradiological study (either CAT scan or air ventriculogram) had been performed at about the same time. We then applied a scoring system to the echo-scans, and to the radiological study, as follows: each echo-scan, or radiological study, was assigned zero points if it was considered normal, 1 point if it was borderline normal, 2 points if the ventricles were mildly dilated, 3 points if moderately dilated, and 4 points if severely dilated. The x-ray studies and echo-scans were scored independently, with the observer for one test being unaware of the result of the other test. Each individual patient was assigned a points difference score, which represented the difference between the points scored for the echo-scan and the points scored for the radiological study. The lower the points difference score, the closer the correlation between echo-scan and x-ray results for that patient.

Table III shows the close correlations between the results of echo-scan and neuroradiology in the 29 patients we have studied so far in this manner.

Table I. Results of echoencephalography in the first 100 patients

Diagnosis	No. of patients
Normal	44
Hydrocephalus	34
Miscellaneous	10
Cerebral atrophy	9
Unsatisfactory	3

Table II. Echoencephalogram diagnoses in the miscellaneous group of patients (table I)

Diagnosis	Number
Microcephaly	1
Hydranencephaly	1
Holoprosencephaly	1
Cystic astrocytoma	1
Undiagnosed abnormalities	2
Dilated ventricles of unknown cause	3
Mid-line shift of unknown cause	1

Table III. Close agreement between ultrasound and radiological findings in 29 patients with hydrocephalus (see text for scoring system)

No. of patients	Points difference score
21	0
8	1
0	> 1

Table IV. Comparison of CAT and the echo-scan in paediatric neurology

Feature	CAT	Echo-scan
Anatomical detail	Excellent	Fair
Anaesthesia	Required < 6 years	Not required
Value in infancy	Suboptimal	Optimal
Hazards	? 5-10 rads	None documented
Repeatability	Cumulative toxicity	Toxicity not documented
Availability (paediatric and obstetric units)	Poor	Good
Future technology	Stable	Expanding

A series of illustrative echo-scans is shown (figs. 3-12) in which the left side of the picture represents the anterior region of the head and the lower margin the right side of the head.

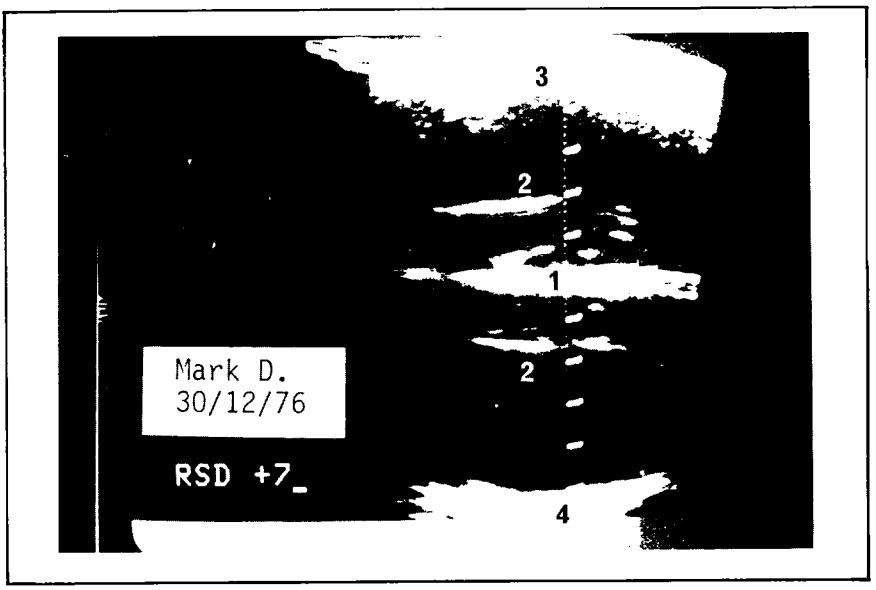


Fig. 3. A normal 6-month-old infant. Transverse scan 7cm above the external auditory meatus (EAM). There is a central mid-line echo from the falx and the inter-hemispheric fissure (1). Symmetrically, on either side, are echoes from the walls of the lateral ventricles (2), which are diverging posteriorly. Echoes are seen from the transducer head on the left side of the skull (3), and from the inner table of the right side of the skull (4).

Fig. 4. The same infant as fig. 3; scan 5cm above the EAM. The superior part of the third ventricle is visualised in the mid-line (5). Anteriorly to this is a triple echo, representing the lateral walls of the anterior horns (6), and the septum pellucidum centrally (7). Posteriorly are the occipital horns (8), and the inter-hemispheric fissure (9). The thalamic nuclei are also suggested but not clearly defined (10).

Discussion

On the basis of our experience so far, we would suggest that two-dimensional echoencephalography is most likely to be of benefit in the following clinical situations:

1) Screening for hydrocephalus in infants with unusually large heads
2) Investigating infants with developmental delay or neurological abnormalities, where the possibility of cerebral malformation is suspected
3) Monitoring the progress of established hydrocephalus in infants before and after shunting.

It should be added that we do not have much faith in the ability of this technique in our hands to detect mass lesions such as tumours, haematomas, and abscesses,

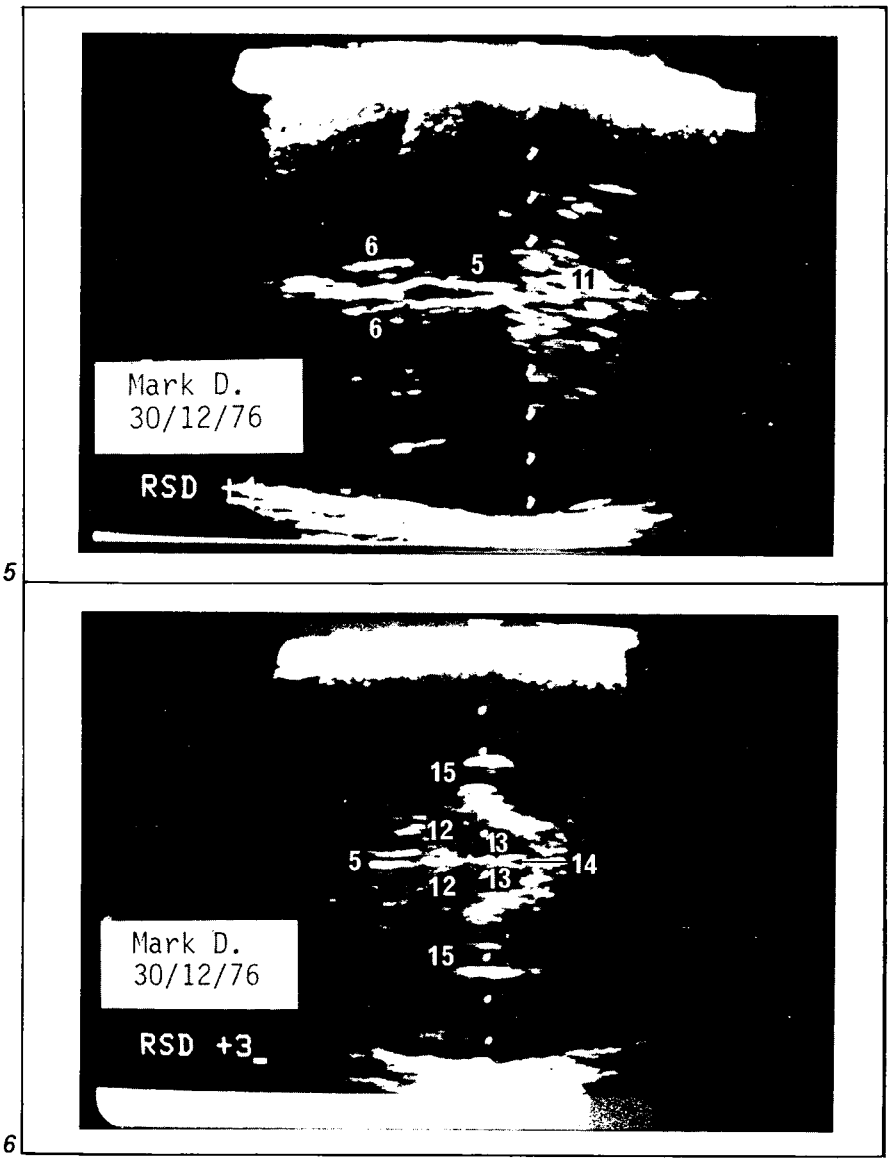
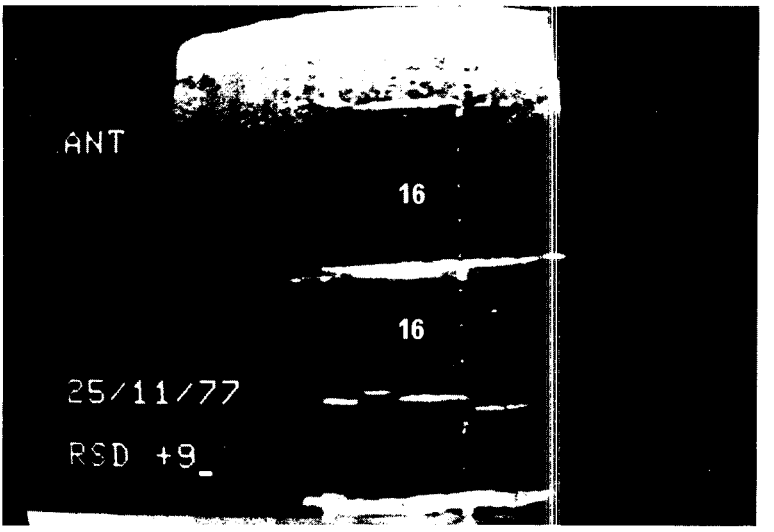


Fig. 5. A scan 4cm above the EAM in the same infant, at the level of the third ventricle (5). Echoes from the inferior portions of the frontal horns (6), and from the pineal region (11), are visible.

Fig. 6. A scan at 3cm above the EAM in the same infant, at the level of the mid-brain. The cerebral peduncles (12), and the superior corpora quadrigemina (13), are well defined. Echoes from the third ventricle (5), and the aqueduct of Sylvius (14), can also be seen. The temporal horns can be seen laterally (15).



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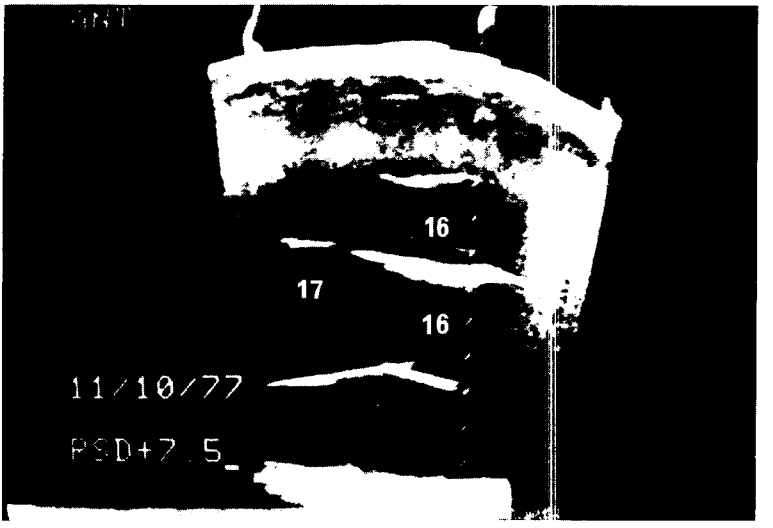

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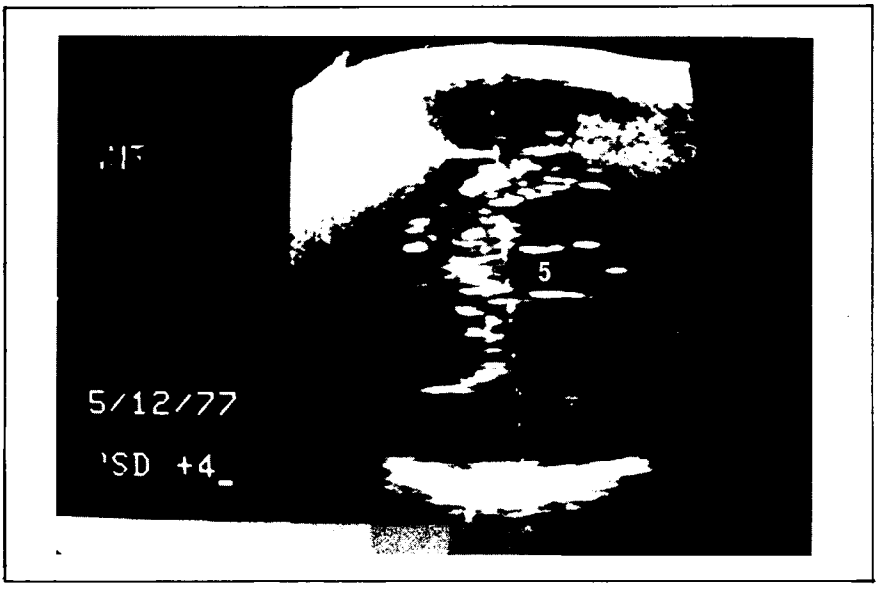

Fig. 9. Transverse scan of an infant with a meningomyelocele who was not overtly hydrocephalic. The scan was taken 4cm above the EAM and shows the widely dilated third ventricle (5), measuring 15mm in diameter.

because such lesions are sufficiently similar to brain tissue in their ultrasonic reflection properties to pass undetected, except insofar as they may shift the mid-line, or produce distortion and dilatation of the lateral ventricles.

Finally, it is relevant to question the future role of this investigation, in the face of technological advances in x-ray computerised axial tomography (CAT). Table IV lists the relative advantages and disadvantages of the two procedures. Our view is that the two procedures may well be complementary in paediatric neurology of the future. The echoencephalogram may be safer and more informative in the young infant, whilst CAT will be more useful, and also more technically feasible, in the older child.

Fig. 7. Transverse scan taken 9cm above the EAM of a 3-year-old boy who presented with a spastic triplegia, and a large head. The echoencephalogram showed marked dilatation of the lateral ventricles (16), more so on the left side.

Fig. 8. Transverse scan taken 7.5cm above the EAM in a 3-month-old infant with multiple congenital abnormalities and a large head. The echoencephalogram shows dilatation of both lateral ventricles (16), particularly the right one, which had a marked degree of dilatation of the frontal horn (17). This localised dilatation of the right frontal horn was also confirmed by CAT scan.

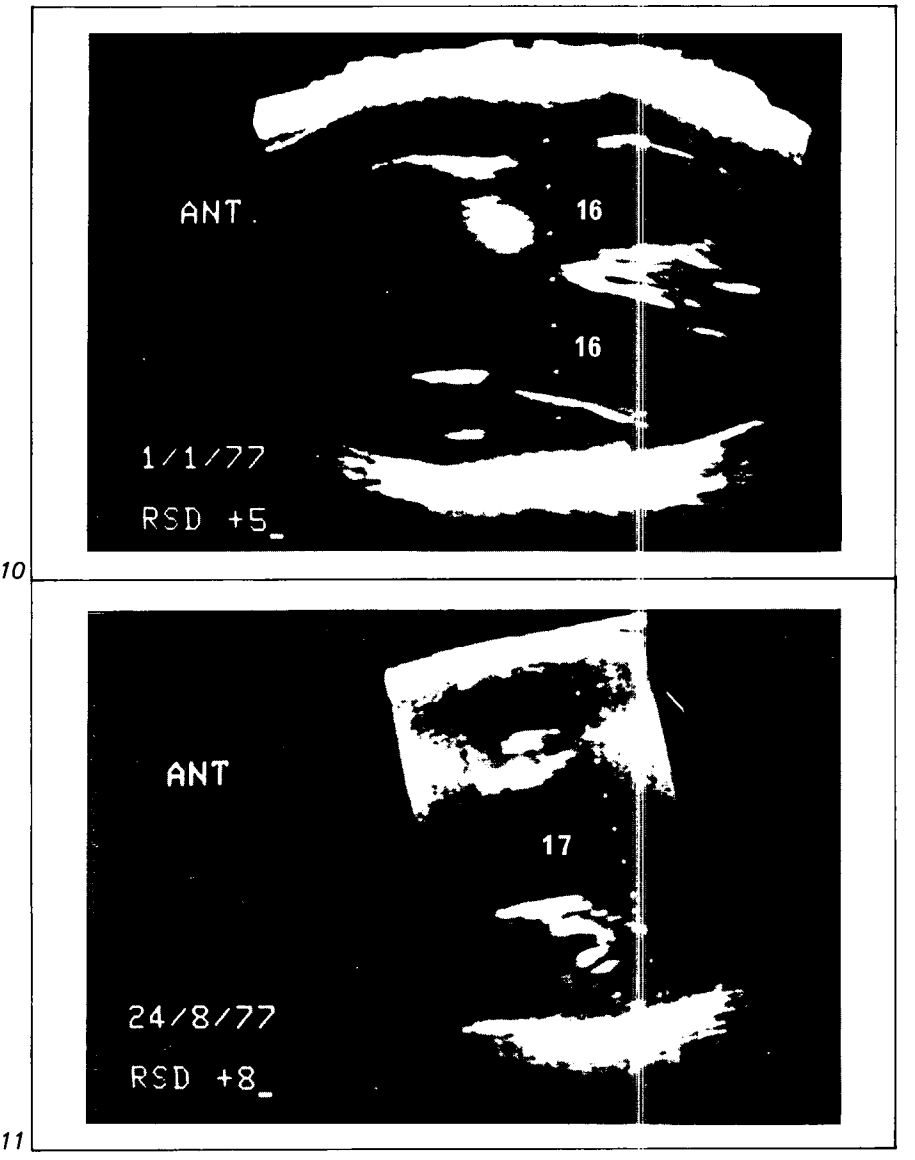

Fig. 10. Echoencephalogram of a 4-week-old spina bifida infant with hydrocephalus. The lateral ventricles (16) are markedly dilated, and they fuse anteriorly, the septum pellucidum being absent.

Fig. 11. Echoencephalogram of an 8-month-old infant who presented with infantile myoclonic seizures. A large mid-line cavity with absent mid-line structures was displayed (17). The air encephalogram revealed holoprosencephaly with a mid-line single ventricle.

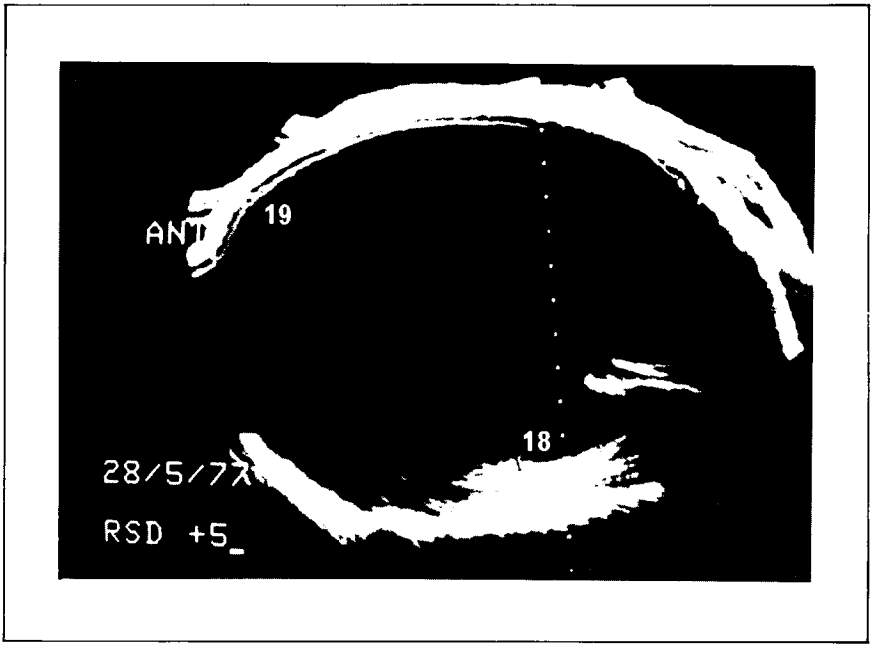

Fig. 12. Echoencephalogram of a grossly hydrocephalic infant with only 1cm thickness of right parietal cortex (18), and a fine ribbon of cortex on the left (19).

Summary

Two-dimensional echoencephalography is a useful procedure in screening young infants for hydrocephalus and cerebral malformation. The procedure is noninvasive and easily repeated. The procedure is less reliable in detecting mass lesions except insofar as they disturb the anatomy of the ventricular system. The procedure can be considered as complementary to computerised axial tomography in the investigation of cerebral anatomy in paediatric neurology.

Acknowledgements

We would like to acknowledge the active encouragement and support of Mr D.A. Simpson and Dr Lloyd Morris. We wish to express our gratitude to Miss June Schroeder for the technical work, and to the Department of Photography at The Adelaide Children's Hospital for the preparation of the illustrations.

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Carbamazepine in Two Pregnancies

*E.P. Hicks**

The combination of pregnancy with epilepsy produces a conflict between the interests of the health of the mother and her child. Current neurological practice demands control of the epilepsy except in the mildest cases (Eadie and Tyrer, 1974; Eadie, 1976). It is well known that anticonvulsants such as phenytoin and the barbiturates may double the risk of fetal malformation, and that epilepsy itself and possible genetic factors associated with epilepsy may also play a part (Federick, 1973; Meyer, 1973; Eadie and Tyrer, 1974; Starreveld-Zimmerman et al., 1974; Bodendorfer, 1978). Investigation of such problems is difficult because of the relative rarity of pregnancy with epilepsy. This is stated to lie between 0.1 and 0.4 % (Bodendorfer, 1978).

Carbamazepine was synthesised in 1957 (Gagneux, 1976), and has been in clinical use since 1962. As a teratogen it has been variously regarded as having little risk, (Eadie, 1976), as being acceptably safe (Meyer, 1973; Starreveld-Zimmerman et al., 1973, 1974), and as being without any documented effects (Bodendorfer, 1978). However on re-examination of the literature one finds that carbamazepine in combination with phenytoin and barbiturate resulted in 1 case of fetal malformation (Fedrick, 1973). In another series, 50 cases of carbamazepine combination therapy in the first trimester have been reported with no fetal abnormality, with 1 stillbirth which was not related to the therapy; Starreveld-Zimmerman et al. (1974) reported 1 case of carbamazepine therapy which resulted in a normal child. In the same series a further 3 cases of normal offspring were quoted from the German literature of Hagen

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and a personal communication from Sonnen was cited in which atresia of the anus developed in the child of a carbamazepine-treated mother. In another study, 2 malformations were found in 199 children of mothers on combination carbamazepine therapy (Meyer, 1973). One of these had a refractive error and the other a club foot.

This information constitutes the basis upon which the present approach to the use of carbamazepine in pregnancy has been formulated. This report is submitted with the intention of augmenting the literature on carbamazepine therapy in pregnancy.

Patients and Methods

2 patients were available for study. In both the epilepsy was judged to be of sufficient severity to justify the use of an anticonvulsant during pregnancy, in accordance with standard neurological practice at the relevant times. A clearly defined period of therapy with carbamazepine was identifiable and monotherapy was practised in each case, except during brief changeover periods which did not overlap the monotherapy sections of this study. Both cases were private patients of consultant obstetricians.

Case Histories

Case 1

Mrs M.A.A., a housewife aged 33 years, experienced a nocturnal generalised seizure in September, 1976. 12 hours later, after an aura of faintness, she had another generalised seizure. She was at that time at 10 weeks' gestation in her second pregnancy. The EEG demonstrated a sharp wave focus in the left temporal area. She was treated with phenytoin 30mg thrice daily, increasing to 100mg twice daily after a few days. In retrospect it was apparent that she had suffered previously from episodes of vagueness, blinking of eyelids and momentary lapses of awareness without falling. She was not aware of these episodes which were reported by her husband. The exact date of their onset could not be determined.

No abnormalities were found on examination, and the pregnancy continued uneventfully until fetal movements ceased at 34 weeks of gestation. She was delivered of a macerated female child who, on external examination and on subsequent autopsy on 28 February, 1977 failed to demonstrate any congenital abnormalities. The cause of death was intrauterine asphyxia.

She remained free from seizure activity on phenytoin. However, on 12 April, 1977 she notified her intention of having a third pregnancy. A change of anticonvulsant to carbamazepine was made because of its low teratogenic risk (fig. 1). Carbamazepine was started with a dose of 100mg 4 times daily. On 26 August, 1977 her serum carbamazepine level was 18μmols/litre.

On 24 October, 1977 Mrs A. reported that her last menstrual period started on 18/8/77. The date of conception was estimated to lie between 1 and 14 September, 1977. She agreed to continue carbamazepine, but 6 months later revealed that she stopped this medication on or about 26 October, 1977. The pregnancy proceeded normally until 24 February, 1978 when fetal death in utero was confirmed and delivery was effected on 27 February, 1978 at 25 weeks of gestation. The female fetus was grossly deformed. The autopsy results are recorded in table I. The chromosomes of both parents were normal but maceration precluded evaluation of fetal chromosomes. Analysis of formalin-fixed tissue blocks failed to identify carbamazepine in either the tissue or the formalin.

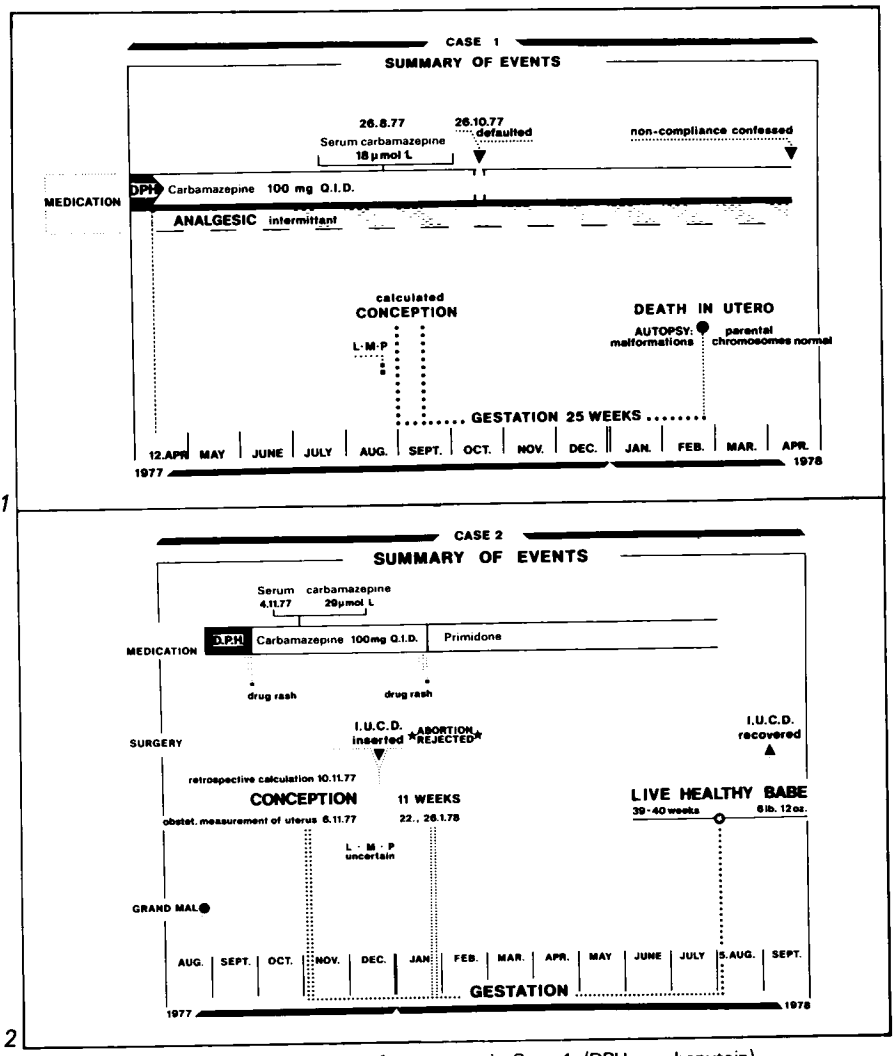

Fig. 1. Summary of main events of pregnancy in Case 1. (DPH = phenytoin).

Fig. 2. Summary of main events of pregnancy in Case 2. (DPH = phenytoin).

With the exception of very occasional compound analgesic powders containing paracetamol 250mg, aspirin 500mg, and caffeine 150mg, for the relief of severe headaches, she had taken no drugs other than carbamazepine during this pregnancy.

A review of her medical history indicated occasional fainting attacks from the age of 12 years, and intermittent migraine headaches from the age of 17 years, one of which was accompanied by transient numbness of the right arm. She had a mild attack of gouty arthritis in the right great toe at the age of 26

Table I. Results of autopsy examination of fetus in case 1

Body characteristics	Weight 522g, crown/rump length 20.5cm, crown/heel length 30.5cm
External examination	Eyes closely set. Flat, poorly developed nose with single central opening into nasopharynx which was also poorly developed. Mouth small. External genitalia small. An extra digit was present laterally on each foot. Fingers partly fused
Cardiovascular	Large inter-atrial septal defect of primum type. Widely patent ductus arteriosus
Respiratory	Larynx not identified. Poorly developed tracheal rings
Gastrointestinal	Proximal oesophagus absent. Distal oesophagus ended blindly in inferior mediastinum. Malrotation of small and large bowel. Caecum at splenic flexure
Biliary	No gallbladder could be identified. Liver autolysed
Urinary	Fetal lobulation of kidneys was marked
Genital	Uterus and ovaries small but normal
Endocrine	Pituitary not identified. No thyroid identified in neck
Haemopoietic	Thymus and spleen normal
Musculo-skeletal	Sternum sunken. Non-fusion of anterior mandible. Muscles normal
Central nervous system	Anterior fontanelle collapsed. Posterior fontanelle intact. Falx cerebri absent. Tentorium cerebelli absent. Meninges poorly developed. Posterior cranial fossa shallow. Brain autolysed

years. In 1972 a healthy male child was delivered by Caesarean operation because of her contracted pelvis. The family history was unblemished except for a great-aunt who suffered epileptic fits, and a grandfather who had gout. Mr A's family history was completely healthy.

Case 2

Mrs A.N.R., a 26-year-old housewife, suffered a nocturnal generalised seizure on 28 August, 1977. An EEG demonstrated a left temporal lobe sharp wave focus. Her husband confirmed that she had suffered intermittent dreamy states of brief duration during the previous 7 years of marriage. Prophylactic phenytoin was started at a dose of 100mg in the morning and 200mg at night. This was withdrawn after 4 weeks because of the development of a skin rash. On 30 September, 1977 carbamazepine was substituted at a dosage of 100mg 4 times daily. On 27 October, 1977 she was reported to be well and on 4 November, 1977 her serum carbamazepine level was 29μmols/litre (fig. 2).

On 24 January, 1978 she reported that she was pregnant for the fourth time, having lost an intrauterine contraceptive device, which had been inserted on 12 December, 1977. The date of the last menstrual period was uncertain but uterine size suggested a gestation of about 11 weeks. She considered termination of pregnancy at this time, but decided to accept all risks knowing that she had conceived while taking carbamazepine. At the same time as these events she developed an exfoliative dermatitis of the palms and soles and carbamazepine was withdrawn on 24 January, 1978. Primidone was substituted at a dose of 250mg morning and evening.

On 5 August, 1978 she delivered a live male child weighing 6lb 12oz. A paediatrician confirmed that the baby was normal. Subsequent progress of mother and child, including 2 months of breast feeding, has been normal. The missing intrauterine device was recovered surgically after delivery of the baby. Retrospective calculations based on the maturity of the baby suggested that the date of conception was 10 November, 1977.

The medical history revealed that Mrs R. was born 2 months prematurely and suffered an acquired congenital deformity of the right side of her body with a shortened right leg and associated signs of a left hemisphere cerebral palsy. She had had 3 previous pregnancies. The first 2 were normal with living children, but the third pregnancy produced a male child which failed to thrive and at the age of 8 months was found to have signs of congenital heart disease. This child died at the age of 12 months on 9 June, 1976 some time after corrective surgery for ventricular septal defect. The family history was not helpful.

Discussion

There are many similarities in these cases. The epilepsy was similar in duration, type and focal characteristics. With the exception of a great-aunt with epilepsy in Case 1, there was no family history of epilepsy. Carbamazepine therapy resulted in complete control of the epilepsy in both cases. No seizures were reported in either woman's pregnancy. Both were on carbamazepine before and after conception — Case 1 for approximately 60%, and Case 2 for 68% of the duration of the first trimester. Both cases received the same dosage of carbamazepine, namely 100mg 4 times daily. Both cases had previously suffered loss of offspring. The first loss for Case 1 occurred during phenytoin therapy. However, Case 2 was not on any medication during her third pregnancy which resulted in the postnatal loss of her child from congenital heart malformation. Neither case could be regarded as in the old age group from the obstetric point of view, but it is noted that increasing maternal age is associated with an increase of obstetric complications, stillbirths and fetal malformations (Janz, 1975). Nevertheless, it is conceded that there is a relative age difference in these mothers. It is also noted that carbamazepine readily passes the placenta and enters the cerebral cortex, heart, liver and kidneys of the fetus. Carbamazepine is also detectable in breast milk at the level of 60% of the corresponding plasma value (Pynnonen, 1977).

There are, however, some differences in these cases. The most striking is the difference in the result of the pregnancies. Case 1 produced a macerated malformed stillbirth despite serum carbamazepine levels of 18μmols/litre, and Case 2 a normal infant in the presence of 29μmols/litre of serum carbamazepine.

However, it is recognised that some malformations, including atresias of the ureter and ventricular septal defects, may not become manifest until much later in life. Similar considerations apply to mental and growth retardation (Annegers et al., 1974). Case 1 was on carbamazepine for 5 months prior to conception, but for Case 2 therapy lasted for only 6 weeks. This could raise the suspicion that prolonged priming had a connection with the unhappy outcome of Case 1. Furthermore, Case 1 had previously had a stillbirth (not malformed), while taking phenytoin. Finally, Case 1 had also been exposed to intermittent doses of a relatively potent non-prescription compound analgesic during the first trimester, and this may have set up a drug interaction as postulated by Bodendorfer (1978).

Experience with these cases has made it clear that absolute compliance with therapy can never be guaranteed and that for various reasons the use of additional non-prescription medications may be overlooked. Only personal supervision of such cases is likely to provide this information.

The unfavourable outcome of Case 1 may possibly have been the result of a mutant genetic factor. Normal chromosome studies of the mother and the father tend to dismiss such a possibility unless it is considered to be drug-enhanced or induced in the mother after conception. Indeed, such a possibility may have no connection of any kind with carbamazepine.

The conclusions drawn from this study are that carbamazepine is a drug of low risk for fetal malformation, but that extreme caution is required when dealing with subjects whose obstetric history contains stillbirth, malformations or difficulties in pregnancy and labour. This appears to be more important in the slightly older subject. Therefore, the minimal effective dosage should be ensured by careful monitoring of carbamazepine blood levels during pregnancy. Finally, it is clear that in some instances non-treatment of epilepsy could be preferred, since no differences in the malformation rates could be statistically validated when control normal populations were compared with untreated mothers with epilepsy (Starreveld-Zimmerman et al., 1974; Janz, 1975; Bodendorfer, 1978).

Unfortunately specific information regarding carbamazepine in this context is not yet available, and pooling of such data will continue to be required.

In the meantime, there does not appear to be any compelling reason to withhold carbamazepine in uncomplicated pregnancies because fetal hazards, as documented in the literature, are of a very low order.

Summary

2 patients with epilepsy in pregnancy are described. Both received carbamazepine prior to conception, and during the greater portion of the first trimester. Both had partial and generalised epilepsy of late onset.

Case 1 resulted in stillbirth at 25 weeks' gestation. The malformations included closely set eyes, atresia of multiple hollow viscera, and non-fusion of the mandible without hare lip or cleft palate. A possible interaction with a compound analgesic is discussed.

Case 2 resulted in a normal baby.

The literature, although favouring carbamazepine in pregnancy, is not yet sufficiently decisive to indicate a clear preference between no treatment and carbamazepine with carefully monitored serum levels for epilepsy in pregnancy.

This study emphasises the need for continued pooling of data, and for added caution when there is a history of fetal malformation or obstetric problems.

The teratogenicity of carbamazepine is neither confirmed nor denied by this limited study.

Acknowledgements

Grateful thanks are given to Dr Roger Hutton and Dr Eric Green for obstetric services and access to their patients, Cases 1 and 2 respectively. Thanks are also due to Dr A Holoyda, who performed the autopsy in Case 1 at the Department of Pathology, Modbury Hospital. Valuable clerical assistance was provided by Mrs M. Frank, Neurology Secretary, The Queen Elizabeth Hospital. The helpful criticism of Dr R.H.C. Rischbieth and the complete cooperation of the Ciba-Geigy company are recorded with pleasure.

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Lepromatous Leprosy as a Model of Schwann Cell Pathology and Lysosomal Activity

*D.K. Dastur and G.L. Porwal**

It is now well recognised that leprosy is not just a tropical disease, an infectious disease, or a dermatological disorder, but is probably the most common peripheral nerve disorder in the world, with at least 15 million persons affected (Dastur, 1956). According to a recent bulletin of the American Leprosy Missions, leprosy produces more hand paralysis than all other diseases put together. In tuberculoid leprosy the nerve changes occur earlier and are more severe than in the lepromatous variety which, worldwide, is much less frequent, the tuberculoid variety accounting for over two-thirds of all leprosy patients. It may be recalled that these two types differ in the degree of bacillation with *Mycobacterium leprae* (enormous numbers being found in the skin and nerves in lepromatous leprosy), in the host's cell-mediated immunity (well developed in the tuberculoid variety), and in the response to chemotherapy (poor in the lepromatous type). In fact, these two forms of leprosy almost constitute two separate diseases (Dastur, 1977).

That the Schwann cell is one of the target cells, if not *the* target cell in leprosy, has been recognised since the mid 1960's when light microscopic studies on peripheral nerves were carried out by investigators in different parts of the world (Dastur, 1967; Weddell, personal communication). The role of the Schwann cell as then understood was exhaustively discussed by Lumsden (1964). Nishiura (1960) had already suggested through electronmicroscopy that perhaps the Schwann cell was bacillated along with the axon, the latter view being first advanced by Khanolkar

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(1951). Dastur (1956, 1978) illustrated that the bacilli in lepromatous nerves were clearly along the streaming cytoplasm of nerve sheath cells. Detailed accounts of the fine structural changes of nerves in lepromatous leprosy have come from Job (1970) and Dastur et al. (1973). An intriguing aspect of leprous neuritis which is beginning to be considered is the histochemistry of lysosomal enzymes (Dastur and Dabholkar, 1974; Dastur et al., 1974). The fine structural and histochemical aspects will be stressed in the present communication.

Material and Methods

The material for this report is drawn from light and electronmicroscopic studies carried out over the past 9 years, the patients being selected mainly from the Acworth

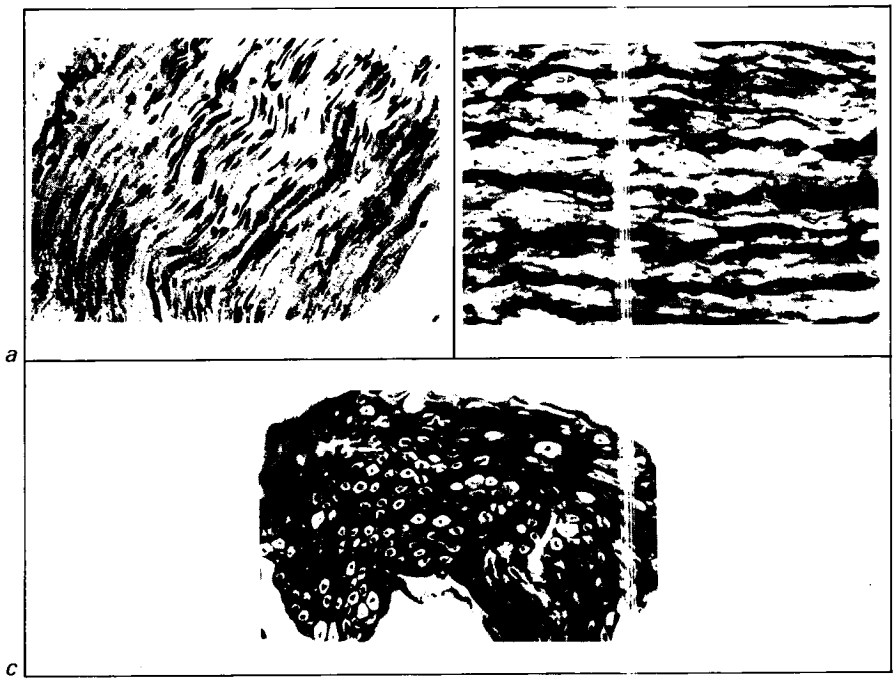


Fig. 1. a) Longitudinal section of one nerve bundle from a case of early leprosy, clinically asymptomatic except for 1 or 2 anesthetic skin lesions. Note the prominence of nerve sheath nuclei, mainly of Schwann cells, for a given thickness of section. (Haematoxylin and eosin x 250).

b) Degeneration in the form of beading of thick axons in a nerve from a similar patient. (Holmes' silver impregnation x 625).

c) Cross section of a nerve funiculus from a similar patient showing diffuse increase of endoneurial collagen, slight depletion of nerve fibres but the remainder well preserved. (Holmes' silver impregnation x 625). There was no sensory loss or motor weakness in any of the above patients.

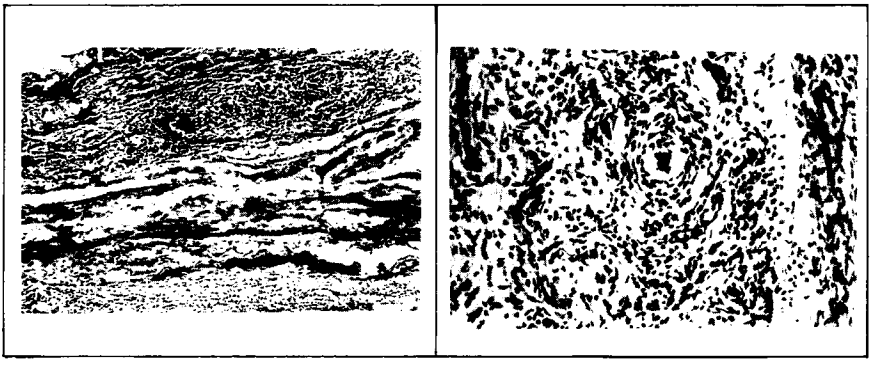


Fig. 2. a) Parts of 2 nerve bundles almost totally replaced by inflammatory cells in the index branch of the radial cutaneous nerve from a treated lepromatous patient. (Haematoxylin and eosin, paraffin section x 100).

b) Closer view of a nerve bundle infiltrated and almost destroyed by large and small mononuclear cells from a treated lepromatous patient. In the centre is a thickened blood vessel with vasculitis. Along the right is part of another nerve funiculus with sheath cell proliferation. (Haematoxylin and eosin, frozen section x 250).

Leprosy Hospital in Bombay. The observations included are mainly from unpublished data of the past 3 years, on 4 selected categories of leprosy patient:

1) Very early cases with no neurological signs or symptoms and only 1 or 2 skin lesions
2) Patients with established untreated tuberculoid leprosy
3) Patients with established untreated lepromatous leprosy
4) Patients with adequately treated lepromatous leprosy.

The types of nerve lesion biopsied are indicated in the legends to the figures. The histological, histochemical and fine structural methods are also briefly mentioned there and are more fully described in the publications already mentioned. Relevant clinical details are included. The observations are considered in 2 sections — light microscopy and electronmicroscopy. The light microscopy section includes observations made on:

1) Variously stained paraffin sections
2) Histochemistry of lysosomal enzymes in frozen sections
3) Changes in teased fibre preparations
4) Detailed histological changes in semi-thin (1 µm) cross-sections of araldite-embedded nerves.

The fine structural changes are described from transmission electronmicrographs of ultra-thin sections of the same araldite-embedded material.

Results

The findings of the study are indicated in the legends to the figures.

Discussion

Our continuing investigation of the fine structure of nerves in lepromatous leprosy has confirmed the predominant bacillation of Schwann cells of unmyelinated

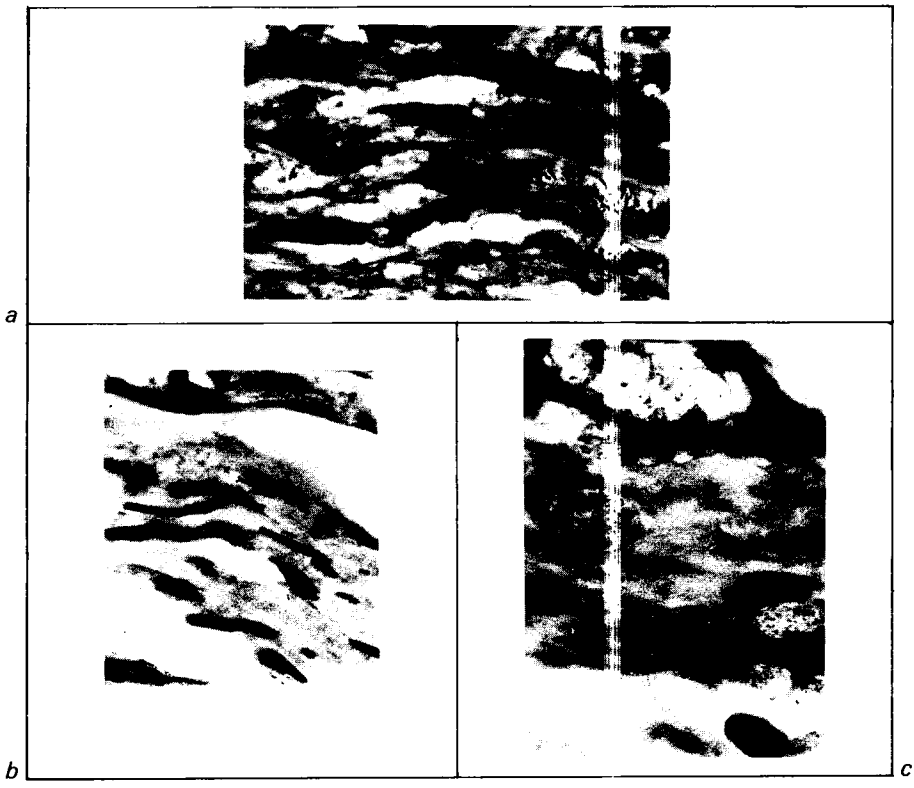


Fig. 3. a) Very heavy bacillation of Schwann cells defining the outlines of the Schwann tubes and their parallel arrangement, in an advanced untreated lepromatous patient. (Paraffin section x 1400).

b) Solid rod-shaped bacilli amongst streaming Schwann cells in a nerve from a treated lepromatous patient. (Frozen section x 1400).

c) Nerve from another treated lepromatous patient showing globi in doubtful Schwann cells, containing finely granular acid-fast material, possibly degenerated bacilli. Also note the 2 mast cells with intensely fuchsinophilic cytoplasm (in the lower right quadrant). (Frozen section x 1150).

All stained by Fite-Faraco's method for acid-fast bacilli.

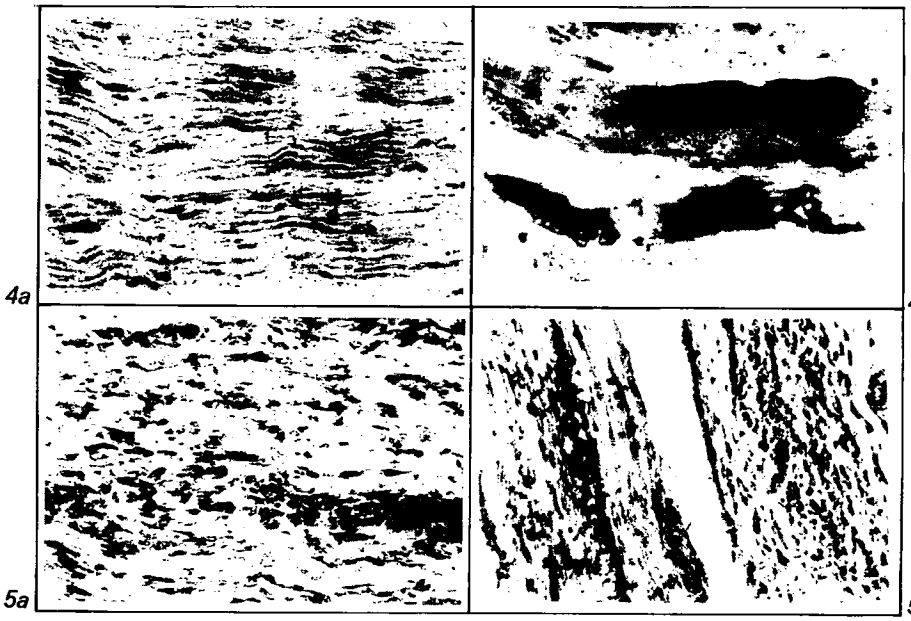


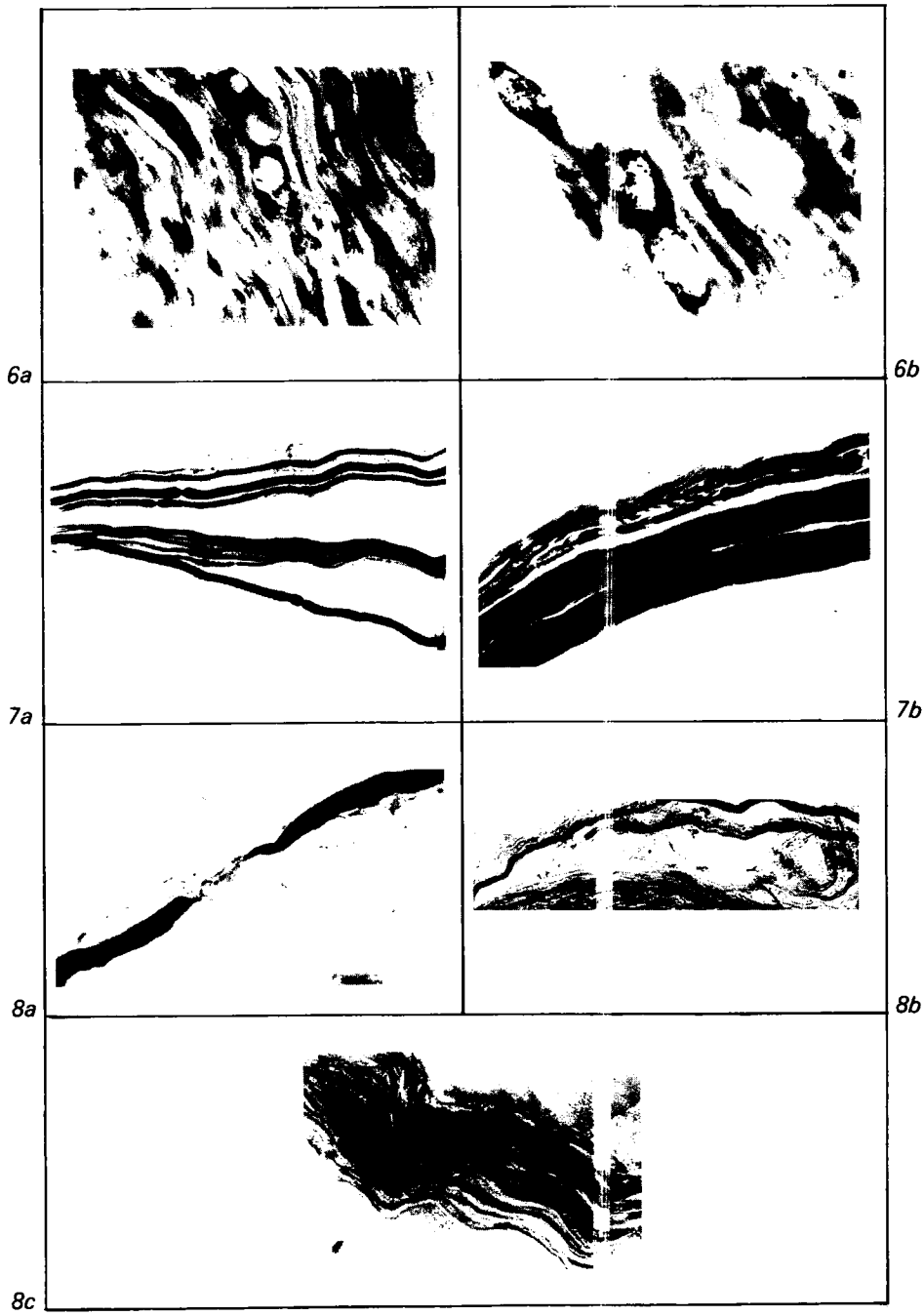
Fig. 4. a) The usual pattern of single and paried spots of acid phosphatase (AcPhase) enzyme product along the nerve fibres of a nerve showing mild degenerative changes. (No such activity is seen in a normal nerve).

b) Appearance of AcPase activity in the tender ulnar nerve of a patient with slightly more advanced leprosy. Note the enzyme product extending throughout the breadth of the 'fibre' indicating its presence in the Schwann cytoplasm. The paired spots are paranodal in location, the central clear space being the node of Ranvier. In one of the fibres there is only fine granular activity. [Gomori's acid phosphatase reaction on frozen sections, (a) x 150; (b) x 1400].

Fig. 5. a) The radial cutaneous nerve of an untreated lepromatous patient with advanced degenerative changes including infiltration by inflammatory cells. Note the enzyme activity in the large mononuclear cells in the centre of the funiculus and in the perineurium (along the upper border) apart from irregular spots in the Schwann cells. (AcPase reaction x 250).

b) A nerve from a treated lepromatous patient showing the activity of another lysosomal enzyme β-glucuronidase (β-Gase) prominently in the inflammatory cells in both the bundles illustrated and somewhat faintly and diffusely in the Schwann cells in the funiculus on the left. [β-Gase reaction x 250 — method of Hayashi et al. (1964)].

fibres. It is further evident that there is consequent preferential degeneration and loss of the unmyelinated fibres, a situation that appears unique among neuropathies. The light microscopy of teased fibre preparations has again confirmed the predominantly axonal degeneration even in lepromatous nerves, the early cases also showing segmental demyelination, as reported earlier (Dastur and Razzak, 1971; Shetty et al., 1977).



6a 6b

7a 7b

8a 8b

8c

Baccillation of Schwann cells of myelinated fibres is very infrequent and the bacillation of an axon is distinctly rare [fig. 12 (b)]. Occasionally bacilli can be seen in the axons of intradermal nerves (Dastur, 1978). It is impossible to be certain but Boddingius (1977) feels that the portal of entry of *M. leprae* into the body may be the axons of small nerves in the skin. However, in both human and experimental lepromatous leprosy, Boddingius (1974) found only about 5% of the organisms in the nerves to be intra-axonal, the overwhelming number being within the Schwann cytoplasm. Therefore the significant role of the Schwann cell in harbouring and almost protecting the bacilli, stressed by various investigators (Job, 1970; Dastur et al., 1973), remains valid. Heavy bacillation of the Schwann cell endangers the wellbeing of the normal inhabitants of the 'house of Schwann', namely myelin and axon. Other features of Schwann cell pathology have been discussed elsewhere (Dastur, 1978).

The rare intra-axonal presence of the bacilli does not militate against their predominantly vascular spread in lepromatous leprosy, whereby any organ can show some organisms in the vessel wall or in the perivascular macrophages. We have seen this clearly in striated muscles in treated and untreated lepromatous leprosy, by both light and electronmicroscopy (Dastur and Daver, unpublished work; Daver, unpublished work). In this context it also appears important to note the mural changes in the blood vessels, even those that do not show bacilli, as in the majority of blood vessels in the present study but in contrast to earlier reports based on more floridly lepromatous patients (Job, 1970; Dastur et al., 1973; Dastur, 1977). Loosening of the tight junctions described in the present paper would indicate damage to the blood-

Fig. 6. a) β-Gase enzyme product mainly around distended circular chambers in the Schwann cytoplasm of one 'fibre' in the centre and other fibres showing only faint and irregular activity. (β-Gase activity x 850).

b) Combined stain for β-Gase and acid-fast bacilli showing the enzyme activity around vacuoles in Schwann cytoplasm harbouring granular forms of bacilli, this being a nerve from a treated lepromatous patient. (β-Gase and Fite-Faraco × 1400).

Fig. 7. a) Teased nerve fibre preparation showing thick and thin normally myelinated fibres, from a clinically normal nerve.

b) Treated fibres from another clinically normal nerve showing 2 of the thin fibres undergoing early axonal degeneration indicated by marked increase of Schmidt-Lantermann clefts and thinning of myelin; the 2 thick fibres are much better preserved. [Sudan black stain, (a) x 250; (b) x 850].

Fig. 8. a) Early segmental demyelination marked by paranodal loss of myelin, from a treated lepromatous patient.

b) More advanced segmental demyelination in 2 thin fibres, and empty nerve sheath tissue, from the thickened nerve of an untreated lepromatous patient.

c) A group of nerve fibres in various stages of axonal degeneration from a treated lepromatous patient. [Sudan black, (a) and (c) x 850, (b) x 250].

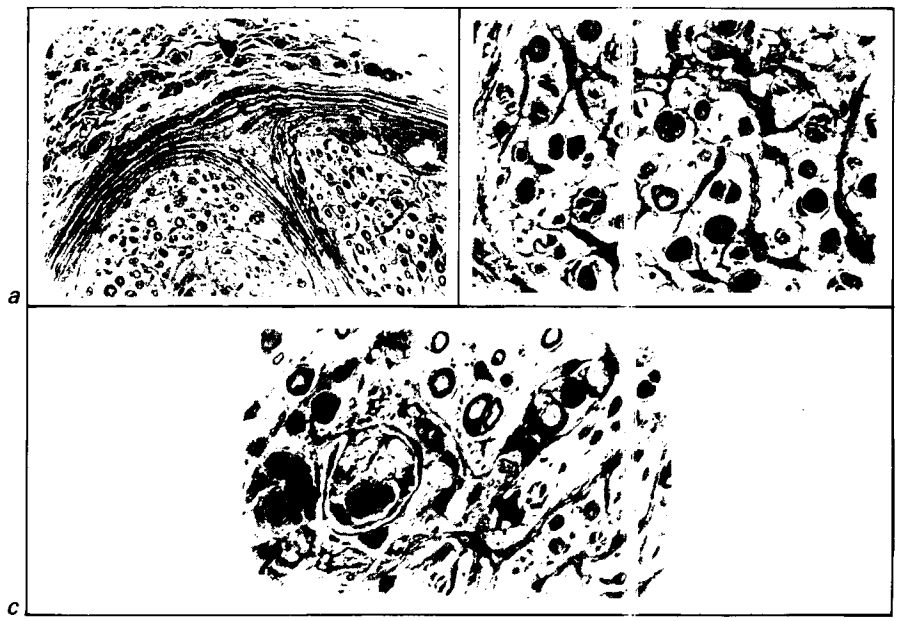


Fig. 9. a) Part of a nerve bundle with thickened perineurium and depleted large myelinated fibres, from the nerve of an untreated lepromatous patient. Note cellular and vascular reaction outside the perineurium.

b) Closer view of part of the above, showing few remaining small and medium-sized fibres and increased endoneurial fibrovascular connective tissue.

c) Another similar nerve with a depleted myelinated fibre count, also showing perivascular vacuolated macrophages containing few granular bacilli. [Semi-thin araldite sections stained with osmium tetroxide (OsO_4) and toluidine blue, (1) × 250; (b) and (c) × 850].

nerve barrier, such as demonstrated through tracer studies in mice with leprosy neuropathy (Boddingius et al., 1972). A breach of this barrier would naturally lead to exudation of plasma and later of cellular components of blood, including monocytes, into the surrounding inter- or intrafunicular tissues. The resultant oedema and inflammatory reaction would be highly detrimental to the Schwann cells and thereby to axons and myelin. Despite this, a slight regenerative effort on the part of nerve fibres seems possible, as evidenced in semi-thin sections by the clusters of small myelinated fibres within single Schwann cells.

Schwann cell activity and turnover were clearly manifested by the histochemical demonstration of lysosomal enzymes by light microscopy, while in normal nerve such activity was not visible by the same methods. It was interesting that demonstrable activity was seen in clinically very slightly affected nerves which had no inflammatory reaction and no bacilli. At this stage only the acid phosphatase (AcPase) reaction product could be demonstrated; β-glucuronidase (β-Gase) activity was not detectable. In the more affected (thickened and/or tender) nerves, the same feature of fewer

Schwann cells was again evident, and lesser activity demonstrated by β-Gase than by AcPase. This feature was noticeable with the infiltrating macrophages also. This would suggest that there was an inherent smaller amount of β-Gase than of AcPase, that the latter was more nonspecifically reacting than the former, or that both of these mechanisms applied.

A point of special interest was the demonstration of β-Gase activity along the periphery of vacuolar areas in Schwann cells, in the centre of which granular or solid-staining acid-fast bacilli were seen in nerves of treated lepromatous patients (of category 4). The enzyme activity was not in the centre of these vacuolar areas, or on the bacilli, and appeared to be clearly related to the cytoplasm of the cell concerned. This fact favours more the recent finding of Prabhakaran et al. (1976) that on chemical analysis of experimental mouse tissue, the apparent mycobacterial activity of β-Gase actually resided in the host cell cytoplasm.

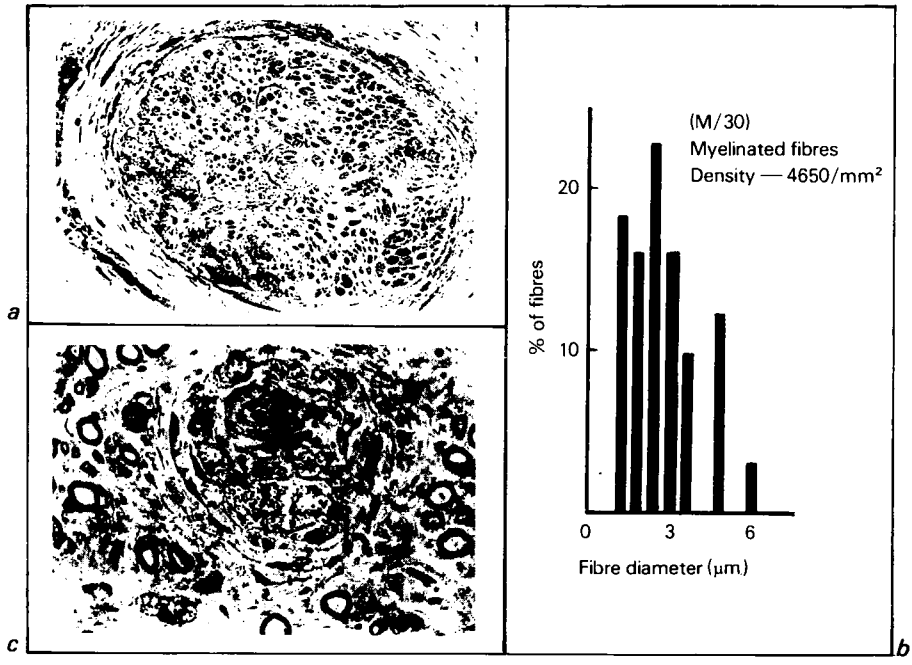
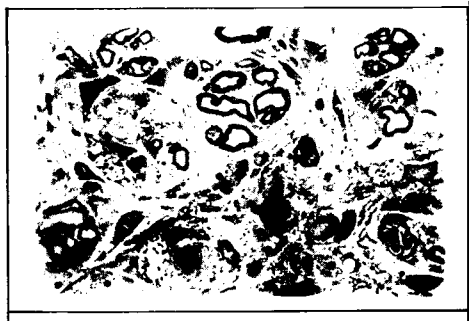


Fig. 10. a) Entire nerve bundle of a treated lepromatous patient showing marked depletion of myelinated fibres and thickened perineurium.

b) Histogram of nerve fibre diameters of the same nerve showing relative prominence of small myelinated fibres.

c) Nerve from a similar case showing lesser depletion of fibres but many bacilli. Note the collar of distended macrophages containing granular AFB around an arteriole in the endoneurium. [Stain as for figure 9, (a) x 250; (c) x 850].



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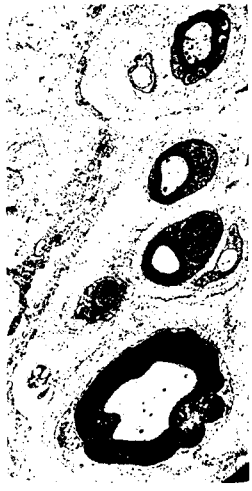

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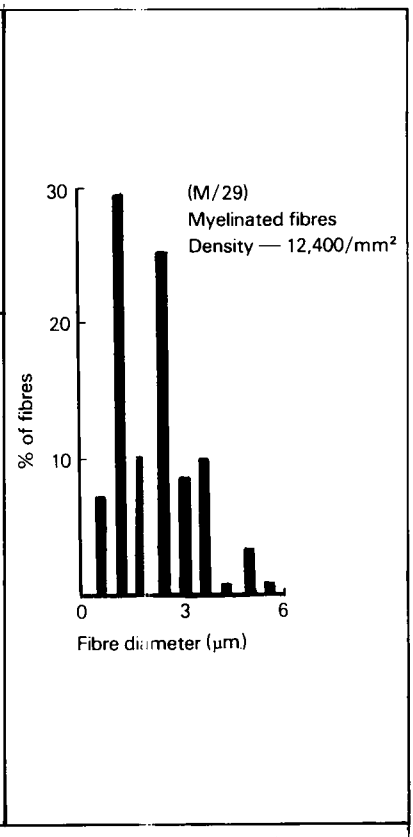

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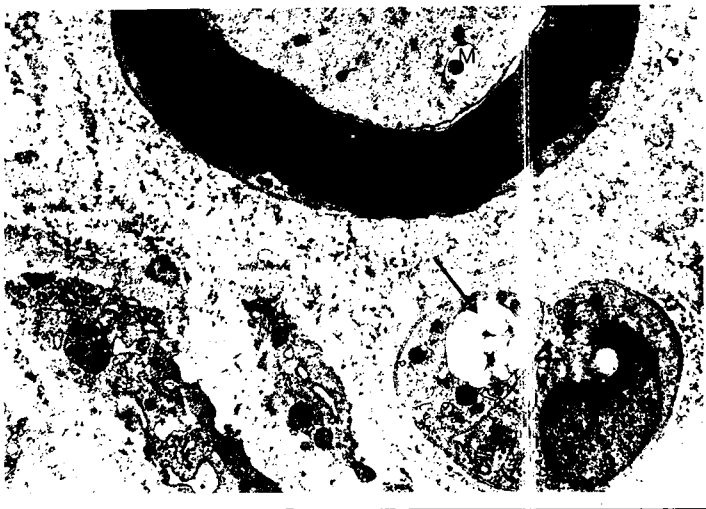


12b

The electron microscopic finding which further corroborated the above was the presence of *M. leprae* within lysosome-like bodies in the Schwann cells of unmyelinated fibres. At times, these membrane-bound bodies showed only structureless osmiophilic debris, constituting phagolysosomes; less frequently, the entire Schwann cell had become a bag of breakdown products of tissue with or without bacilli, within intact plasma and basement membranes; rarely, such a cell was invaded by a macrophage.

Finally the differences between the nerves from the treated and untreated patients, especially from the point of view of the appearance of the Mycobacteria should be mentioned. As illustrated by the difference between figures 3(a) and 3(c), or between figures 6 and 11(a), even light microscopy showed more frequently granular forms of bacilli in the nerves of treated cases, compared with the more solid rod-shaped organisms in the untreated. Electronmicroscopy also showed crumpled or fragmented forms of *M. leprae* more frequently in the treated cases, and uniformly osmiophilic forms in the untreated [figs. 15(a) and 15(b)].

Summary

A brief illustrated account is presented of the light microscopic pathology, histochemistry of lysosomal enzymes, and fine structural changes in the nerves of patients with untreated or treated lepromatous leprosy. Predominant bacillation of the Schwann cells of unmyelinated fibres, degeneration of their axons, prominence of phagolysosomes, and disappearance of these cells with endoneurial collagenosis were observed on electronmicroscopic examination of the index branch of the radial cutaneous nerve. Although there were changes in the blood vessels and proliferation

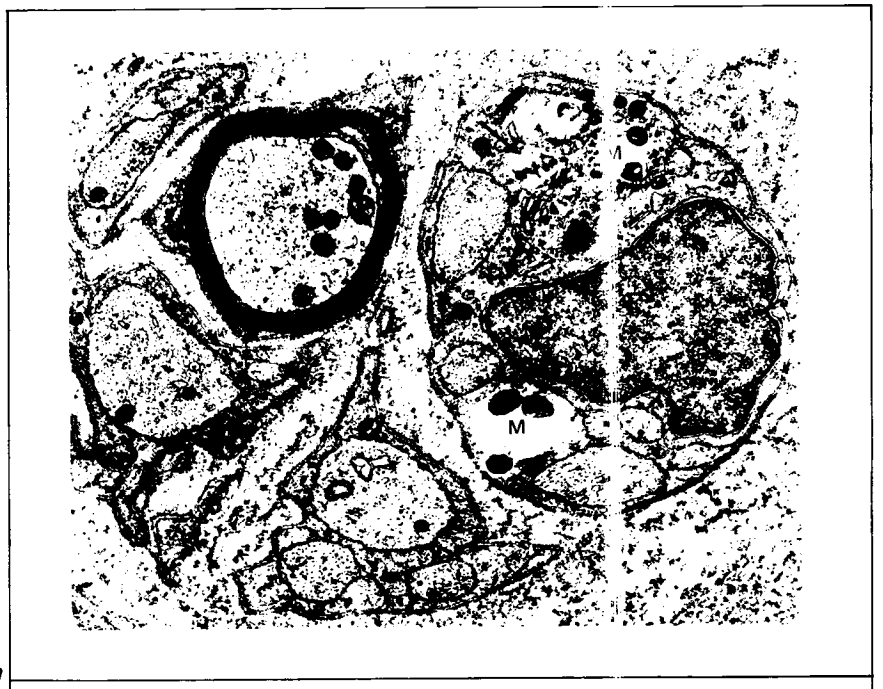
Fig. 11. a) Nerve of another treated lepromatous patient showing mainly granular forms of bacilli in Schwann cell of unmyelinated fibre. Also note clustering of small myelinated fibres in single Schwann cells, suggesting regeneration.

b) Histogram of myelinated fibres of this nerve showing almost all fibres below 6μm in size, with an overall increase in density of fibres (12,400/mm²) compared to normal density (7,000-10,000/mm²). (Stain as for 9, x 1400).

Fig. 12. a) Moderately thickened nerve of an established untreated lepromatous patient, with the unusual feature of bacilli in the Schwann cytoplasm of one of the myelinated fibres.

b) The still more unusual feature of a Mycobacterium (M) in the axon of a myelinated fibre.

In (a), the endoneurial collagen is grossly increased and there is marked depletion of unmyelinated fibre groups. In (b), the Schwann cytoplasm of the unmyelinated fibre shows a membrane-bound body with some debris in it, probably a phagolysosome (arrow) and Golgi tubules. [Ultra-thin osmicated araldite sections stained with uranyl acetate and lead citrate, (a) × 6350-reduced; (b) × 11,900].



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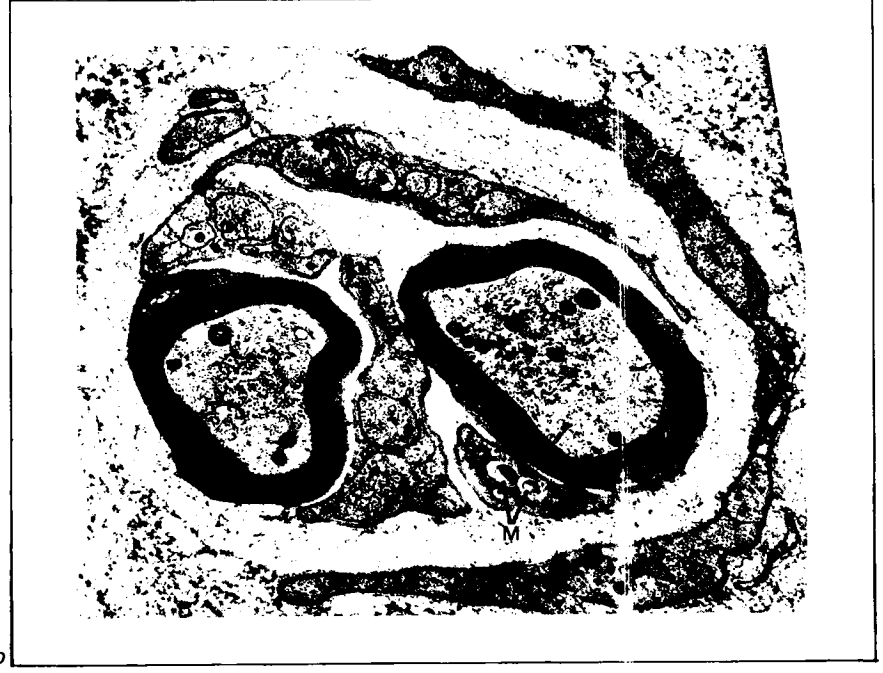


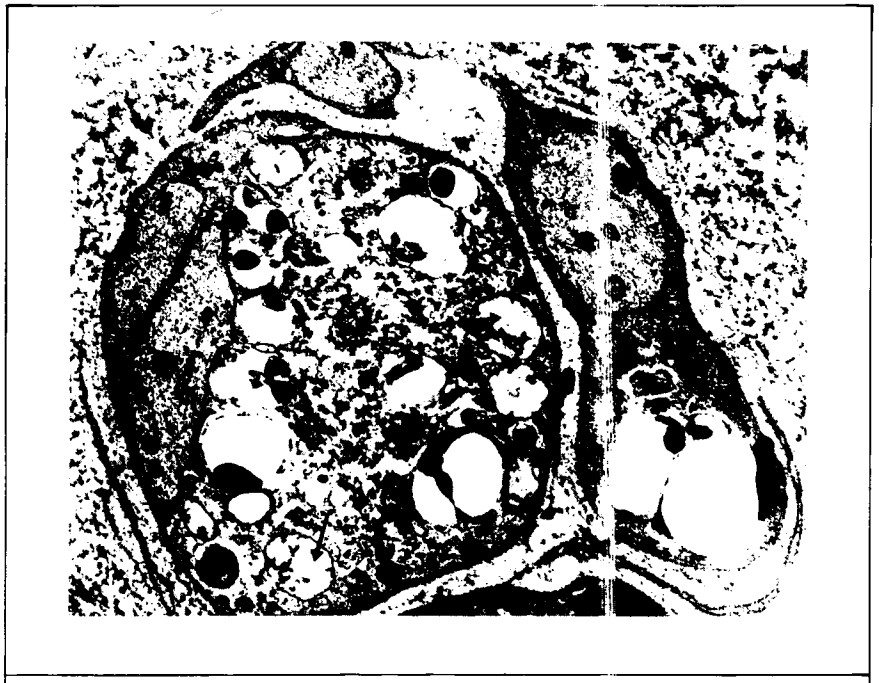
13b

Fig. 14. a) Area of slightly affected nerve showing degeneration of myelinated fibres, accumulation of osmiophilic debris, breakup of basement and plasma membranes and increase of endoneurial collagen.

b) Clusters of very small unmyelinated fibres in the Schwann cells of an early case of leprosy, suggesting their regeneration. One lymphocyte is also included. [Stain as for figure 12, (a) × 15,300; (b) × 29,700-reduced].

of perineurium, bacillation of endothelial or perineurial cells was much less conspicuous. Intact and degenerating forms of *M. leprae* were found in both treated and untreated patients, fragmenting or crumpled forms being more frequent in the treated. Both groups of patients also showed increased lysosomal enzyme activity, evidenced by single or paired paranodal spots of acid phosphatase and β-glucuronidase in Schwann cells in histochemical preparations of the nerve. There was lesser activity, and activity in fewer cells, in the case of β-glucuronidase than of acid phosphatase. Diffuse β-glucuronidase activity was found in the wall of empty-looking oval chambers in the Schwann cells, and acid-fast bacilli were seen in these chambers. In teased fibre preparations, both axonal degeneration and segmental demyelination were found. In semi-thin araldite sections, the myelinated fibre density was either preserved or reduced; large diameter fibres were more frequently depleted, with tall peaks of smaller fibres seen on plotting diameter spectra.

Fig. 13. The same nerve as in figure 12 showing the typical selective bacillation of Schwann cytoplasm of unmyelinated fibres. In both (a) and (b) intact *M. leprae* (M) are seen in their characteristic halos. The other circular bodies in the Schwann cytoplasm or axons are mitochondria. In (a) note the unmyelinated axons of the Schwann cell on the right, pushed to the periphery; and a phagolysosome (arrow) and Golgi tubules in its cytoplasm. The myelinated fibres in both (a) and (b) with a thin myelin sheath could be regenerating. In (b) the arcades of unmyelinated fibres surrounding the myelinated often accompany such regeneration. [Stain as for figure 12, (a) x 15,100; (b) x 12,100].



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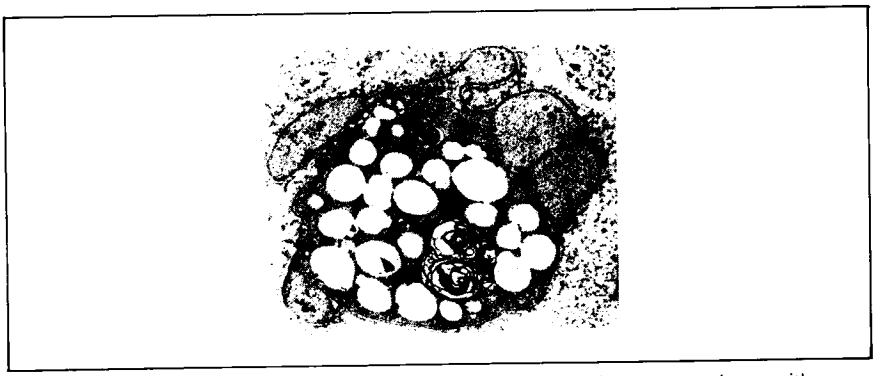

Fig. 16. Part of a very slightly affected nerve showing a large macrophage with many vacuoles and some myelinic figures, which has infiltrated the Schwann cell cytoplasm of an unmyelinated fibre group with the axons pushed to the periphery. There were no bacilli in this or any other part of the nerve. (Stain as for figure 12, x 21,100).

Acknowledgements

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Fig. 15. a) Same nerve as in figure 12 with a Schwann cell showing more degenerative changes with formation of several phagolysosomes (arrows on 2 of them), osmiophilic debris, depletion of other organelles and the persistence of many intact bacilli.

b) Nerve of a treated lepromatous patient showing distended Schwann cell of an unmyelinated fibre group, with only basement membrane and plasma membrane intact, all axons having degenerated except perhaps the one on the right attached by a short strand of basement membrane (long arrow). Note the degenerating *M. leprae* (short arrows) within the distended cell, collapsed and distorted, with depleted osmiophilic content in all the bacilli. Also note 2 dense osmiophilic lysosome-like bodies (L) and scattered osmiophilic 'dust', possibly of same origin. [Stain as for 12, (1) x 13,200; (b) x 30,000].

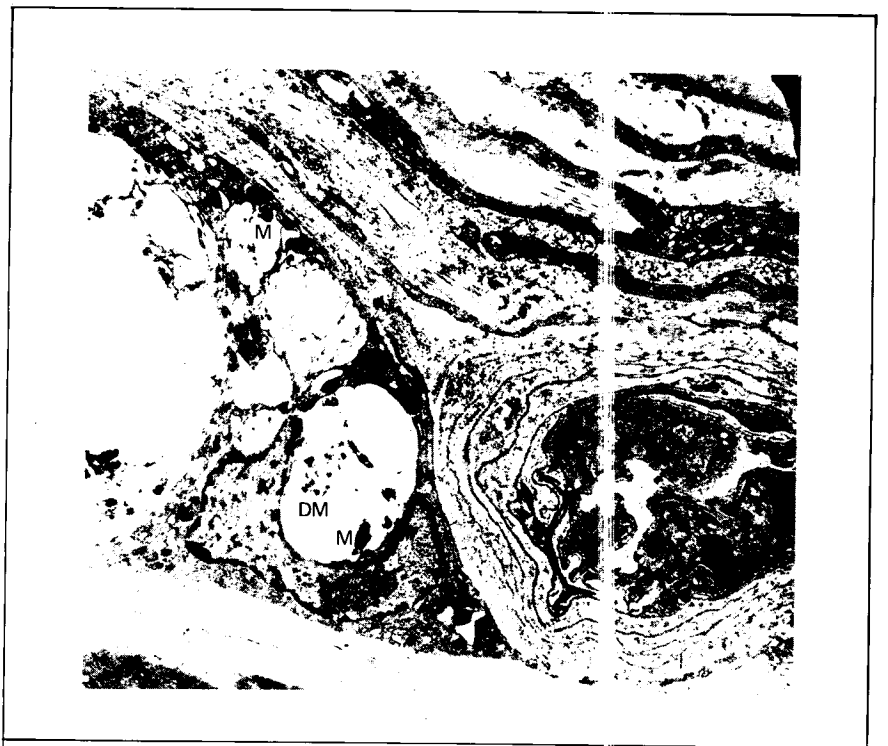

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Fig. 17. a) Nerve from a treated lepromatous patient showing thickened perineurium (along top right) with increased collagen amidst proliferated perineurial cells. In the lower right is an extrafunicular blood vessel with somewhat thickened endothelial cells, one small tight junction, and proliferated basement membrane lamellae. Along the left side is a greater part of a macrophage with vacuoles containing pale fluidy material and some Mycobacteria (M) some of which appear degenerating (DM).

b) Another extrafunicular blood vessel from the same nerve as in figure 14 (a) showing one tight junction which is beginning to be fenestrated (arrow) and 2 others with big gaps (X) and only a small area of contact. Also note prominent pinocytotic vesicles in endothelial cells, osmiophilic material in one pericyte on the right, and proliferated basement membrane. [Stain as for figure 12, (a) x 5350; (b) x 11,000].

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The Neuropathology of a Case of Pick's Disease

*R.A. Rodda**

Pick's disease is a relatively rare presenile or senile dementing disorder characterised by localised cortical atrophy in one or more lobes of the cerebral hemispheres and presenting a variety of neuronal changes in the affected areas. There are few descriptions of Australian cases and it seems appropriate to report the pathological features of a Tasmanian case.

Case Report

Clinical History

J.W.R. was an unmarried woman who was born in England but had lived in Tasmania since the age of 5 years. She had been a highly regarded high school science teacher but retired in 1971 at the age of 53 because of an obvious deterioration in her teaching ability. Over the previous 6 years she had gradually developed personality changes and had become dogmatic and childish with frequent temper tantrums. Her intellectual deterioration had been apparent for about a year. There was no family history of any similar mental deterioration. Clinical examination in July 1971 showed no focal neurological signs except loss of ankle reflexes, a mild memory deficit and a lack of insight into her mental state. A pneumoencephalogram in August 1971 showed cerebral atrophy with ventricular enlargement and a diagnosis of presenile dementia was made. Her intellectual deterioration progressed and she was admitted to the Royal Derwent Hospital in November 1972. From the middle of 1973 she spent most of her time sitting in a chair, smiling vacantly and unable to hold any conversation. From early 1974 she was doubly incontinent and required total nursing care. At no time did she have any epileptiform seizures. She had pneumonia in May 1975 and remained in a totally vegetative state until her death in January 1976 at the age of 58 years.

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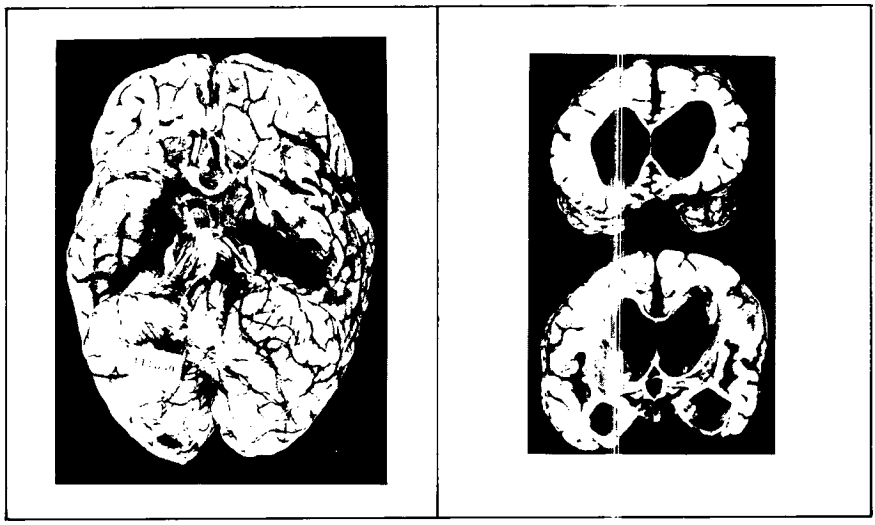

Fig. 1. Undersurface of 1130g brain showing temporal and frontal atrophy with obvious walnut appearance of left inferior frontal gyrus.

Fig. 2. Coronal brain slices showing ventricular dilatation, severe atrophy of corpus striatum particularly the caudate nucleus and of the orbital, cingulate and inferior temporal gyri. The corpus callosum and septum pellucidum are markedly thinned.

Postmortem Examination

A necropsy was done in Hobart on 28 January 1976 by Dr B.T. French who noted some degree of physical wasting and a bilateral bronchopneumonia.

Neuropathology

The freshly removed brain weighed 1130g. Examination after adequate fixation showed a focal cerebral atrophy involving particularly the temporal and the frontal lobes (fig. 1). The temporal atrophy was more severe on the left side where there was a striking walnut appearance of the polar and anterior parts of the temporal gyri. The posterior parts of both superior temporal gyri were remarkably normal in appearance. The frontal atrophy was most obvious inferiorly in the medial orbital and rectus gyri and superiorly in the anterior cingulate gyri. The cerebellum was of normal size. The spinal cord appeared normal.

Serial coronal slicing of the cerebral hemispheres showed appreciable dilatation of the lateral ventricles, most marked in the frontal and temporal horns (fig. 2). The bulbous frontal horns measured from 3.2 to 4.5cm in diameter and the dilated temporal horns from 1.8 to 2.5cm in diameter. The septum pellucidum was paper-thin and fenestrated. The gyri recti, the inferior temporal and the anterior cingulate gyri were the most severely atrophied but the anterior parts of the parahippocampal gyri were also considerably atrophied. Beneath these severely atrophied gyri the white matter was very thin. The corpus callosum was attenuated and elongated. The corpus striatum was also atrophic with extreme flattening and a brownish discoloration of the caudate nucleus and a marked shrinkage of the globus pallidus. The

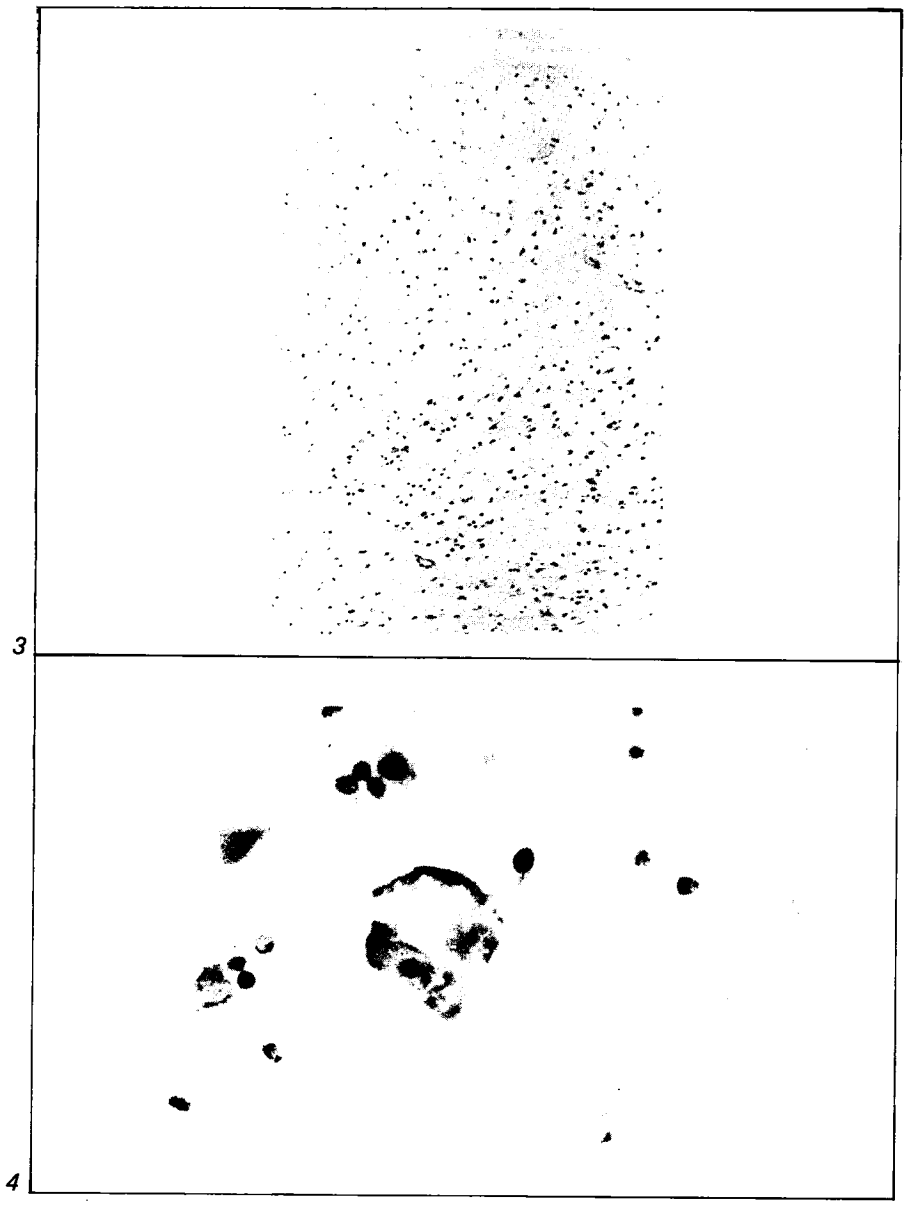

Fig. 3. Thin atrophic orbital gyrus showing severe nerve cell loss and disarray of the few large neurones remaining in the middle layers. The superficial white matter is gliotic. (Haematoxylin and eosin x 80).

Fig. 4. Swollen vacuolated Pick cell in temporal cortex. (Celloidin, Nissl × 500).

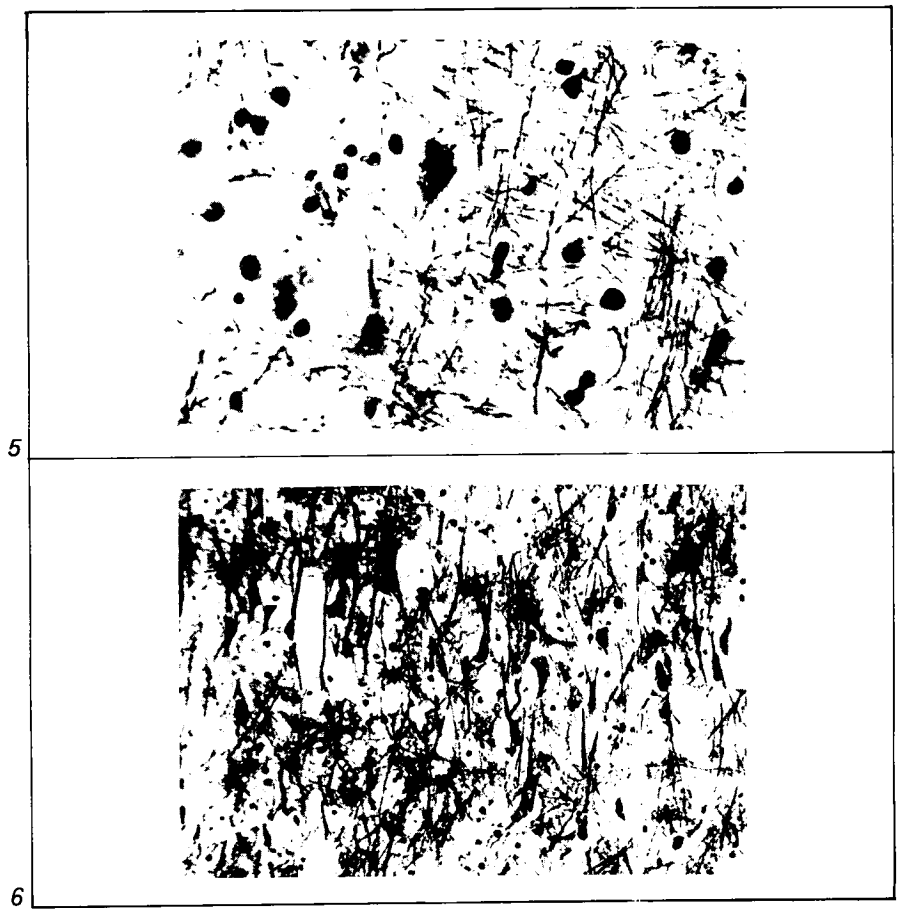

Fig. 5. Degenerate neurones in frontal cortex. Upper cell contains dense argyrophilic material, lower cell is vacuolated with loss of neurofibrils. (Frozen, von Braunmuhl × 300).

Fig. 6. Pyramidal neurones of hippocampus containing dense argyrophilic material. (Frozen, Bielschowsky × 140).

thalamus was but little shrunken. The substantia nigra appeared pale. Slicing of the pons, medulla and cerebellum showed no gross atrophy.

Histological sections of the markedly thinned cerebral cortex in the atrophic gyri showed an extreme loss of nerve cells (fig. 3) with a status spongiosus in the more superficial parts of some gyri. There was a lack of alignment of the remaining neurones and most were remarkably shrunken but very occasional large swollen vacuolated neurones with a severe loss of Nissl substance were seen in the rather less severely affected cortex (fig. 4). In frozen sections stained by the von Braunmuhl and Bielschowsky methods the neuronal cytoplasm contained dense argyrophilic material with few intact neurofibrils (fig. 5) but dense globular intracellular Pick bodies were not seen. Small quantities of extracellular pigmented and PAS positive granular debris were present in the areas of marked nerve cell loss. In the deeper parts of the

affected cortex and in the subcortical white matter there was a striking cellular and fibrous gliosis. In the less severely atrophic gyri, the cortical nerve cell loss seemed most obvious in layer 3. No senile plaques were seen in any part of the brain. In the hippocampus, there was a loss of neurofibrils in some swollen neurones and abnormal argyrophilic material was seen in many of the remaining pyramidal cells (fig. 6) but no granulovacuolar degeneration was discernible. There was a loss of nerve cells in the Somer sector of Ammon's horn (fig. 7) with abundant extracellular PAS positive lipochrome pigment debris and an astrocytic fibrous gliosis. A marked neuronal loss with disarray of the remaining neurones was evident in the end-plate.

In the extremely atrophic caudate nucleus very few nerve cells remained but there was an intense cellular and fibrous replacement gliosis (fig. 8). Similar but less severe changes were seen in the globus

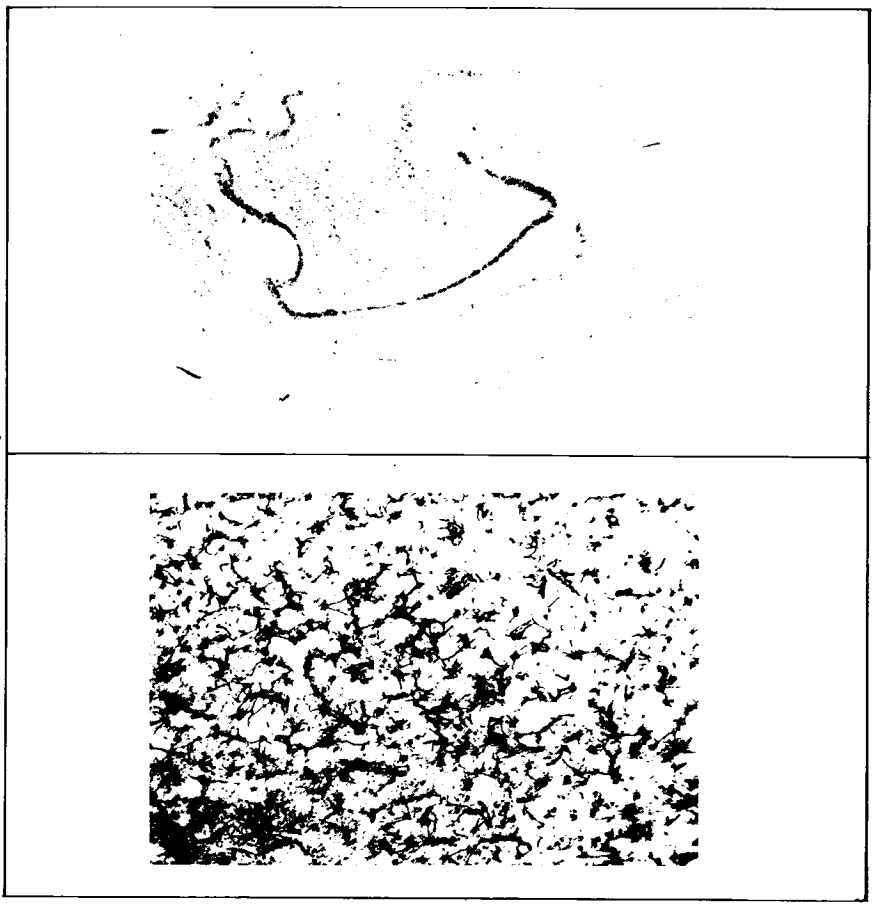

Fig. 7. Severe nerve cell loss in Somer sector of Ammon's horn. (Celloidin, Nissl × 7).

Fig. 8. Intense gliosis in shrunken caudate nucleus. (Frozen, Cajal × 65).

pallidus. In the putamen, abundant lipochrome pigment was present in many nerve cells but there appeared to be much less nerve cell loss and the gliosis was less striking. In the dorsal thalamus there was obvious nerve cell loss and again a cellular and fibrous gliosis. The substantia nigra and the locus coeruleus showed some cell loss with abundant extracellular pigment remaining. The cerebellum showed a limited patchy Purkinje cell loss on the crests of a few folia with a related Bergmann astrocytosis. There were no other changes in the pons, medulla, or spinal cord.

Discussion

The insidious intellectual impairment with emotional disturbances, the loss of initiative and general inertia with but a limited memory loss, progressing to apathy and an inert negative existence with a fatal outcome, follows the clinical pattern of Pick's disease outlined by Jervis (1971).

Although there is no history of any similar illness in the family of the present case, there have been many reports (von Braunmuhl, 1928; Malamud and Waggoner, 1943; Sjogren, 1952) of the disease occurring in members of the same family, and a hereditary factor which may be a major autosomal gene (Slater and Cowie, 1971) appears to play a part in the causation of the disorder. It seems likely that further cases will occur in the family of this patient. Pick's disease may occur in old age (Binns and Robertson, 1962) as well as in the presenium; it is clinically indistinguishable from the Alzheimer dementias (Wells, 1971) and it would be advisable that the diagnosis be established by adequate pathological study of possible cases in this family, whatever the age at onset of any neuropsychiatric disorder.

The focal atrophy of the cerebral cortex, identified in 1892 by Pick (Jervis, 1971) as the characteristic gross feature of this disorder, may involve various parts of the cerebral hemispheres but the frontotemporal type with severe gyral atrophy of the medial-frontal and medial-anterior temporal lobes, as in the present case, and with slightly more severe involvement of the left side (Mansvelt, 1954) is the most commonly seen pattern. The cortical atrophy, characterised in the most severely affected cortex by a marked loss of nerve cells from all except the first layer, and in the less severely affected cortex from the middle layers, conforms with that described in the larger series of reported cases (von Bagh, 1942; Malamud and Waggoner, 1943; Lindgren, 1952; Schenk and Mansvelt, 1955; Jakob, 1961).

Although a few swollen vacuolated nerve cells were seen in the present case, most of the degenerate neurones showed shrinkage, some lipochrome pigment and a condensation of argyrophilic fibre material, but cells containing globular argyrophilic Pick bodies and paraneuronal Hirano bodies were not seen. Although some authorities (Torvik, 1970) reserve the diagnosis of Pick's disease for such cases which show all these characteristic features, Corsellis (1976) has emphasised that these striking cellular changes are not found in all cases of Pick's disease (Hassin and Levitin, 1941; Stern and Reed, 1945-46). Indeed they are not all pathognomonic of

the disorder and some are found in the neuronal degenerations of other disorders (Williams, 1935; Hirano et al., 1968; Schochet et al., 1968).

In the present case, there was severe involvement of the basal ganglia, and quite a number of reports describe a similar atrophy, particularly of the caudate nucleus (von Braunmuhl, 1930; Lowenberg et al., 1939; Akelaitis, 1944; Winkelman and Book, 1949).

The bilateral loss of nerve cells selectively in the Somer sector of Ammon's horn in the present case does not have the features of the hippocampal lesion associated with epilepsy, but is the type of lesion which has been recorded as common in presenile and senile dementias (Corsellis, 1957).

In the deeper aspects of the affected cortex and in the superficial underlying white matter, there was a marked cellular and fibrous gliosis. This gliosis was even more striking throughout the corpus striatum and particularly in the grossly atrophic caudate nucleus. Although Neumann (1949) and Neumann and Cohn (1967) have suggested that some cases with limited nerve cell loss and lacking typical Pick cells but with an appreciable degree of gliosis should be regarded as a distinct form of presenile dementia, the present case is undoubtedly one of Pick's disease.

Summary

The clinical features are outlined and the pathological findings described in a case of Pick's disease occurring in an English-born Tasmanian. No similar illness is known of in her family.

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Idiopathic Scoliosis, Scheurmann's Disease and Myopathy: Two Case Reports

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Because scoliosis is often seen in association with the various neuromuscular disorders, it has been proposed that otherwise subclinical cases of myopathy may be responsible for some cases of apparently idiopathic scoliosis (Spencer and Zorab, 1976; Yarom and Robin, 1979). These authors described abnormalities in the paraspinal muscle of scoliotic patients, in whom there was no other evidence of neuromuscular disease.

In the present paper 2 cases of apparently idiopathic back curvature are reported. One is a case of kyphoscoliosis with back curvature since infancy, and the other an instance of otherwise classical Scheurmann's disease. In both cases the paraspinal muscles appeared abnormal when compared with control scoliotic muscle. Electromyography (EMG) of limb muscles in each case subsequently confirmed the presence of a myopathy.

Method

Specimens of sacrospinalis and deep rotator muscles (Case 2) and of sacrospinalis only (Case 1) were obtained at the time of Harrington rod instrumentation of the spine. The specimens were taken from above, below and at the apex of the spinal curve. The microscopic appearances were compared with those of muscles taken from analagous sites in patients suffering from scoliosis of known cause, other

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than neuromuscular disease. The muscle was frozen in isopentane, cooled in liquid nitrogen and prepared for light microscopy by standard methods (McLeod et al., 1972). The following stains and histochemical reactions were performed: haematoxylin and eosin, modified Gomori trichrome, succinic dehydrogenase, myosin adenosine triphosphatase, oil red O stain for fat, and periodic-acid Schiff reaction for glycogen. Phosphorylase and phosphofructokinase reactions were also performed on muscle from Case 2. Material for electronmicroscopy was fixed in ice-cold glutaraldehyde (pH 7.3) postfixed in osmium tetroxide, dehydrated in graded alcohols, and blocked in Spurr's embedding medium.

Case Reports

Case 1

P.B. was the younger of 2 children, and was born as a breech delivery in January 1963. Soon thereafter a squint was noted. At the age of 4 months bilateral inguinal herniae were repaired. He sat up at 8 months, but did not walk until the age of 2 years. This delay was attributed to his deformities, which by then included kyphosis as well as bilateral hip and knee contractures. In 1967 a recurrence of his left inguinal hernia was repaired, and soon afterwards recession/resection operations were performed because of a right divergent strabismus. Hip and knee release operations were performed with considerable functional improvement in 1970. However the spinal curvature continued to progress, and by 1975 it was clear that a scoliosis, convex to the left, was also developing. Harrington rod instrumentation for correction of the kyphoscoliosis was performed in 1977. Until that time he had been examined on numerous occasions, and no limb weakness had been detected, although it had been noted that the latissimus dorsi and pectoralis muscles appeared poorly developed.

There was no family history of muscle disease or of spinal curvature.

On examination in 1977 it was found that he had a long thin face and a high arched palate. His temporal fossae appeared hollow. He was able to bury his eyelashes normally, although he had a rather tent-shaped mouth. The trapezii and pectoralis muscles appeared poorly developed. Hip and knee flexion were still partly restricted by contractures, and there was a correspondingly decreased bulk of the quadriceps muscles. He was able to sit up from the lying position without using his hands. No limb weakness could be detected by any examiner.

Investigations

ECG and serum CPK activity were normal. EMG sampling of the right deltoid and lateral head of triceps muscles was performed at the Royal Prince Alfred Hospital. No abnormality was detected in the triceps muscle, but a myopathic pattern was demonstrated in areas of the deltoid muscle. In these areas there were large numbers of low-amplitude polyphasic units, and the overall amplitude of the interference pattern did not exceed 2mV. Muscle biopsies of the paraspinal muscle revealed that the most striking feature in all specimens was the profound predominance of Type I fibres. In some specimens Type II fibres were completely absent. Such an overall predominance of Type I fibres was not seen in muscle from any of the control cases. Other nonspecific findings included increased variability in fibre size, patchy increase in interstitial connective tissue, and many collections of subsarcolemmal mitochondria. Occasional cores were seen in some specimens, but these were no more frequent than in the control muscle. Electronmicroscopic features were also nonspecific. Mitochondrial collections and some areas of myofibrillar disarray were seen.

Case 2

S.W., born in 1961, was the second of 5 children, and was mildly mentally retarded. His development was otherwise normal until the age of 3 years, when his grandparents noted that he was stumbling excessively. At the age of 8 years a definite kyphosis was noted. This progressed until he was aged 17, when a Harrington rod instrumentation was performed to correct the kyphosis.

There was no family history of muscle disease. His paternal grandfather developed a late-onset kyphosis, but there was no other family history of back curvature. Examination in 1978 revealed that he was mildly mentally retarded. He had mild facial weakness, evidenced by his inability to overcome the examiner's attempts to open his eyes, and a pouting expression of the lower face. The trapezii appeared poorly developed. There was weakness of neck flexion. There was no other evidence of cranial nerve abnormality. Limb muscles were of normal bulk, and no weakness of these muscles could be detected by any observer.

Investigations

ECG and serum CPK were normal. Spinal x-rays showed the classical changes of Scheurmann's disease, namely thoracic kyphosis, anterior wedging of vertebrae, and Schmorl's nodes. EMG sampling of the right deltoid, lateral head of triceps, biceps, abductor pollicis brevis and vastus medialis muscles was performed. There was no spontaneous activity. On maximum effort there was a clearly myopathic pattern with many low-amplitude polyphasic units seen in all the muscles sampled except for the abductor pollicis brevis. Nerve conduction studies were normal. Muscle biopsies (paraspinal muscle) revealed nonspecific abnormalities which were considered significant when compared with the control muscle. These included areas of increased interstitial connective tissue, central rimmed vacuoles in some fibres, and abnormal variation in fibre diameter. Many fibres had a granular appearance. Histochemical reactions for phosphorylase and phosphofructokinase were normal. On electronmicroscopy the most striking feature was the presence in some fibres of an excessive amount of glycogen (fig. 1). Biochemical estimations of total muscle glycogen, alpha- 1,4-glucosidase (acid maltase) and amylo-1,6-glucosidase (debranching enzyme) were within the same range as the control muscle.

Fig. 1. Case 2. Excessive glycogen in fibres of the paraspinal muscle. (Bar = 1 micron).

Discussion

The 2 cases described had both suffered from back curvature without detectable limb weakness. Examination of paraspinal muscle revealed abnormalities which were considered significant when compared with control material. In both cases the findings were nonspecific and did not suggest a recognised myopathy or dystrophy.

Considerable care must be taken in the interpretation of scoliotic muscle, because muscle changes may be secondary to the scoliosis itself, and because of the variations which may be seen in normal muscle which is adjacent to tendinous insertions. In Case 1 occasional cores were seen, but because these were no more frequent than in the control material it is felt that a label of 'central core disease' is not justified. Type I fibres may normally be more common in paraspinal muscle than in limb muscle (Johnson et al., 1973). However the overall predominance of Type I fibres observed in all muscle specimens from Case 1 was not seen in any control case, and is therefore considered pathological.

Because of the suspicion aroused by microscopy in these 2 patients, EMG's were subsequently performed on limb muscles, and in both cases were unequivocally myopathic. EMG examination of limb muscles of scoliotic patients without neuromuscular disease in the Department of Medicine in the University of Sydney has generally been normal, and the findings in the present patients are not likely to be secondary to the back curvature.

Dubowitz (1978) applied the term 'minimal change myopathy' to cases of myopathy in which microscopy demonstrates minor nonspecific abnormalities. Both cases reported in this paper would be histologically consistent with this classification.

Scheurmann's disease is generally considered to be due to an osteochondritis. However, the disease is frequently subclinical, and radiological changes of Scheurmann's disease may be seen in approximately 5% of the normal young adult population (Jaffe, 1972). It is therefore possible that the coincidence of such spinal pathology together with myopathy may predispose to the development of clinical kyphosis.

The present cases provide further evidence that myopathy may occasionally present as back curvature without more distal weakness. The presence of associated myopathic features, such as recurrent herniae or contractures (as in Case 1) may also cause muscle disease to be suspected. A family with the myopathy, multicore disease, has been described in which the propositus presented as idiopathic infantile scoliosis, and in which subsequently affected members of the family suffered from both scoliosis and limb weakness (Fitzsimons and Tyer, to be published).

Summary

2 cases of back curvature considered to be due to myopathy, but without associated limb weakness, are described. 1 case presented as infantile kyphosis with subse-

quent progression to scoliosis. There were some associated myopathic clinical features, including recurrent herniae and hip and knee contractures. The second case presented as an otherwise classical instance of Scheurmann's disease. Paraspinal muscle in both cases showed nonspecific abnormalities consistent with varieties of minimal change myopathy. EMG examination of limb muscles revealed myopathic abnormalities. These cases support the hypothesis that myopathy may underly some cases of apparently idiopathic scoliosis or kyphosis.

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Computerised Tomography in the Leucodystrophies

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The leucodystrophies are a rare group of inherited diseases characterised by an inherent defect of cerebral white matter. They present as degenerative neurological disorders in childhood with a preponderance of long tract signs, and often visual loss, which overshadow dementia and epilepsy. In some an enzyme defect is well defined (e.g. Krabbe's disease, metachromatic leucodystrophy), whereas in others (e.g. adrenoleucodystrophy) no enzyme defect has been discovered.

Diagnosis

The CAT scan findings on 11 children in whom a diagnosis of leucodystrophy has been made, are described below.

Metachromatic Leucodystrophy

This disorder is inherited as an autosomal recessive trait and is due to a deficiency of the enzyme aryl-sulphatase A. Symptoms most commonly begin in the second or third year of life but the onset may sometimes be later. There is gradual but progressive gait disability, spasticity, speech impairment and intellectual deterioration. The deep tendon reflexes become reduced and are later absent. CSF protein concentration is raised and nerve conduction velocities are slow. Optic atrophy appears later. Death usually occurs from 6 months to 4 years after the onset of symptoms.

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All 4 patients reported here had a deficiency of aryl-sulphatase A and cerebroside sulphate sulphatase in their white blood cells. 2 children, aged 5 and 8, had abnormal CAT scans with areas of decreased density of white matter in both cerebral hemispheres, especially adjacent to the lateral ventricles (fig. 1). Symptoms of a neurological degenerative disease had been present for about 6 months in each child. Clinical examination showed dementia, spastic quadriplegia and areflexia in the first child. Dementia, behaviour disorder and asymmetrical pyramidal signs with increased deep tendon reflexes were present in the 8-year-old child. Nerve conduction velocities were slow and CSF protein was elevated in both children.

The sister of the 5-year-old child described above was shown to have biochemical metachromatic leucodystrophy by fibroblast culture of the umbilical cord. The enzyme deficiency was later confirmed in peripheral blood leucocytes. A CAT scan performed at the age of 6 months was normal. When last examined at the age of 12 months she was clinically and developmentally normal.

The fourth patient presented at the age of 4 years with speech regression and hyperactive behaviour disorder. No neurological signs were present, and nerve conduction velocities and CSF examination were normal. However electronmicroscopy of a sural nerve biopsy showed 'tuff-stone' inclusions typical of metachromatic leucodystrophy. The CAT scan was normal.

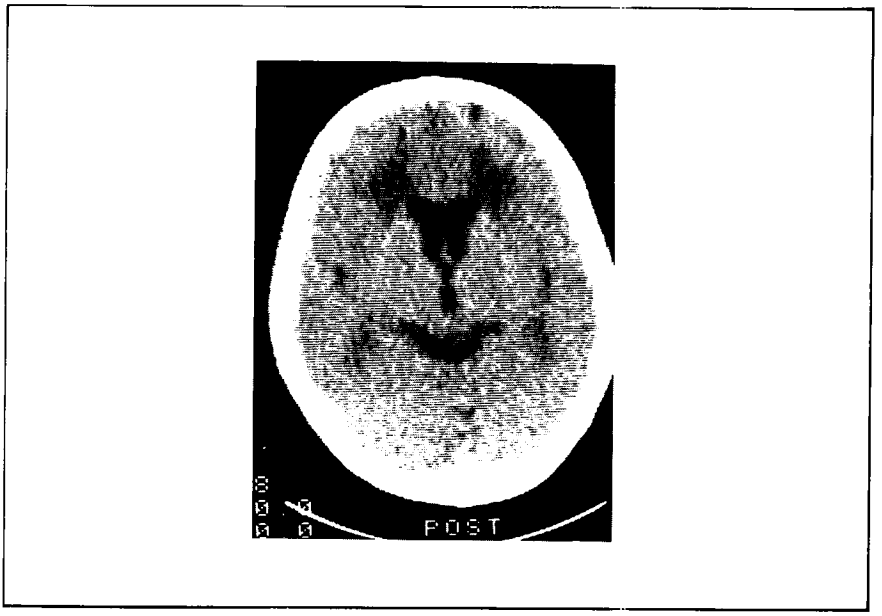

Fig. 1. CAT scan from a child aged 8 with metachromatic leucodystrophy, showing areas of decreased density adjacent to the frontal horns.

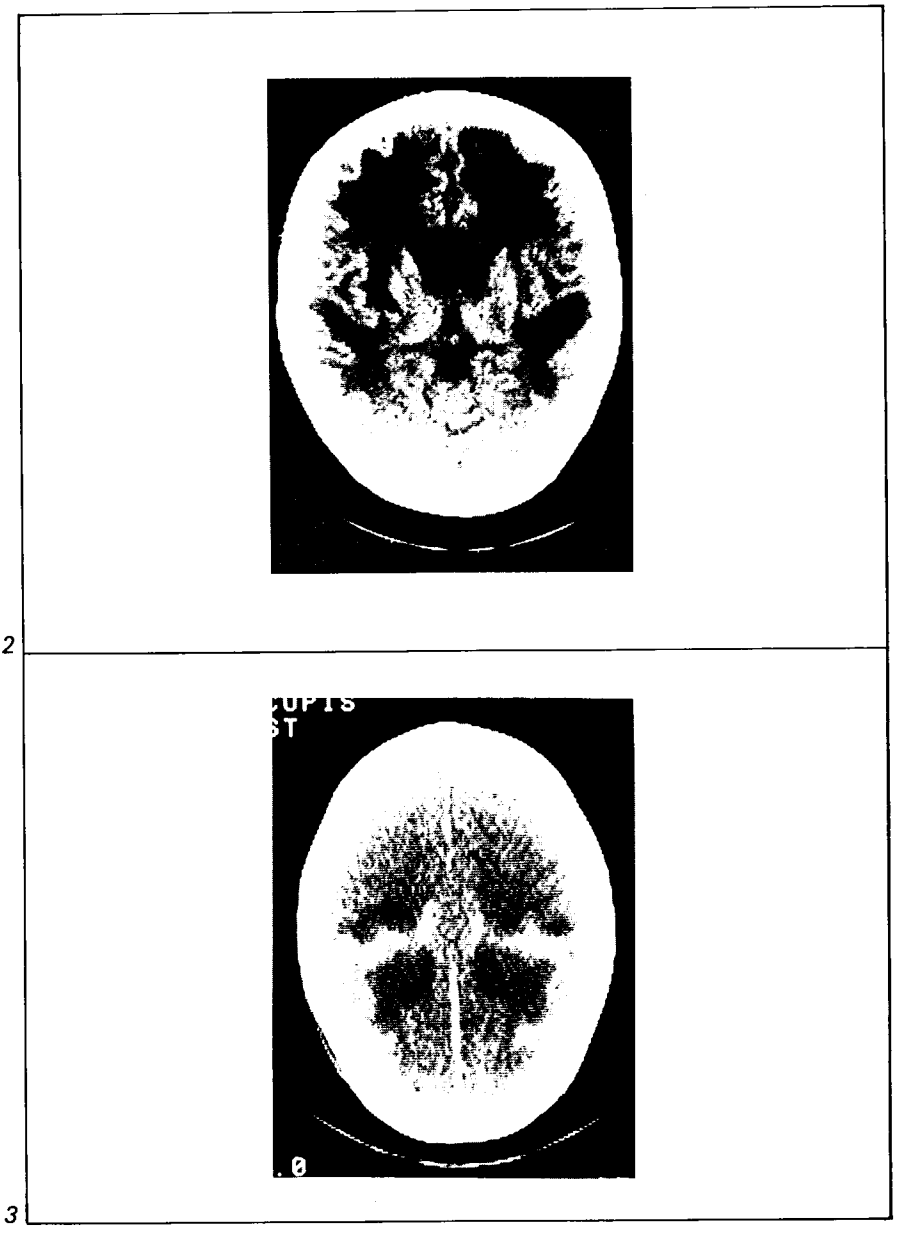

Fig. 2. Diffuse low density areas in white matter in a child with megalencephalic leucodystrophy.

Fig. 3. Low density areas in white matter with contrast enhancement at the anterior borders in a child with adrenoleucodystrophy.

Megalencephalic Leucodystrophy

3 siblings presented with heads pathologically enlarged since early infancy. All had progressive dementia and the development of bilateral pyramidal signs. CAT scans showed marked diffuse low density areas in the white matter of the cerebral hemispheres (fig. 2). A brain biopsy on the eldest child showed marked atrophy and gliosis, but no definite diagnosis could be made.

Adrenoleucodystrophy

The clinical and biochemical features of 4 boys with adrenoleucodystrophy have been described elsewhere in this volume (Procopis and Ouvrier, 1979). 3 of these children had CAT scans. In all, large confluent low density areas were present throughout the central white matter with no particular predilection for the occipital lobes. In 2 patients symmetrical enhancement occurred at the borders of the low density areas after infusion of contrast material (fig. 3). In the other patient no enhancement occurred.

Spongy Degeneration

A 15-year-old girl had had progressive ataxia and some mental deterioration from the age of 6 years. Examination showed marked bilateral pyramidal signs, intention tremor and truncal ataxia. An older sister had died from a similar disease and autopsy had shown marked spongy degeneration of the white matter. CAT scan showed ventricular enlargement and a small margin of decreased density around the frontal horns and bodies of the lateral ventricles.

Discussion

Since the CAT scanner has become a widely used tool for neurological diagnosis, many authors have reported areas of low density in white matter due to demyelination. For example, Cala and Mastaglia (1978) found low density areas in the scans of 51 % of patients with multiple sclerosis. A similar, but larger, lesion was present in another patient with 'Schilder's disease'. Robertson et al. (1977) reported on the CAT scan findings in 14 patients with a clinical diagnosis of demyelinating disorder. Scans showed areas of diminished density in 2 children with a myelinoclastic demyelinating disease and in 3 children with various leucodystrophies (metachromatic leucodystrophy, adrenoleucodystrophy and Pelizaeus-Merzbacher disease). Similar changes have been seen in a scan from a patient with Canavan's disease (Lane et al., 1978). The latter authors also reported a normal scan from a patient with Krabbe's disease. Abnormal scans are a consistent feature in patients with adrenoleucodystrophy (Greenberg et al., 1977; Robertson et al., 1977; Lane et al., 1978). A common finding is contrast

enhancement of the areas adjacent to and anterior to the low density areas. This is thought to correspond to a zone of active demyelination with associated inflammation (Greenberg et al., 1977).

In the past the diagnosis of many of the degenerative disorders of childhood was difficult. Often a pathological diagnosis could not be made before postmortem examination, even after full electroencephalographic, chemical and neuroradiological investigation. Brain biopsy helped in some cases, but was often of little value. In recent years methods for quantitatively estimating specific enzymes in leucocytes and fibroblasts have become available enabling biochemical diagnosis of some of the leucodystrophies (e.g. Krabbe's disease, metachromatic leucodystrophy). However in those conditions where a specific enzyme defect has not been identified (e.g. adrenoleucodystrophy), an anatomical diagnosis of demyelination of cerebral white matter is now available by use of the CAT scanner. Nuclear scans are also of use but their sensitivity in detecting the extent of areas of demyelination is less than that of the CAT scanner.

Summary

11 patients with a diagnosis of leucodystrophy are reported. In 9 the CAT scan was abnormal and showed areas of markedly decreased density in the white matter. 3 of these patients had adrenoleucodystrophy. In 2, contrast enhancement at the anterior borders of the low density areas was present. The 2 negative scans were from children with metachromatic leucodystrophy; one had an atypical form of the disease and the other had the biochemical defect, but was still presymptomatic and had no neurological deficit.

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Familial Trigeminal and Glossopharyngeal Neuralgia

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Neuralgia of the cranial nerves is recognised clinically by a history of short, sharp, severe paroxysms of pain in the sensory distribution of either the trigeminal or the glossopharyngeal nerve. Pain in the distribution of the trigeminal nerve was first described by Andre (1756) who coined the term 'tic douloureux'. Later Fothergill (1773) described the various features of trigeminal neuralgia in 14 patients.

Neuralgia in the distribution of the glossopharyngeal nerve was originally described in 1920 by Sicard and Robinson, and later by Bohm and Strang (1962) who described the numerous clinical presentations of the syndrome. The following case study is of a family with glossopharyngeal and trigeminal neuralgia. A familial inheritance of trigeminal neuralgia has been recorded previously, but not of glossopharyngeal neuralgia.

Case Reports

Case 1

The first member of the family (fig. 1) was the grandfather of the propositus (Case 3). His wife and others recall the onset of severe, intermittent, right-sided, facial pain in his middle 30's. He migrated to Western Australia in late 1940 and after a number of years of increasingly severe intractable pain he was treated surgically in Sydney in about 1945. He had a good result from the operation, and was pain-free until he died at the age of 84.

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Case 2

The second affected member, a civil servant, and father of Case 3, at 50 years of age first experienced a sudden onset of sharp, severe pain deep in the left ear. The pain lasted 1 to 2 minutes and did not radiate. These paroxysms of pain, frequently triggered by eating, occurred about once or twice a week for 3 to 4 months at a time, followed by a remission for a similar period.

4 years after the onset of this glossopharyngeal neuralgia, he experienced his first attack of trigeminal neuralgia. The latter was characterised at first by sudden, sharp, severe pain in the left forehead but later involving the whole of the left side of the face, and always lasting for 1 to 2 minutes. The pain occurred 3 to 4 times a day for some weeks, and then remitted for some months. There were no trigger zones. With the onset of trigeminal neuralgia, the glossopharyngeal neuralgia became less frequent. Examination revealed no neurological abnormality. X-rays of the base of the skull and cranial CAT were both normal.

Treatment with carbamazepine was started 14 months after the onset of trigeminal neuralgia, but the drug was withdrawn following a hypersensitivity reaction. He was then treated with glossopharyngeal and third division trigeminal nerve blocks with a good result. He died suddenly of a myocardial infarction before the intended administration of first and second division nerve blocks. There was no necropsy.

Case 3

The last affected member, a 29-year-old social worker, complained of a sudden onset of sharp, severe pain deep in her right ear, radiating to the parietal region of the scalp. The paroxysms of pain each lasted a few seconds and recurred every 10 to 20 seconds for 4 days. She recognised a trigger zone in the right parietal scalp, but there were no other precipitating factors. No palpitation or syncope was associated with the onset of the pain. Examination was normal except for apparent diminished sensation on the right side of the pharynx and the base of the tongue. Skull x-ray was normal.

Treatment with carbamazepine rapidly abolished the pain. She remained pain-free until 6 months after the first bout when she experienced the abrupt return of sharp, severe, paroxysmal right aural pain, radiating downwards into the right sternomastoid muscle. This attack was again treated successfully with carbamazepine.

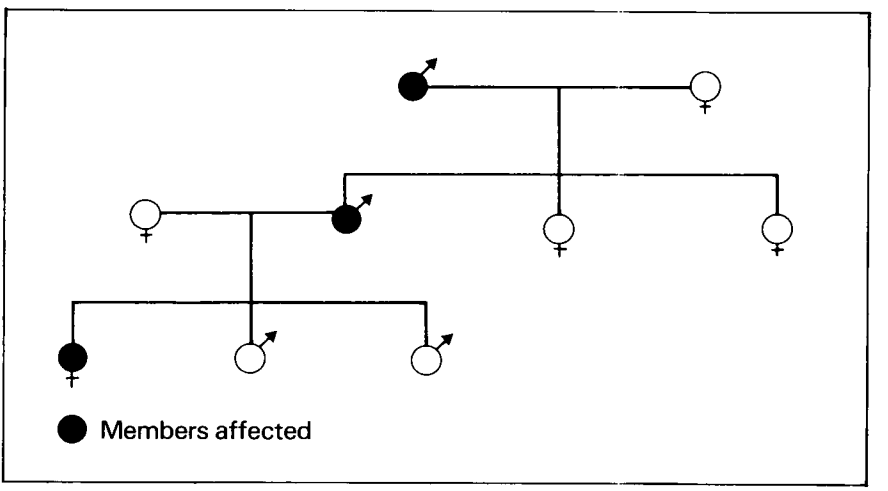

Fig. 1. Pedigree of a family affected with glossopharyngeal and trigeminal neuralgia.

Table I. A summary of the reports of the coincidence of trigeminal (T) and glossopharyngeal neuralgia (GN)

Author	No. cases with GN	No. cases with T and GN
Peet (1935)	14	5
Brzustowicz (1955)	34	9
Chawla and Falconer (1967)	10	1
Laha and Jannetta (1977)	6	1

Discussion

This family illustrates 2 interesting features: a familial inheritance of cranial neuralgias, and the concurrence of trigeminal and glossopharyngeal neuralgia in 1 of the 3 patients. A familial inheritance pattern of trigeminal neuralgia was noted initially by Patrick and in the literature of the familial incidence of trigeminal neuralgia Patrick (1914) and Harris (1936) reported 7 of 220 cases and 30 of 1433 cases respectively; Levy and Grant (1938) found a familial association in 6% of patients. A familial inheritance of glossopharyngeal neuralgia has not been reported previously.

The presentation of both trigeminal and glossopharyngeal neuralgia in a single patient was first reported by Peet (1935). His report together with other reports is shown in table I. Glossopharyngeal neuralgia is rare in that it has an incidence about 1% of that of trigeminal neuralgia. Bohm and Strang (1962) and Brzustowicz (1955) estimated that the combination of the 2 cranial neuralgias occurred more rarely still (in about 0.3% of patients with trigeminal neuralgia). These interesting variants of trigeminal and glossopharyngeal neuralgia, when considered in conjunction with the central connections of these nerves, may yield further understanding of the pathogenesis of the cranial neuralgias.

Pain, temperature and a portion of light touch sensations (Smyth, 1939) from the head and neck are transmitted in the trigeminal, facial, glossopharyngeal and vagal cranial nerves, and in the second and third cervical nerves to the spinal tract and nucleus of the trigeminal nerve (Dandy-Brown and Yanagisawa, 1973).

The trigeminal sensory fibres are arranged in a laminated fashion with the ophthalmic division caudally and the maxillary division cephalically (Smyth, 1939) in the spinal tract and nucleus of the nerve. The other nerves are randomly distributed in the lower portion of the spinal nucleus of the trigeminal (Kerr, 1967). The fibres after synapsing in the spinal nucleus are conveyed in the trigeminothalamic tract to the thalamus.

With the anatomical convergence of the trigeminal and glossopharyngeal nerves in the spinal tract and nucleus of the trigeminal nerve, central aetiological factors can be postulated. These include demyelination (King, 1967), epileptic activity (Black, 1974) and metabolic and ischaemic abnormalities (List, 1963). A central mechanism of pain such as the 'open gate' theory (Selby, 1973) or 'dorsal root reflex' (Crue, 1959), could explain the coincidence of the 2 cranial neuralgias in 1 patient. A centrally integrated mechanism of pain may account for the trigger zone occurring in a different sensory distribution from the pain as seen in the last patient.

Summary

A family incorporating 2 interesting variants of trigeminal and glossopharyngeal neuralgia is presented. The familial occurrence of these cranial neuralgias spanning 3 generations is very unusual. In the case of glossopharyngeal neuralgia it has not been documented previously. Furthermore, the coincidence of trigeminal and glossopharyngeal neuralgia in the same person is quite exceptional, despite the anatomical contiguity of the sensory territories of the fifth and ninth cranial nerves.

These features suggest firstly that there must be an important constitutional factor in the aetiology of the cranial neuralgia, and secondly that in many cases there is a centronuclear rather than cranial nerve ganglionic pathogenesis of the pain.

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Lipoma of the Cauda Equina: Case Report and Review of the Literature

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Lipoma of the cauda equina is an uncommon condition, said by Russell and Rubinstein (1959) to account for 1 % of all spinal canal tumours. Only one such case has been seen in the 20-year history of the Department of Neurology and Neurosurgery at The Queen Elizabeth Hospital, Adelaide. This case is described both because of the chronicity of the symptoms before the patient was referred for a neurological opinion, and because of the patient's improvement which followed surgery and which has been sustained over the 10-year period since.

Case Report

Mrs C. McC. was first seen in neurological consultation in July, 1968, at the age of 41 years. She gave a history of a left foot deformity noticed at the age of 4 years, of numbness of the left leg since the age of 7, and of an operation on the left foot 7 years later.

At the age of 17 she had osteomyelitis of the left leg, and occasional incontinence and diarrhoea. At the age of 21 there was a flaccid left leg with sensory loss below the left knee, and a below-knee amputation was performed at the Royal Adelaide Hospital. At the age of 25, during her second pregnancy, glycosuria was noted and she developed a sinus in the left buttock. Over the next 15 years she was treated somewhat sporadically for her diabetes and for non-healing ulcers of her right foot, while attempts were made to excise her left buttock sinus.

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At the age of 36 she began to complain of recurrent urinary infection and continuous dribbling incontinence developed 3 years later. Intravenous pyelography revealed hydronephrosis bilaterally with a contracted bladder. This was demonstrated at cystoscopy to be trabeculated with a bumpy mucosa. A transurethral biopsy showed chronic inflammation of the bladder wall.

A urinary diversion operation was recommended but was declined by the patient, as was a paniculectomy (offered because of her gross obesity). An indwelling catheter was inserted.

When seen in consultation on 10 July 1968 the patient had mild diabetic retinopathy, gross obesity, sinuses and scars in the left thigh and buttock and a left below-knee amputation. There was a sensory impairment affecting the right fifth lumbar and first 2 sacral segments with abolished sensation over the distribution of S3, S4 and S5. The right calf was fasciculating and the right knee jerk was absent. The findings were clearly those of an insidiously progressive cauda equina space-occupying lesion of over 30 years' duration. The differential diagnosis was thought to lie between a lipoma and a dermoid, there being no overlying dimple or hair tuft. Myelography showed a complete block at the level of the lamina of L3, no dye proceeding further inferiorly, and the column of Myodil from L2 to T12 being somewhat fragmented. The CSF was normal.

Exploration was performed on 24 July 1967. Laminectomies of L3, L4 and L5 were performed, the report stating:

'There was no pulsation of the dura below the upper border of L3. Opening the dura revealed that the nerve roots of the cauda equina were completely matted together as part of a severe arachnoiditis and the nerve roots on the left side and those centrally situated in the canal were so compressed and distorted as to be scarcely recognisable as neural tissue. At the level of L4 there was a large calcified plaque situated amongst the nerve roots. Retraction of the nerve roots to the right in this region showed that there was an ill defined tumour mass situated anteriorly to the cauda equina. This was encapsulated and it was of rather fatty and gelatinous consistency. It was possible to scrape out quite large pieces of the tumour using a pituitary spoon, although on two occasions quite fierce bleeding was encountered. In the setting of the severe secondary arachnoiditis and the presence of this tumour for such a long period, it was quite clear that total removal could not be hoped for. As much tumour as could be removed relatively easily was removed with restoration of better pulsation to the cauda equina.'

Postoperatively there was some definite improvement in sacral sensation over the S2, S3, S4 and S5 segments, although there was still marked perianal sensory loss. Lente insulin 48 units each morning was instituted.

By 4 September 1967 she had lost her diurnal and nocturnal incontinence, although she continued to have diurnal urinary urgency and to lack bowel control. Subsequently, undoubted improvement in sensation in the first and second sacral dermatomes occurred with the reappearance of partial sensation over the lower sacral segmental areas. Fluctuations in the activity of the left buttock and leg sinuses occurred once or twice a year over the next 5 or 6 years.

X-rays on 5 August 1976 showed an ill defined margin to the left ischium just below the acetabulum with subperiosteal new bone formation consistent with chronic infection. A sinogram confirmed the presence of a chronic sinus cavity extending towards the left ischial tuberosity. Her ESR was elevated at 58mm/hour and a further attempt was made to explore the left thigh sinus deep to the fascia lata for a distance of 5 to 6 inches above the level of the patella. A high renal threshold for glucose led to the substitution of monotard insulin 56 units daily.

The patient reported in May 1978 that following the laminectomy she had improved greatly in many respects. She had lost the backaches she had suffered all her adult life. She had continued to have loose bowels, but no longer faecal incontinence. Although there was still urinary incontinence this was well controlled with napkins and hyoscine butylbromide, and she had become able for the first time for many years to leave her house to visit friends, attend church and dine out at a hotel. She was able to do all her own housework again. She had regained pain sensation in the right sole as well as in the left thigh where the sinus would become painful if it became acutely infected, and there was some improvement in perianal sensation.

Discussion

Taniguchi and Mufson (1950) report intraspinal lipomas as accounting for 1 % of all tumours of the spinal cord, being equally distributed between the sexes and presenting in infancy, at puberty or in young or middle-aged adults. Caram et al. (1957) tabulated 51 recorded cases of intraspinal lipoma, most of which were thoracic or cervicothoracic in site, tending to cover the posterior surface of the cord. However, it is well known that lumbosacral lipomas are a fairly frequent accompaniment of spina bifida, especially in its occult forms. They spread longitudinally over several segments, being firmly blended with the cord and embedding the emerging spinal roots so that their total surgical removal is not practicable.

Microscopically the presence of adipose cells is of course characteristic, along with at times a considerable amount of collagen occurring as bands, or as a fine network of collagen and reticulum fibres which may separate individual nerve fibres. There may be a good deal of reactive gliosis. Occasional ganglion cells with islands of fibrillary neuroglia may occupy adjacent parts of the lipoma. At times there is striped and unstriped muscle and fibro-osseous tissue within the tumour.

It seems that the first reported case of spinal lipoma was that of Gowers (1876), affecting the conus. Ehni and Love (1945) collected 26 cases of intradural lipoma of the spinal cord and added 4 of their own. Additional cases were reported by Meltzer (1967) and by Riser et al. (1942) before Taniguchi and Mufson (1950) reported their case who had a 5-year history of symptoms emanating from the thoracic cord and who benefitted from decompression. By 1957 Caram et al. were able to review a total of 51 cases — 17 with autopsy reports — and added 2 cases of their own. Only 5 of these recorded tumours were situated in the conus or cauda equina region alone, 1 other involved the thoraco sacral region, 1 the lumbosacral region and 5 more extended the whole way from the cervical region to the cauda equina. 13 cases in all showed associated anomalies such as widening of the spinal canal, erosion of the pedicles and vertebral bodies, scoliosis or kyphosis or ivory vertebrae. However in only 1 cauda equina lesion case could an overlying subcutaneous lipoma be palpated.

In 1966 Giuffre reviewed 99 cases of spinal lipoma and reported an additional case. He stated that most intraspinal lipomas were subpial, were situated in the thoracic segment of the spine and were never completely enclosed by nervous tissue. He confirmed that roughly a third of the cases had various associated congenital abnormalities. Fearnside and Adams (1978) in their review of 70 consecutive cases of intrathecal cauda equina tumours seen at Oxford over a 40-year period, reported a single case of cauda equina lipoma which they said was removed totally.

It would seem that lipoma of the cauda equina and conus region is an uncommon lesion, probably accounting for little more than 1 % of intrathecal cauda equina tumours. While spinal intrathecal lipomas may be very extensive, perhaps only 10 to 15 % of all spinal lipomas affect the cauda equina and conus region. There are less than 25 such conus lipomas so far reported in the literature.

Summary

Lipoma of the cauda equina is an uncommon condition, accounting for some 1 % of spinal tumours.

The literature is reviewed and the case is reported of a 41-year-old diabetic woman, who was seen in 1968 with a 37-year history of left foot deformity followed by left leg weakness and sensory loss resulting in a left below-knee amputation, with subsequent development of osteomyelitis and a chronic sinus, and of urinary incontinence and sensory loss in the right foot. A complete spinal block was evident below L3.

Biopsy and limited removal of a portion of a lipoma of the cauda equina associated with considerable arachnoiditis was performed in 1967 and resulted in the disappearance of chronic back pain and cessation of faecal incontinence. There was partial restoration of bladder function and of perianal and left thigh sensation. This led to the patient being able to resume her household duties, and to visit friends and social functions after having been deprived of these pleasures for many years. Her condition has been well maintained since.

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Some Aspects of the Clinical Use of Clonazepam in Refractory Epilepsy

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Although the majority of epileptic patients can be satisfactorily controlled by treatment with one or more of the conventional anticonvulsants (Reynolds et al., 1976), there remains a hard core of patients whose seizures cannot be controlled adequately. In this group of patients new anticonvulsant drugs are used increasingly in an attempt to achieve satisfactory control.

Clonazepam has been shown to be effective in the treatment of various types of epilepsy (Birket-Smith et al., 1973; Chandra, 1973; Edwards and Eadie, 1973). It has been used in Australia in selective trials since 1972 (Bladin, 1973). Side effects have been a common problem, and most patients experience drowsiness when the drug is first given.

Sodium valproate was introduced by Meunier in 1960 (Meunier et al., 1963). It also is an anticonvulsant with a broad spectrum of activity. It is structurally quite different from the traditionally prescribed anticonvulsants, and its side effects are reported to be uncommon. The most frequent adverse symptoms are gastrointestinal, namely nausea, vomiting and diarrhoea (Simon and Penry, 1975; Noronha and Bevan, 1976).

Combination therapy with sodium valproate and clonazepam might be expected to offer some benefits. However, this combination has been criticised by Jeavons et al. (1977), because it was found that in a group of 12 patients on the combination, 5 developed absence status epilepticus and 9 patients showed severe drowsiness.

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Table I. Personal characteristics of 17 epileptic patients on sodium valproate and clonazepam therapy and details of medication

Patient	Age (yrs)	Type of epilepsy	Drugs taken concurrently with valproate and clonazepam	Duration of valproate and clonazepam therapy (m)	Max. dose clonazepam (mg/day)	Max. dose valproate (g/day)
1	24	Lennox-Gastaut	Thioridazine	18	6	2.6
2	35	Generalised	Phenytoin	11	6	4.0
3	15	Generalised	Phenytoin	23	4	3.2
4	30	Lennox-Gastaut	Phenytoin	14	8	8.0
5	42	Left temporal lobe	Carbamazepine	19	12	4.0
6	9	Generalised	Phenytoin	13	2	1.6
7	20	Lennox-Gastaut	Phenytoin	11	8	5.2
8	12	Right frontal focal	Phenytoin	11	8	1.6
9	32	Temporal lobe	Carbamazepine	3	3	2.8
10	42	Generalised	Phenytoin	6	8	1.6
11	33	Generalised	Nil	4	2	2.0
12	50	Generalised	Nil	?	12	4.4
13	25	Temporal lobe	Diazepam, carbamazepine	2	2	3.6
14	13	Generalised and absence	Phenytoin	0.5	8	1.6
15	27	Lennox-Gastaut	Phenytoin, diazepam	0.25	6	2.0
16	31	Generalised	Phenytoin	0.75	3	1.8
17	24	Left temporal lobe	Phenytoin, carbamazepine	0.25	6	1.2

Lance and Anthony (1977) reported a trial of sodium valproate and clonazepam used sequentially in an overlapping group of 32 patients. They found the drugs varied in effectiveness depending on the type of epilepsy, and found both medications to be safe and useful additions to anticonvulsant therapy. The present communication describes our experience with the combination of valproate and clonazepam.

Patients and Methods

1. Combination Therapy

17 patients, aged 9 to 42 years (mean 24 years), comprising 6 females and 11 males, were studied. All had severe epilepsy refractory to conventional anticonvulsants. All patients were attending the Neurology Unit of the Austin Hospital and were assessed on each occasion by the same team of observers. Measurements of plasma levels of drugs were used to guide dose adjustments wherever possible. Details of personal characteristics, diagnosis and maximum doses of sodium valproate and clonazepam prescribed are shown in table I.

The duration of treatment in the 17 patients ranged from 1 week to 23 months. 13 patients received combination therapy for at least 2 months and are still receiving treatment. 3 patients were prescribed a combination of valproate and clonazepam during a short period of transition from treatment with one drug to treatment with the other. 1 patient receiving both drugs stopped treatment after 2 weeks because of adverse effects.

All EEG's were reported by 1 observer and the reports were classified into 3 categories. Each was coded 'clear' if no abnormalities were noted, 'paroxysmal' if there was activity consistent with epilepsy and 'others' if these were intermediate abnormalities such as slowing, flattening or high voltage abnormal waves.

2. Clonazepam Therapy

In the second part of this report, 40 patients, (14 males and 26 females) aged from 8 to 60 years with a mean age of 28.3 years were reviewed. All these patients were taking clonazepam. Their diagnosis was generalised epilepsy in 33 patients and focal epilepsy in the remainder. The adverse effects associated with clonazepam therapy were evaluated on the basis of improvement after reduction of the dose or cessation of clonazepam therapy.

Results

17 patients were treated with a combination of clonazepam and sodium valproate and in 13 this combination has been continued up to the present. All were evaluated clinically and by serial EEG's.

Table II. Comparison of the number of fits suffered per week by 17 epileptic patients before and during valproate-clonazepam therapy

Patient	Fits prior to combination therapy (fits/week)	Fits during combination therapy (fits/week)
1	0.5-1	Nil for 16w, then 1
2	2-4	2-4
3	14	4
4	7	7
5	0.25-0.5	0.25
6	7-14	Nil for 6m, then 1-3
7	14	14
8	50 absences +0.5 T/C[1]	30 absences +0.5 T/C[1]
9	20	20
10	2-3	2-3
11	3-4	0
12	3-4	2-3
13	1	1
14	60	30
15	25	0
16	0.25	0
17	2-3	1

1 T/C = Tonic-clonic seizures.

Table II shows the clinical control of patients expressed as altered frequency of fits in comparison to pre-combination treatment. Before valproate and clonazepam were given, all patients had frequent seizures as often as daily or weekly. Only 3 patients showed marked improvement on combination therapy (Cases 1, 6 and 11); one of these remains completely fit-free, but 2 (Cases 1 and 6) have suffered relapses at 4 and 6 months respectively.

2 patients have shown a considerable reduction in total seizure frequency (Cases 3 and 12). 8 patients had no observable clinical benefit (Cases 2, 4, 5, 7, 8, 9, 10 and 13). 1 patient developed absence status epilepticus and had to stop treatment (Case 14). 3 patients have not been treated for an adequate time to allow evaluation of therapeutic benefit because they were in transition from treatment with clonazepam to treatment with valproate.

Table III shows the number of standard EEG's performed on the 17 patients before and during combination therapy, coded according to the type of abnormalities mentioned above and giving the incidence of abnormal EEG's before and during

Table III. Number and classification of EEG's performed on 17 epileptic patients before and during valproate-clonazepam therapy, showing the incidence of abnormalities in each period

Patient	No. EEG's before combination therapy				No. EEG's during combination therapy			
	total	clear	other	paroxysmal (% of total)	total	clear	other	paroxysmal (% of total)
1	16	0	0	16 (100)	6	4	2	0 (0)
2	6	1	1	4 (66)	10	1	0	9 (90)
3	5	0	3	2 (40)	14	0	3	11 (80)
4	20	0	5	15 (75)	13	6	1	6 (45)
5	3	0	1	2 (66)	10	4	6	0 (0)
6	11	1	4	6 (55)	2	0	0	2 (100)
7	40	2	14	24 (60)	8	0	0	8 (100)
8	21	8	9	4 (20)	4	2	1	1 (25)
9	12	4	7	1 (8)	1	1	0	0 (0)
10	16	3	0	13 (80)	24	8	3	15 (63)
11	7	1	4	2 (30)	1	1	0	0 (0)
12	6	0	1	5 (82)	6	0	2	4 (66)
13	5	0	4	1 (20)	1	0	1	0 (0)
14	71	10	6	55 (80)	9	2	0	7 (80)
15	1	0	0	1 (100)	2	0	0	2 (100)
16	5	3	0	2 (40)	5	5	0	0 (0)
17	15	3	4	8 (55)	1	1	0	0 (0)

clonazepam and valproate treatment. The frequency of EEG abnormalities shows that no consistent changes occurred with the combination of 2 drugs when compared with the tracings of these patients prior to combination therapy. The number of EEG's is not identical during the 2 periods because the pretreatment period had extended in some cases to several years before valproate and clonazepam therapy began.

The majority of patients received additional anticonvulsant therapy and attempts were made to keep plasma concentrations of these drugs in the therapeutic range, but in spite of this the paroxysmal abnormalities persisted as indicated.

5 patients had received sodium valproate prior to the introduction of clonazepam. Plasma levels of valproate showed no significant change after the introduction of clonazepam (table IV). No significant changes in haematological, biochemical, or clotting profiles were noted in this group of patients.

Adverse Effects

The adverse effects experienced by 8 patients receiving combined therapy were drowsiness, ataxia and depression. Most of these responded to a reduction in clonazepam dosage and 3 resolved spontaneously. 1 patient in the group receiving com-

Table IV. Comparison of the range of sodium valproate plasma levels in 5 patients before and after addition of clonazepam

Patient	Valproate plasma levels (μg/ml)	
	valproate alone	valproate and clonazepam
4	105-129	79-112
7	82-122	92-115
9	68-84	68-85
11	92-103	92-98
13	75-105	76-78

bined therapy developed absence status, and both valproate and clonazepam were withdrawn.

In the second group of 40 patients, 22 experienced adverse effects which are shown in table V. 4 patients had more than 1 side effect. The most frequent symptoms were drowsiness, irritability, lack of concentration and aggressive behaviour.

Discussion

The results of treatment in this small group of resistant epileptics are disappointing. This does not justify abandoning this form of combination therapy in cases resistant to conventional drugs, but the prospects of success are only moderate. Admittedly this group of patients is subject to frequent disabling epilepsy, and it is largely in this group that combination therapy would be used as a last resort. Temporary cessation of fits may be worthwhile and the mechanism of relapse may not be understood, but even so over 50 % of patients had no benefit at all from the valproate-clonazepam combination.

The EEG results bear out the clinical observation that the complication feared by Jeavons et al. (1977), namely inducing absence status, does not appear to be a numerically significant risk, although more patients in the previously reported group were subject to absences. The laboratory test results were in agreement with the reported safety of clonazepam and valproate. The incidence of ataxia and drowsiness may be related to high clonazepam plasma concentrations but these were not measured in this study. The incidence of adverse effects was higher in our group of patients than has been previously reported (Lance and Anthony, 1977). That side effects are readily reversible on dose reduction or cessation is in agreement with previously reported studies.

Table V. Adverse effects experienced by 22 of the 40 patients taking clonazepam

Adverse effect	No. of patients (%)
Aggression, irritability	7 (17)
Depression	2 (5)
Drowsiness	7 (17)
Agitation	3 (8)
Disorientation	2 (5)
Concentration difficulty	2 (5)
Ataxia	1 (2)
Blurred vision	1 (2)
Hallucinations	1 (2)

It appears that combination therapy with sodium valproate and clonazepam should be used only as a last resort. Even when adequate plasma levels of drugs are achieved the end results are less than satisfactory.

Summary

Sodium valproate and clonazepam were given in combination to 17 refractory epileptic patients and their progress was reviewed clinically and by EEG's. Even though plasma concentrations of sodium valproate and conventional anticonvulsants were monitored and adjusted according to individual requirements, combination therapy consisting of valproate and clonazepam was ineffective in controlling seizures in the majority of patients. A further 40 patients receiving clonazepam were reviewed in relation to adverse reactions. 22 patients in this group suffered from undesirable effects attributable to clonazepam. These effects were managed by cessation of the drug or a reduction in the dose. The commonest side effects were drowsiness, loss of concentration, irritability and aggression.

Acknowledgements

We wish to thank Mrs P. Morris, J. Miles and R. Lee-tet for laboratory assistance and Miss J. Ball for clerical assistance. Reckitts Australia generously supplied tablets of sodium valproate used in this study.

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Abstract

Current Trends in Research on Murray Valley Encephalitis

*B.H. Kay and R.L. Doherty**

Murray Valley encephalitis (variously known as the mysterious disease of Bourke, Australian X disease, Australian arboencephalitis and Australian encephalitis) has occurred in 9 outbreaks (1917, 1918, 1922, 1925, 1951, 1956, 1971, 1974, 1978) involving approximately 400 cases, most in south-eastern Australia, and in occasional sporadic instances in northern Australia. The clinical features have been described by several observers, most recently by Bennett (1976) and differ little from the acute virus encephalomyelitis syndromes described elsewhere in the world. Recent epidemics in the Murray-Darling basin, in addition to their clinical impact, have resulted in serious economic costs to the region. Some evidence from 1974 and 1978 implicates Kunjin virus as a second agent of arthropod-borne encephalitis in Australia, clinically similar to Murray Valley encephalitis.

The epidemiology of the disease is not yet completely understood in spite of steady progress over 30 years. Early workers suggested that the virus survives in bird-mosquito cycles in northern Australia and spreads south via viraemic birds and mosquitoes following particular rainfall patterns. This hypothesis has recently been questioned in the light of some as yet incomplete evidence for temperate zone survival. Recent investigations in north-west Western Australia have localised foci of persistent infection which will offer important opportunities for research on host-vector-virus associations.

Studies on the major vector, the freshwater breeding mosquito *Culex annulirostris* widespread throughout Australia, add further taxonomic, entomological

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and virological complexities: the vector potential of several mosquitoes like *Culex annulirostris* may require consideration. *Culex annulirostris* feeds predominantly on mammals and yet the suggested major transmission cycle involves waterbirds; naturally occurring mosquito populations, e.g. *Culex annulirostris* from various localities, are known to be heterogeneous in their ability to transmit arboviruses.

More detailed taxonomic, ecological, epidemiological and experimental study is needed, as is continued accumulation of diagnostic, clinical and histopathological data. Increased knowledge of the bionomics of *Culex annulirostris* may eventually lead to better control methods. The most immediate and attainable goal for epidemiological studies of the disease may be a more successful method of predicting epidemics, possibly to be based on combined meteorological, serological and entomological criteria.

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Abstract

Thyrotoxicosis and Myasthenic Syndrome, with Dissociation of Electrical and Mechanical Response

*H. Kranz, A. Williams and D.J. Caddy**

A 56-year-old woman presented with a 4-month history of proximal weakness, especially affecting the legs. There was associated heat intolerance, anorexia, weight loss, and mild peripheral paraesthesiae. She was thin and pale, and appeared depressed and lethargic. There were no systemic signs of thyrotoxicosis. There was generalised proximal weakness (strength 2/5 hips, 3/5 shoulders). Tendon reflexes were difficult to elicit even with reinforcement.

Thyrotoxicosis was diagnosed on the basis of thyroid function tests, and carbimazole 60mg/day was given. This dose was gradually reduced to a maintenance dose of 10mg/day. Thyrotoxicosis was controlled within 5 weeks of starting treatment.

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Initial assessment showed normal motor conduction velocities in upper and lower limbs. The amplitude of the compound action potential (CAP) was low. The effect of exercise on the CAP was assessed in the lateral popliteal and femoral nerves. No change occurred in either site. 3 months later the patient had repeat EMG studies because of persistent weakness in spite of control of the thyrotoxicosis. This time characteristic features of the myasthenic syndrome were present: low amplitude of CAP, post-exercise potentiation of 120% and potentiation on stimulation at 20 stimuli/sec of 265%. Treatment with guanidine hydrochloride 15mg/kg/day was started and gradually increased to 27.5mg/kg/day.

In spite of treatment for 5 months and the return to normal of the electrophysiological features of the myasthenic syndrome, the patient continued to be weak. The tension record of distal and proximal muscles showed a persistent slow development of tension, with facilitation of maximal tension reached with repeated contractions. Muscle biopsy showed only minor histological changes. *In vitro* tests were performed on excitation-contraction coupling in a segment of muscle using graded concentrations of caffeine. The muscle response was normal.

It is tentatively postulated that cholinergic transmission may be impaired at levels in the motor pathways proximal to the myoneural junction pathways, possibly at the anterior horn cell. Guanidine hydrochloride may not be effective at this level because of inability to cross the blood-brain barrier.

This case focuses attention on a number of aspects: the diagnostic criteria for the myasthenic syndrome, the value of repeated testing in a patient with unexplained weakness, the usefulness of measuring tension as well as electrical activity, and some consideration of the underlying pathophysiology. It is hoped that a re-appraisal of these aspects may help to define a number of patients who present with weakness of unknown cause.

Abstract

Carrier Detection in Duchenne Muscular Dystrophy

*G.A. Nicholson**

At the present time, the only hope of reducing the incidence of Duchenne muscular dystrophy (DMD) is through a program based on genetic counselling and detecting carrier females. Serum creatine kinase (SCK) estimation is the best single test for DMD-carrier detection. However, the test is elevated in only 50 to 60% of known DMD carriers.

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In this study of SCK levels, a group of adult known DMD carriers and a group of daughters of known carriers were compared. 45 % of the daughters had elevated levels compared to 53 % of adult group. On the basis of classical Mendelian genetics, 50 % of the daughters would be expected to be carriers. These results suggest that most of the carrier daughters are detected, in contrast to only half of the adult carriers being detected. Studies on individual carriers over 10 years also showed an age-dependent decrease in SCK activities in adult carriers. Age-corrected SCK density functions have been estimated from these results and should enable more precise genetic counselling in DMD.

Estimates based on the rate of change with age of SCK in carriers suggests that most carriers may be identifiable in infancy as females with high SCK levels. These results suggest the need for defining a specific abnormality to identify DMD carriers from other infants with raised SCK levels.

Abstract

Frequency Domain Analysis in Estimation of Nerve Conduction Velocity Spectrum

*D. Caddy, A. Williams and H. Kranz**

The maximal conduction velocity is the only velocity-related parameter used at present in the physiological assessment of peripheral nerve function. Information on the distribution of the spectrum of conduction velocities (SCV) within a nerve might improve our understanding in a number of areas, including mechanism of pathological processes, natural history of diseases, and response to treatment. By using the known relationship between conduction velocity and axonal diameter, an SCV could provide a non-invasive means of estimating the fibre diameter distribution in a nerve. Our method analyses the compound action potentials (CAP's) evoked by stimulating a nerve trunk at 2 points.

A nerve can be modelled as a signal transmission system consisting of multiple parallel paths. Given an input and output waveform in the idealised system, one can calculate the propagation delays in the different paths. In a peripheral nerve, the input waveform to each motor fibre can be considered as the motor unit action potential (MUAP) recorded from the muscle. Assuming supra-maximal stimulation, a CAP is formed by summation of all MUAP's. The idealised input waveform (CAP) would be

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obtained by simultaneous activation of all MUAP's at the motor point. In practice, this idealised input is not available because it involves stimulating and recording at the motor point, so the CAP recorded after most distal stimulation is used as an initial approximation to it. The output waveform is a CAP obtained by more proximal motor nerve stimulation, hence the CAP is formed by summation of the MUAP's, each delayed from the stimulus by an interval which depends on fibre conduction velocity.

In our analysis method, a first estimate of the SCV is calculated from the output waveform and initial input waveform approximation, using frequency domain methods. This estimated SCV enables improvement of the original input approximation. Further estimates of the SCV are obtained by repeating these calculations. The potential resolution of the method has been tested with simulated CAP's generated by placing known delay profiles on template action potentials. So far we have found that the most critical factor affecting resolution is the highest frequency component of the CAP. Preliminary extensions to patient data show that resolution can be improved by modifying techniques in order to maximise the band-width of the CAP's. We have also found that it is possible to improve the results by processing steps such as differentiating, filtering and scaling.

Abstract

Intermittent Claudication of One Cerebral Hemisphere

*D. Milder**

A 16-year-old girl presented with a 3-year history of transient left-sided sensorimotor symptoms occurring after hyperventilation and lasting from several seconds to half an hour. These included a sense of heaviness and increasing size of the left upper limp, and numbness and weakness of the left upper and lower limbs. Jerking movements of the mouth and arm and difficulty in comprehending speech were present during some episodes.

Angiography revealed a marked narrowing of the right internal carotid artery immediately above the common carotid bifurcation. The right anterior and middle cerebral arteries failed to fill after right carotid injection. Injection of the left carotid revealed normal filling of the left middle cerebral artery with delayed filling of the right and left anterior cerebral arteries and the right middle cerebral artery. These ab-

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normalities are presumed to cause an insufficiency of the right hemisphere, symptomatically apparent during periods of cerebral vasoconstriction, for example after hyperventilation.

Abstract

Pressure Palsy of the Common Peroneal (Lateral Popliteal) Nerve in Tetraplegia

*S.S. Gubbay, W.M. Carroll and G.M. Bedbrook**

19 patients, who at some time had been severely tetraplegic as the result of trauma, were submitted to electrodiagnostic tests in order to determine the incidence of common peroneal nerve palsy. Positive evidence of common peroneal nerve dysfunction was observed in 11 of these patients, the abnormalities being bilateral in 5. Nursing techniques ensuring physical protection to the vulnerable segment of the nerve at the knee might obviate this problem.

Common peroneal nerve palsy in paraglegic, tetraplegic and other immobile patients is a preventable hazard which can escape recognition and delay rehabilitation.

Abstract

The Anterior Tarsal Tunnel Syndrome

S. Hammond and G. Danta†

Compression of the deep peroneal nerve in the anterior tarsal tunnel constitutes one of the rarest of the entrapment neuropathies. Designated the anterior tarsal tunnel syndrome, it was first described in 1963 but since then only 7 cases have been reported.

The deep peroneal nerve supplies the extensor digitorum brevis muscle through its lateral branch, and its medial branch supplies the cleft of skin between the first and second toes dorsally after innervating the first and second interossei. Compression may affect the main nerve trunk or either of its branches separately giving rise to complete or partial syndromes.

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The most common symptoms are pain over the dorsum of the foot (which may cause nocturnal awakening), and sensory disturbance in the appropriate distribution, although occasionally weakness of the toe extension is noted. Examination may reveal tenderness over the nerve in the anterior tarsal tunnel with a positive Tinel's sign, sensory abnormalities in the appropriate distribution, and weakness and wasting of the extensor digitorum brevis muscle.

EMG and nerve conduction studies are useful in diagnosis. The expected findings are isolated denervation of the extensor digitorum brevis muscle and a prolonged distal motor latency to this muscle. No reports of sensory studies in relation to this syndrome have appeared in the literature.

We report a further case in which the deep peroneal nerve was compressed in the anterior tarsal tunnel by a ganglion of an extensor digitorum longus tendon. Routine EMG and motor conduction studies were performed preoperatively. Sensory conduction studies of the deep peroneal nerve were performed before and after operation using surface electrodes and averaging techniques. The diagnostic value of this technique in the anterior tarsel tunnel syndrome is discussed.

Abstract

Central Nervous System Manifestations of Cryptococcal Infection

*M. Pender**

6 patients with cryptococcal meningitis treated at St. Vincent's Hospital, Sydney are reviewed.

2 patients had no obvious predisposing cause. Presenting symptoms were mainly those of raised intracranial pressure, but focal signs including ataxia and isolated cranial nerve palsies were also seen. Fever and neck stiffness were absent in the majority of cases. 1 patient first presented with symptoms due to cryptococcal endophthalmitis. In none of the cases was the provisional diagnosis the correct one. The CSF most frequently showed elevated protein and depressed glucose levels and a pleocytosis usually with lymphocytes predominating, but in 1 case polymorphs only were present. Repeated CSF examinations were on occasions necessary in order to demonstrate the cryptococcal organisms. 5 patients had normal chest x-rays.

Patients were treated with amphotericin B and/or 5-fluorocytosine, although 1 patient initially presented prior to the availability of chemotherapy. The response to

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therapy and its complications will be discussed but the responses were in the main good, although permanent residual deficits were seen in 3 patients.

Noteworthy complications of the disease were disseminated cerebral invasion causing death, relapse of meningitis after apparently successful treatment, hydrocephalus with obstruction at the tentorial and aqueductal levels and late development of cryptococcal epididymitis and of arachnoiditis of unknown cause.

Persistence of cryptococci in the CSF, as demonstrated on Indian ink preparation but not on culture, occurred in 1 patient after treatment. There was no evidence of clinical recurrence.

Abstract

Paroxysmal Encephalopathy

J.R. Merory and G.R. Donnan†*

5 patients with paroxysmal encephalopathy are described. All had depression of consciousness and non-focal paroxysmal EEG activity. The cause in 3 patients was metrizamide introduced for lumbar myelography. The 2 other patients had metabolic derangements: one had hepatic failure, related to alcoholic liver disease, and the other had a combination of cardio-respiratory, renal, and hepatic dysfunction. Myoclonus was a feature in those patients who had received metrizamide.

In all cases, the paroxysmal EEG activity was remarkably reduced by intravenous diazepam or clonazepam. In 4 patients this was accompanied by considerable clinical improvement.

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† Austin Hospital, Heidelberg, Victoria (Australia).

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2) Summary
3) Text pages
   - Introduction
   - Methods
   - Results
   - Discussion
4) Acknowledgements
5) List of references
6) Tables
7) Figures and captions
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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).

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