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Contents

Graeme Robertson and the Golden Age of Neurology <i>R. Hooper</i>	1
Central Pain Mechanisms <i>A.W. Duggan</i>	11
A Review of Some Aspects of the Pharmacology of Levodopa <i>J.G.L. Morris</i>	24
The Pharmacology of Anticonvulsant Drugs <i>M.J. Eadie</i>	51
A Case of Spinal Cysticercosis <i>I.T. Lorentz</i>	85
Parasitic Diseases of the Nervous System in Thailand <i>A. Vejjajiva</i>	92
Vertebral Metastases and Spinal Cord Compression <i>B.A. Kakulas, C.G. Harper, K. Shibasaki and G.M. Bedbrook</i>	98
Wernicke-Korsakov Syndrome Lesions in Coronial Necropsies <i>R. Rodda, R. Cummings and K.S. Millingen</i>	114
Association of Central Nervous System Sarcoma with Familial Polyposis Coli <i>P.M. Williamson and K.V. Smith</i>	127
Preliminary Observations on the Pharmacokinetics of Methylphenobarbi- tone <i>M.J. Eadie, F. Bochner, W.D. Hooper and J.H. Tyrer</i>	131
Sodium Valproate: Dose-Plasma Level Relationships and Interdose Fluctua- tions <i>F.J.E. Vajda, G.W. Mihaly, J.L. Miles, P.M. Morris and P.F. Bladin</i>	144

A Comparison of the Absorption of Phenobarbitone Given via the Oral and the Intramuscular Route <i>J.K. Graham</i>	152
Posterior Fossa Arachnoid Cysts: Two Case Reports <i>G.H. Purdie and R.H.C. Rischbieth</i>	161
The Causalgia Syndrome Treated with Regional Intravenous Guanethidine <i>J.T. Holland</i>	166
Detection of Experimental Carotid Ulceration by Radionucleotide Labelled Particles <i>G.A. Donnan, W.J. McKay, D.P. Thomas and P.F. Bladin</i>	174
Acupuncture Analgesia for Chronic Low Back Pain <i>G. Mendelson, M.A. Kidson, S.T. Loh, D.F. Scott, T.S. Selwood and H. Kranz</i>	182
Visuo-motor Skill and Visual Perception in Left and Right Handed Children of Superior Intelligence <i>R. Mellick, I. Klajic, Helena Grahame and B. Higgins</i>	186
Individual Free Fatty Acids and Migraine <i>M. Anthony</i>	190
Autonomic Dysfunction in the Landry-Guillain-Barre Syndrome <i>R.R. Tuck and J.G. McLeod</i>	197
Electromyographic Study of Polysynaptic Responses from Muscles not Supplied by the Stimulated Nerve: Preliminary Report <i>J. Vernea</i>	204
Memory Disorder in Vertebrobasilar Disease <i>G.A. Donnan, K.W. Walsh and P.F. Bladin</i>	215
Delayed Radiation-induced Damage to the Brachial Plexus <i>R. Burns</i>	221
An Evaluation of Bromocriptine in the Treatment of Parkinson's Disease <i>R.A. MacKenzie and J.W. Lance</i>	228
Neurological Features of Polyarteritis Nodosa <i>G.L. Walker</i>	237
Primary Empty Sella Syndrome and Benign Intracranial Hypertension <i>S. Davis, B. Tress and J. King</i>	248
Occipital Neuralgia <i>S.R. Hammond and G. Danta</i>	258
Some Specific Neurological Complications of Acute Lymphocytic Leukaemia of Childhood <i>D.B. Appleton, A.F. Isles and J.R. Tiernan</i>	271
The Contribution of Evoked Potentials in the Functional Assessment of the Somatosensory Pathway <i>F.L. Mastaglia, J.L. Black, R. Edis and D.W.K. Collins</i>	279

Patterns of Response to Levodopa in Parkinson's Disease <i>F.J.E. Vajda, G.A. Donnan and P.F. Bladin</i>	299
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Abstracts

Immune Lesions of Central Noradrenergic Nerves in the Rat Produced by Anti- bodies to Dopamine- β -hydroxylase <i>W.W. Blessing, M. Costa, L.B. Geffen and R.A. Rush</i>	307
The Medial Pre-optic Area Rhythmically Inhibits a Hypothalamic Pacemaker Stimulating Growth Hormone Secretion <i>J.O. Willoughby, Judy Audet and J.B. Martin</i>	308
Growth Hormone Secretory Rhythms in Rats are Synchronised by the Suprachiasmatic Nucleus <i>J.O. Willoughby, Judy Audet and J.B. Martin</i>	309

Clinical and Experimental Neurology
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Graeme Robertson and the Golden Age of Neurology

*R. Hooper**

Today I have been given the distinction of presenting the first Graeme Robertson Lecture. This is an honour of which I am deeply appreciative. On these occasions it is always necessary to consider the achievements of the man in relation to his environment and to the time in which he lived and worked.

There are some who unfortunately live ahead of their time. Few of these will achieve much and fewer still will be remembered. Their energies are dissipated in struggles with an environment, if not actively hostile, at least apathetic. The man who lives at the right time is indeed fortunate. Graeme Robertson was such a man. He entered the neurological field at the right time. He developed a method of investigation when it was most needed. In his other achievements in aspects of architectural design, he drew attention to the beauty and utility of those designs and decorations at a time when consciousness of the need for their preservation was developing.

But what of this man who in his quiet, undemonstrative manner achieved so much? What were the influences in his life and work? What was his influence on his time and his environment?

Edward Graeme Robertson was born in Victoria, a second generation Australian, a mixture of Scottish and Cornish genes. He showed early promise as a student and this was recognised by his parents who provided him with facilities and opportunities.

His early education was at Scots College where he obtained Honours in English and an Exhibition in Biology. At Scots College there were two influences which were

*Melbourne (Australia).

important. One was Mr Edmonds, the writing master, a fine figure of a man, physically strong, though with a pen he was gentle and sensitive. There is no doubt that he was largely responsible for Graeme's fine penmanship. But he also started Graeme's life-long interest in tales of mystery and imagination. Mr Edmonds had a great gift for telling stories and if the boys handled him properly with just the right amount of flattery, he would end his lesson with stories from Conan Doyle's 'Sherlock Holmes' and 'The Lost Continent'. To the end of his life Graeme always appreciated tales of mystery and detection.

The other influence at Scots College was Mrs Ada a'Beckett, who taught biology and who was responsible for starting many brilliant men on their careers in medicine.

At the University of Melbourne, Graeme came under the influence of two outstanding but opposite figures. Professor Richard Berry taught anatomy in a rigid and exact manner and his primary interest was in the brain. Professor Osborne delivered his lectures as if reading fine prose. The exactitude of Graeme's anatomical descriptions and the smooth clarity of his writing owes much to these sources.

Graduating with honours, he became a resident and then a registrar at the Melbourne Hospital where he came under the influence of Dr Sydney Sewell, a fine physician who was regarded as the best neurological opinion at that time. Graeme impressed Dr Sewell with his flair for clinical demonstration. On student rounds Dr Sewell would select a patient for case presentation and then borrow specimens from the Pathology Department to illustrate the relevant changes. Years later, these impressions left from Dr Sewell were to be a major factor in Graeme's return to Australia and his appointment to the Honorary Staff of the Melbourne Hospital. After obtaining the MD degree, his move to London was inevitable and he was fortunate to work at the National Hospital for Nervous Diseases in Queen Square when its reputation was at its peak. Here he laid a firm foundation in clinical neurology and was trained in the rapid, systematic and thorough method of neurological examination perfected by Dr Gordon Holmes. He acquired the art of case demonstration for which Queen Square was then world famous. Years later, it was still possible to pick out odd characteristics acquired from Gordon Holmes and George Riddoch.

Longstanding friendships were made at Queen Square. That with Derek Denny-Brown was important for their close association in their work on the physiology of micturition, which gained them a worldwide reputation for careful but brilliant research. This was invaluable for Graeme's later work on pneumoencephalography. At the end of the time 'on the House' at Queen Square, he obtained consultant posts at Bart's and the Hammersmith Postgraduate School. A career as a consultant in London seemed assured.

Just at this time a vacancy for a physician occurred on the staff of what was now the Royal Melbourne Hospital. This was the great decision. Should he return? It was hoped that this appointment would soon be followed by the creation of a position of Neurologist. It was Dr Sewell's intention to get Graeme back to Melbourne before he had reached the point of no return in London. Graeme was appointed but then plans

were delayed for he was to remain as a general physician for nearly ten years, until the transfer to the new Royal Melbourne Hospital in 1944. With this appointment came the creation of the Department of Neurology and Neurosurgery and during the next twenty years Graeme established his worldwide reputation largely as a result of his work in this unit. The symbiotic growth of neurology and neurosurgery thrived. Graeme developed the technique of pneumoencephalography beginning with basic research on mechanisms and anatomy and finally the correlation with a significant volume of clinical material. He became a world authority, publishing four books and many papers on the subject, the last and perhaps the best being published in the Handbook of Clinical Neurology, just before his death after a long illness on December 25th, 1975. His methods and writing had influenced neurologists and radiologists around the world.

During the later portion of the twenty five years after World War II, Graeme utilised his flair for pictorial presentation to remind Australians of some of the hitherto unrecognised beauty of their own surroundings. His books and lectures on an earlier period of Australian architecture became well known.

He held many significant positions in medical and public life. He was a foundation member of this Association, he was largely responsible for the publication of the Proceedings and for the waratah as the ensign of the Association. He rarely missed a relevant meeting, always taking part in the interchange of ideas and opinions so essential at these gatherings. His patients held him in high regard, not only for his knowledge and wisdom, but for his kindness and above all for the sympathetic understanding of their problems. How Graeme listened to all their troubles and still remained punctual in his appointments is extraordinary. Occasionally, he got into trouble. One miserable old man, after finding a sympathetic doctor who would listen to his complaints of headache, made person-to-person telephone calls to Graeme from all parts of Victoria and New South Wales, at all hours, to discuss the latest variation. Graeme would listen patiently at the time, while thinking of a way out. After many months of trunk calls at all hours, the solution came. A frontal lobotomy was suggested and later performed with diverse results. The patient re-married and went off with a young widow: he was happy but his relatives were upset. The surgeon was not paid and he was upset. Graeme had no more telephone calls and he wasn't at all upset.

During these years, Graeme had secretaries who were devoted to his work, Mrs Muriel Thompson, Miss Schrader and Miss Peg Turnbull and, of course, in the later years the devotion of his daughter Joan.

In 1935 Graeme married Jane Duce, who shared his love of beautiful things and until she died in 1973 kept the house in a manner which Graeme loved. Of the two children, Denis carries on the medical tradition while Joan, who had been a collaborator in the later books on architecture, carries this work on to its completion.

Passing now from the man to his background in neurology, it is necessary to consider the rise and development of modern neurology. In historical time, this

period extends over 150 years. Before the Napoleonic Wars, knowledge of the workings of the nervous system was so primitive that it is difficult to believe that it could lag so far behind the discovery of the circulation of the blood.

At the time of the battle of Waterloo, Sir Charles Bell commented upon the state of knowledge of the nervous system: 'There was a singular indifference to the study of the nerves, and an opinion generally held that as the notions of the ancients had descended to us, uncontroverted and unimproved, the subject was entirely exhausted . . . the hypothesis that a nervous fluid was derived from the brain and transmitted by nervous tubes was deemed consistent with anatomical demonstration and there was no hope of improvement'.

In the next 150 years a more intimate knowledge of the normal and the abnormal was obtained by first, the tremendous advances in basic anatomy, physiology and pathology; secondly, the clinical analysis of disease processes and the synthesis of disease groups; and finally, the development of investigations which allowed a visual representation of the disease process in the living patient.

Although there is some overlap, these three factors can be arranged in a useful temporal sequence. The basic sciences occupy the first 50 years. Then came the great clinicians, many of whom had been brought up in the hard school of European anatomy and pathology. Then finally, because correlation between the basic sciences and clinical medicine in itself was not sufficient to keep up with the rapidly increasing demands of surgical enterprise, there came the development of a series of investigational procedures which allowed the diagnosis of position and pathology in the living patient to be carried forwards to an extraordinary degree. It is appropriate to illustrate these periods by referring to the men who contributed to these advances rather than to the changes themselves.

Of the early anatomists, thoughts turn naturally to Sir Charles Bell, who published the 'Idea of a New Anatomy of the Brain' in 1811. Earlier he had published 'Essays on the Anatomy of Expression in Painting' which had been the means of entry of this Scottish anatomist-surgeon into artistic and social circles in London. Subsequently he became a busy surgeon but his interest in neuroanatomy continued. He described the anatomy of the nerves of special senses. He discovered that the posterior nerve roots carry sensory fibres and that the anterior nerve roots carry motor fibres. He described the facial palsy which has been named after him.

Localisation of function within the brain was still to come. Perhaps work in this direction got off to a bad start with Gall and Spurzheim. Gall began by postulating that the grey matter of the cerebral cortex was the origin of mental activity. Gall and Spurzheim went further by asserting that specific mental activities were located in certain specific areas of the cortex and then went further still to assert that these areas were closely associated with bumps and prominences on the skull itself. So phrenology began. Gall, or perhaps it was Spurzheim, had gone too far for their colleagues in Vienna. Gall lost his legitimate practice and went on a lecture tour with Spurzheim to spread their ideas amongst more impressionable people. The lecture

tour was a sensation. Gall later settled in Paris, where it was said that he devoted his time to 'gardening, women and the brain'. In spite of the nonsense that Gall and Spurzheim had generated, the concept of localisation of function had been planted in the minds of men.

Later Paul Broca, in 1861, postulated the localisation of speech in the left third frontal convolution because one of his patients with a longstanding aphasia had died and an area of softening was found in this situation at autopsy. Broca refused to cut the brain. A controversy began which was not terminated when Pierre Marie cut the brain forty years later and found a much larger area of involvement. Between 1860 and 1870 the observations made by Hughlings Jackson on epilepsy, in which seizure patterns were correlated with lesions at autopsy, led more directly to our present concepts. At about the same time Fritsch and Hitzig were exploring the cerebral cortex of dogs with the newly discovered electrical currents. They found that muscles contracted on the opposite side of the body, and that later removal of this part of the cerebral cortex led to weakness in the previously excited areas. It remained for Ferrier, in a more detailed and meticulous study by stimulation with small electric currents, to map out the motor areas. Ferrier linked his work with that of Hughlings Jackson and for the first time surgeons were able to operate on an area of the brain with some chance of finding what they were looking for. Horsley did much to advance this knowledge. William Macewen in Scotland, operating with antiseptic techniques, found a blood clot in the situation where it was predicted to be and was gratified by the rapid recovery of the patient.

This new-found knowledge was a great stimulus to the clinical neurologists who then dominated the field for nearly fifty years. In this group, Jean Martin Charcot must be included, though he lived at an earlier time. He had indicated localisation of function in the cerebral cortex by correlation of disease and pathological changes. Charcot was a giant. At 37 he was made Medical Superintendent of l'Hospice de la Salpetriere with its 5000 or more inmates, many of whom had never been diagnosed. He observed and described many diseases for the first time. He was a great neurologist. Five volumes of his 'Lectures on Diseases of the Nervous System' were translated into English. Charcot was a great demonstrator and drew doctors from the world over. It is probable that he started the first Department of Medical Illustration, employing Richer, a sculptor, and Londe, a photographer. Charcot was himself a formidable caricaturist, making fast sketches of patients which were later polished up for publication by Richer. He had the facility for seeing essentials in the mode of presentation of disease.

In England, Hughlings Jackson and William Gowers had used epilepsy as a model for working out cerebral localisation. Both men survived well into the 20th century. Of more immediate concern are those neurologists who had a direct link with Graeme Robertson: James Collier, Kinnier Wilson, Gordon Holmes, Charles Symonds and F.M.R. Walshe. These were the last of the great clinical neurologists.

Gordon Holmes had a great influence on Graeme Robertson. He graduated from Trinity College, Dublin, and bore this imprint in the clarity of his expression for the rest of his days. Later, having become interested in neurology he went to Europe to study neuroanatomy under Weigert and Edinger. This early grounding was responsible for his almost unerring accuracy in cerebral localisation. He maintained his interest in anatomy and physiology and clearly demonstrated this in his demonstrations and writings. F.M.R. Walshe said of Holmes:

'He had a great gift of making clear to his students the thread of his thought and the grounds on which he reached his conclusions.'

'He never posed as an oracle or a maker of slick diagnoses and he expected the same approach from his students and residents.'

'To be trained by him was a severe but most salutary discipline.'

Gordon Holmes developed and taught a rapid method of examination of the central nervous system, which was not seen before this time. Graeme Robertson brought this method to Australia. In spite of the improvements in clinical diagnosis of cerebral events, the accuracy was not sufficient to meet the increasing efficiency of modern surgery. One of the difficulties was that pathological processes rarely confine their effects to areas evoking abnormal signs during neurological examination. Accurate delineation of a lesion on clinical grounds is not always possible.

Then came the final phase in which new investigations were introduced which were to bring accuracy in diagnosis to almost unbelievable levels. Visualisation of the ventricles was the first major step forwards. It had been noted in 1912 that in some frontal sinus head injuries air passed into the ventricular system and was detected in radiographs of the skull. Some five years after this was reported, Walter Dandy (after realising how the recognition of gas below the diaphragm could lead to the diagnosis of a perforated peptic ulcer) conceived the idea of introducing gas into the lateral ventricles as a method of localising tumours. An extraordinary piece of lateral thinking. This was not enough, and to Dandy it was a logical step to introduce gas into the subarachnoid spaces around the brain by injecting it by lumbar puncture. At that time, there were difficulties in the selection of patients for this type of investigation and there was no certain method of introducing gas into areas where it was particularly wanted. Deaths occurred and accuracy in diagnosis was not high. According to Egas Moniz, in Dandy's first 97 air studies the correct diagnosis was obtained in only 32.

Many workers — neurologists, neurosurgeons and radiologists — studied this problem but it was Graeme Robertson who was largely responsible for working out how gas passed through the ventricular system and how it could be manipulated into areas where it was needed. He studied the hydrostatic problems in models and carefully recorded the appearances of air studies in patients. He was able to work out a method which advanced diagnostic accuracy to a high level. The appearance of various tumours and disease processes was shown with great clarity in drawings and film, his book finally becoming an atlas of pneumoencephalography.

Increasing knowledge of pathology and advances in x-ray technology put ideas into the fertile brain of a very eager Portuguese neurologist, Egas Moniz; after seeing the results of radiographs of limbs in which the blood vessels had been injected with radiopaque solutions he applied this concept to the brain. There were many difficulties but Egas Moniz was not daunted. He established a method which he called arterial encephalography. This provided a new dimension. Not only was it possible to show disturbances of the normal brain anatomy but various tumours could be recognised by their vascular pattern. Abnormalities in the vessels themselves were found which led to a revolution in the diagnosis of cerebral vascular accidents and gave a tremendous impetus to neurosurgical endeavour. Technique of injection improved, contrast media became less toxic and it was then possible to obtain magnified images of small vessels.

With the rapid expansion of electrical technology after World War II, it became possible to record the electrical potentials (shown by Hans Berger to occur on the surface of the brain) and to display these in a meaningful fashion. Variations in the pattern of the wave forms were correlated with different types of epilepsy and also with some local tumour processes. It was hoped that this procedure, which caused no distress and no x-radiation, would aid localisation. Unfortunately, the EEG did not measure up to requirements in this sphere but it has been very useful in the diagnosis of certain viral types of encephalitis and some epilepsies.

Atomic physics, trying to redeem itself after the holocaust of the atomic bomb, now invaded medicine. Radioisotopes can be injected into the bloodstream to produce static pictures of tumours when leakage across the blood brain barrier has occurred or the blood flow through the brain can be demonstrated in a dynamic manner. Injection into the CSF pathway also permits a dynamic scan in disturbances of the CSF circulation. Accuracy and efficiency have improved in a short time.

Finally, in 1963 there came the extraordinary concept of Oldendorf, followed in 1970 by the brilliant work of Hounsfield. His amalgamation of the principles of radiographic tomography, the detection of radiation by scintillographic means and the computerisation of results, was able to produce (without discomfort to the patient, and in a matter of minutes) a final display of brain tissue in a form reminiscent of a post card. Detection and localisation of a vast array of lesions now became possible.

For many this was a radical change — a new orientation. For two or three decades a certain three dimensional concept of the brain had been developed. Then it became necessary to adjust to two or three slices arranged in a way which was unfamiliar. One's mind went back to the motif of that column in the old Sydney 'Bulletin' devoted to 'The Other Fellow's Mind.'

Now there are at least four choices of investigation for intracranial disease: air studies; angiograms; radionuclide scans or computerised tomographic scans. These procedures have been largely taken over by radiologists and it is felt by some that the Golden Age of Neurology has passed and that the Golden Age of Radiology has begun. This is not an idle statement for there is little doubt that the change has been

Table 1. Percentage of accurate diagnoses according to the method of investigation used

Tumour	Radionuclide scan	Angiography	Pneumoencephalography	Computerised tomography
Supratentorial	82.2	95.0	95.2	92.7
Infratentorial	56.9	82.1	97.8	100

condoned and accepted by the neurologist, with the result that the radiologist — the body imager in modern terminology — may determine the length and breadth of the investigational process. This is a matter for some concern. The neurologist should hold the strings of the puppet. After the clinical assessment of the patient, a routine of investigations should then be worked out, due consideration being given to the following factors concerning the investigations being used:

- 1) accuracy in diagnosis
- 2) range of usefulness
- 3) patient reaction
- 4) capacity for detailed information — image display
- 5) safety to the patient
- 6) cost and time to both patient and community.

The choice is not always easy. It is well known that in primates 'choices give you ulcers', but these choices must be made by the neurologist or neurosurgeon. The selection can only be made with full knowledge of the clinical features on the one hand and, on the other, full awareness of the above factors. Accuracy in diagnosis may be taken as an example. This is not the only factor to be considered. In many situations the diagnosis is known and investigations are only required for demonstrating precise anatomical relationships — a necessary prelude to surgery. A child with suprasellar calcification is a classic example. Fine detail is required to assess operability, not gross confirmation of a known diagnosis. Accuracy of course is an important factor and one which lends itself to quantification, as is seen in table I.

Even more desirable is an evaluation of each method of investigation in relation to the clinical problem presenting. This can be set out rather like a school report as in table II. This assessment would indicate that in the case of cerebellar tumours computerised tomography should be done first and followed by air or contrast studies. In the same way, a cerebral arteriovenous malformation deserves computerised tomography followed by meticulous angiography.

All innovations in the diagnostic field are likely to cause a disturbance in the balance of current practice. Three problems have recently arisen. One which affects neurologists acutely is the direct referral of a patient by the family doctor for computerised tomography. If this is negative, the patient may go no further. If a tumour

Table II. An evaluation¹ of various methods of investigating cerebellar tumours

Factor	Pneumoencephalography	Angiography	Radionuclide scan	Computerised tomography
Accuracy	B	C	B-C	A
Range of usefulness	A	C	B-C	A
Patient reaction	C-D	C	A	A
Detailed information	A	C	C	C
Safety	B	A	A	A
Cost	\$150	\$75	\$50	\$150

- 1 A = very good or excellent
 B = good
 C = fair
 D = poor or inadequate

is shown the patient may go straight to the neurosurgeon. This is a serious problem. If the practice continues, the loss of this clinical material may result in significant changes in the clinical experience and sphere of activity of the neurologist. The two other problems are surgical. Because computerised tomography has a high reputation for accuracy, it is thought by some that no further investigations are necessary. This has on occasions resulted in difficulties and inadequate operations, especially in the sellar region. The other problem is more difficult to overcome. Years ago in the training of the general surgeon, the ability to perform a simple emergency exploratory craniotomy for head injury depended on the trainee's experience in a neurosurgical unit. Computerised tomography has greatly diminished the numbers of such procedures. There are also fewer angiograms and fewer pneumoencephalograms. In consequence there is greater difficulty in gaining the experience and expertise so highly desirable. Perhaps some of the answers to these problems are political. All require serious consideration. The present role of the neurologist is not one of active participation in these investigations. It is true that the technological expansion of 'body imaging' has been difficult enough for the majority of radiologists to cope with because of the financial cost and electronic complexity involved. Perhaps it is not right for the neurologists simply to sit back and admire. There is an old radiological aphorism which states 'You only see what you are looking for and you only look for what you know'. A corollary of this is 'The man who sees most in an investigation is the one who knows most about the condition'. When it comes to visual representa-

tion of a disease process, it surely should be the clinician who knows most and sees most.

In a changing world this is becoming increasingly difficult to attain. It is felt that at the present time the traditional guardians of the nervous system should do more to regain their hold on the investigational field. Countries have adopted dual citizenship. Surely it is not too difficult to extend this principle to faculties and colleges. Much may be achieved by ensuring that the trainee neurologist and neurosurgeon of the future obtains a much greater radiological knowledge and competence. The Golden Age of Neurology must not pass away.

Graeme Robertson lived in, worked for and enjoyed to the full the Golden Age of Neurology. He left behind him a valuable heritage in his work with patients, his teaching of students and his writings. He accomplished a great deal because he was a hard worker. Although he was always busy, he did take time to evaluate methods and management and to adjust to changing circumstances. Perhaps, this is the lesson from him to be remembered.

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Central Pain Mechanisms

*A.W. Duggan**

When investigated by older neuroanatomical techniques, impulses conveying nociceptive information were considered to be carried to the spinal cord by unmyelinated fibres, which synapsed in the dorsal horn and ascended to the thalamus by the lateral spinothalamic tract. As with most sensory pathways, this description has been considerably modified with the advent of modern neurophysiological and neuroanatomical techniques. The evidence obtained with these techniques will be briefly reviewed.

One of the major aims of research into pain mechanisms is to interrupt, selectively, the transmission of nociceptive impulses at several levels of the nervous system. Two of the more interesting findings in recent research are relevant to this aim. Firstly, analgesia has been produced by stimulation of midline areas of the midbrain and medulla. There are early reports that analgesia can be produced in man by stimulation near these areas. Secondly, peptides have been isolated from brain which act at the same central receptors as opiate analgesics. This raises the possibility that activation of appropriate central pathways might result in the release of these peptides, the endorphins, to produce segmental or whole body analgesia. Both of these aspects of pain research will be discussed.

Nociceptive Afferents

Recordings from small filaments of peripheral nerve have shown that noxious skin stimuli produce impulses in two types of fibre: unmyelinated (C) fibres with con-

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duction velocities of less than 5m/sec and small myelinated (A δ) fibres conducting at 5 to 30m/sec (Bessou and Perl, 1969; Burgess and Perl, 1967). The noxious stimuli used in these experiments were mechanical or thermal and, although receptors specific to each type of stimulus exist, most are polymodal and are excited by both stimuli.

Spinal Connections

In primates, unmyelinated fibres enter the spinal cord in the lateral division of the dorsal root, enter into Lissauer's fasciculus, and terminate almost exclusively in the substantia gelatinosa (Szentagothai, 1964; Lamotte, 1976). There is evidence that the A δ myelinated fibres conveying nociceptive information terminate superficial to the substantia gelatinosa in Rexed's lamina I (Kumazawa and Perl, 1978). In much of the discussion which follows reference will be made to the laminar structure of the spinal cord (Rexed, 1952). This is a cytoarchitectonic division of the spinal grey matter into nine areas. In the dorsal horn, six transverse areas were described. Laminae II and III are the substantia gelatinosa, lamina I is dorsal to this area while laminae IV, V and VI occupy approximately equal parts of the dorsal horn ventral to the substantia gelatinosa.

Both myelinated and unmyelinated primary afferents enter the substantia gelatinosa. Unmyelinated fibres enter dorsally while myelinated afferents, having coursed medially over the dorsal horn, enter from the ventral side. Each primary afferent branches extensively in a rostro-caudal direction with little lateral spread. This results in sagittally oriented sheets of neuropil, the 'bushy arbors' (Scheibel and Scheibel, 1968). The intrinsic neurones of this area have axons which do not leave the substantia gelatinosa, but may project several segments via Lissauer's fasciculus. Dendrites of deeper neurones, particularly those of lamina IV, penetrate the substantia gelatinosa radially (Szentagothai, 1964) and this is probably the major means of forward conduction from the area. Unusual groupings of nerve terminals, synaptic glomeruli, occur in the substantia gelatinosa but there is disagreement over the source of the structures within each glomerulus. The central process is probably a bulbous expansion of an unmyelinated primary afferent (Rethelyi, 1977, but see Kerr, 1975). A number of axon terminals and dendrites establish connections with the central process and, on the basis of synaptic morphology, not only axo-dendritic but axo-axonic, and dendro-dendritic connections have been described (Gobel, 1975). It is this complex synaptic arrangement which has caused the substantia gelatinosa to figure prominently in theories of pain transmission within the spinal cord (Melzack and Wall, 1965; Kerr, 1975).

When a microelectrode is introduced into the spinal cord, it is unusual to record from dorsal horn neurones excited only by nociceptive afferents. Christensen and Perl (1970) described such cells in Rexed's lamina I, but even in this layer, most neurones

are excited both by noxious and non-noxious cutaneous stimuli. The anatomy suggests that specifically nociceptive cells might be common in the substantia gelatinosa. The neurones of this area are small and extracellular recordings are difficult to obtain. Kumazawa and Perl (1978) observed neurones in the substantia gelatinosa excited solely by impulses in unmyelinated fibres but Wall (1978) found cells responding to stimulation of both myelinated and unmyelinated primary afferents. Other investigators (Cervero et al., 1977) found neurones of the substantia gelatinosa to be mainly inhibited by cutaneous stimuli. These studies are at an early stage, but it appears that the simple expectation that substantia gelatinosa neurones would be excited by nociceptive afferents alone is improbable. Deep to the substantia gelatinosa, neurones of lamina IV respond readily to innocuous mechanical skin stimulation. Although earlier reports classed neurones of this layer as non-nociceptive (Pomeranz et al., 1968), several investigators have found that noxious heating of the skin excites many neurones of lamina IV (Handwerker et al., 1975; Duggan et al., 1977). Deeper dorsal horn neurones of lamina V also respond to both noxious and non-noxious skin stimuli (Pomeranz et al., 1968).

Thus, the rarity with which specifically nociceptive neurones are encountered in microelectrode penetrations of the spinal cord is puzzling, and raises questions as to whether nociceptive information is conveyed by a specific group of fibres or is encoded in the impulses of fibres also conveying information from other receptors. One problem in interpreting results from microelectrode studies, however, is that both the electrical properties of the recording electrode and the geometry of neurones result in a bias in the size and type of cells sampled. It is rare to record from small neurones.

The Transmitter Released by Primary Afferent Fibres

Recent evidence suggests that the polypeptide substance P may be the transmitter released by nociceptive afferents. Relatively high levels of substance P occur in dorsal root ganglia, dorsal roots and the upper dorsal horn of the spinal cord. Section of dorsal roots produces a marked fall in the levels of substance P in the dorsal horn (Takahashi and Otsuka, 1975).

Distribution studies of peptides at the cellular level have been made possible by the use of immunofluorescent techniques. A peptide such as substance P is first complexed to a protein and antibodies to this complex raised in, for example, a rabbit. These antibodies are then allowed to react with a tissue slice and the antigen-antibody complexes located by a further reaction with fluorescein-conjugated antibodies to rabbit immunoglobulin raised in another animal. The technique has shown that terminals containing substance P are abundant in the substantia gelatinosa and, in dorsal root ganglia, only small diameter primary afferent neurones contain this peptide (Hokfelt et al., 1975).

Administered from micropipettes substance P, excites neurones in many areas of the central nervous system (Henry, 1976; Phillis and Limacher, 1974; Davies and Dray, 1976), but both the onset and offset of excitation are prolonged when compared with an excitant amino acid such as L-glutamate. In the dorsal horn, it was found that neurones excited by noxious skin stimuli were more sensitive to substance P than neurones not excited by this type of stimulus (Henry, 1976). It was not known, however, if nociceptive afferents synapsed directly with the cells studied or if polysynaptic pathways were involved, making the significance of this finding uncertain.

Inhibition of Spinal Transmission of Nociceptive Impulses

Inhibition by Impulses in Other Afferent Fibres

The gate control theory of pain, as proposed by Melzack and Wall (1965), suggested that the spinal transmission of nociceptive impulses could be interrupted by impulses in large myelinated fibres such as those carrying information from cutaneous mechanoreceptors. It was proposed that impulses in the large fibres excited neurones of the substantia gelatinosa which then presynaptically inhibited the transmission of nociceptive information. Presynaptic inhibition is a process whereby an inhibitory neurone forms a contact with an excitatory nerve ending, an axo-axonic synapse, and, by depolarising this ending, reduces the amount of excitatory transmitters released by incoming impulses (Schmidt, 1971). In the spinal cord, γ -aminobutyric acid is probably the transmitter released at axo-axonic synapses (Levy, 1977).

Part of the gate control theory has received experimental support. The excitation of dorsal horn neurones by noxious heating of the skin was inhibited by concurrent electrical excitation of large myelinated fibres (Handwerker et al., 1975). A similar inhibition was produced by stimulation of the dorsal columns, a not unexpected finding since these fasciculi are mainly composed of branches of large myelinated primary afferents ascending to the gracile and cuneate nuclei. The inhibition in these experiments rarely outlasted the electrical stimulus by more than a minute, which contrasts with the clinical situation. Although there is considerable variation, relief of pain for hours following the cessation of transcutaneous stimulation in humans is well documented (Melzack, 1975). Thus, in its original form, the gate control theory is inadequate to explain the clinical situation.

It is probable, however, that transcutaneous stimulation activates many fibres in addition to those of large diameter and the effects of these on the spinal transmission of nociceptive information is unknown.

Spinal mechanisms have been considered important in the relief of pain by acupuncture (Chan and Fung, 1975) but the fibre types activated by this procedure are unknown.

Inhibition by Supraspinal Stimulation

Reynolds (1969) described analgesia produced by stimulation of the periaqueductal grey matter of the rat. This analgesia was such as to permit laparotomy to be carried out on the conscious animal. In the rat the sites from which analgesia can be produced by stimulation have been systematically explored and include the periaqueductal grey matter, the dorsal raphe nucleus, the locus caeruleus, the nucleus raphe magnus and nucleus centralis inferior (Akil and Mayer, 1972; Segal and Sandberg, 1977; Oliveras et al., 1975; Fields et al., 1977). These sites include the 5-HT containing neurones of the brain stem raphe as well as some catecholamine containing cells.

Analgesia produced by such stimulation has been reduced by a number of procedures which purport to deplete the brain of 5-HT or to antagonise the postsynaptic action of this substance (Akil and Mayer, 1972; Guilbaud et al., 1973; Hayes et al. 1977). As a consequence it has been proposed that stimulation at these sites activates descending amine containing fibres, impulses which inhibit the transmission of nociceptive information at the level of the spinal cord. Stimulation at these sites has been shown to inhibit the responses of both trigeminal and dorsal horn neurones to noxious stimuli (Oliveras et al., 1974; Fields et al., 1977; Yokota and Hashimoto, 1976). Such a finding is illustrated in figure 1. The records were obtained from a lamina IV spinal neurone of a cat which was excited alternately by noxious and non-noxious skin stimuli. Electrical stimulation in the region of the medullary raphe nuclei selectively inhibited responses to noxious skin stimuli. The inhibition however, was brief, outlasting the stimulus by less than 2 minutes.

Further support for this proposal of inhibition of spinal neurones by descending amine containing fibres comes from the finding that both 5-hydroxytryptamine and noradrenaline, when administered in the substantia gelatinosa, selectively reduced the responses of neurones of laminae IV and V to noxious skin stimuli (Headley et al., 1978).

Analgesia produced by cortical stimulation has been used in attempts to control intractable pain in humans (Adams, 1976; Hosobuchi et al., 1977). The areas stimulated have been anterior to the sites used in animals, being at the level of the posterior commissure and 2 to 3mm lateral to the wall of the third ventricle. The possible participation of enkephalins in this form of analgesia will be discussed later.

Ascending Pathways From the Spinal Cord

There is no evidence that nociceptive impulses are conveyed in lemniscal pathways. Microelectrode recordings have shown that, in both cats and primates, ascending fibres in the anterolateral fasciculus are activated by noxious cutaneous stimuli (Pomeranz, 1973; Trevino et al., 1973; Albe-Fessard et al., 1974). As with dorsal horn neurones, fibres responding only to noxious stimuli were rare, most units being

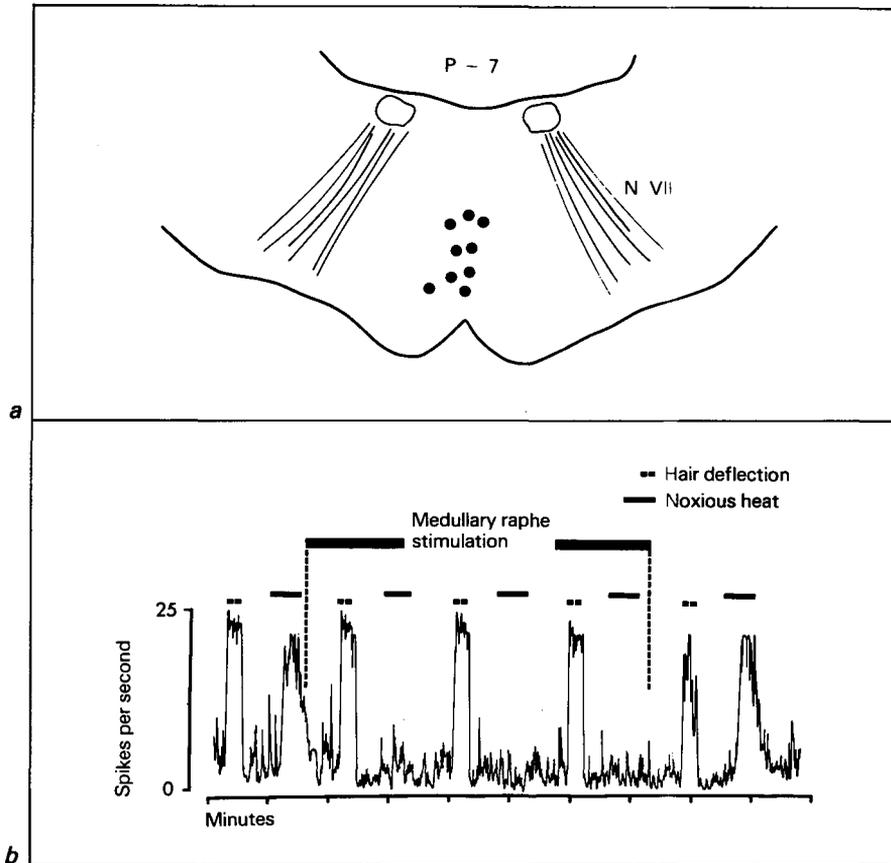


Fig. 1. Inhibition, during medullary raphe stimulation, of the excitation of a dorsal horn neurone of the cat by noxious skin stimuli.

The neurone, which was located in spinal lamina IV, was excited alternately by heating of the skin of the fourth digital pad of the left hind limb above 45°C with a focused light beam and by deflection of adjacent hairs with a moving airjet. A pair of needles insulated to within 0.5mm of the tips and separated by 1.5mm was used to stimulate the medullary raphe area 2mm dorsal to the pyramids. Stimulus parameters: 0.5ms pulses of 400 μ A delivered as groups of 15 pulses at 310Hz at intervals of 330ms.

- a) The sites from which inhibition was obtained.
- b) A ratemeter record of firing rate in spikes per second.

activated by noxious and innocuous skin stimuli. Unlike nociceptive primary afferents, fibres in the anterolateral fasciculus conveying nociceptive information appear to be only myelinated with conduction velocities of 10 to 100m/sec. These extra-lemniscal fibres synapse in many areas of the brain stem and diencephalon. In the

cat there appear to be few spinothalamic fibres, most terminating in reticular nuclei such as the nucleus giganto-cellularis (Casey, 1971; Albe-Fessard et al., 1974). The long latency of activation of neurones of the intralaminar and posterior nuclei of the thalamus of the cat indicate that many synapses are interposed between the periphery and these areas (Albe-Fessard and Kruger, 1962). In the monkey, a large proportion of anterolateral fibres ascend to the thalamus (Albe-Fessard et al., 1974).

Axons of the spino-cervical tract are also excited by noxious skin stimuli (Brown and Franz, 1969). These fibres are found in the posterolateral fasciculus of the spinal cord and synapse with neurones of the lateral cervical nucleus and ascend thence to the thalamus.

Both anatomical and neurophysiological studies indicate that extra-lemniscal fibres terminate mainly in the intralaminar (centre-median, parafascicularis) and posterior thalamic nuclei (Bowsher, 1974; Albe-Fessard and Kruger, 1962). These regions of the thalamus have been ablated in humans for relief of pain, but results are variable and any relief obtained is usually transitory (Pagni, 1974).

Although the intralaminar and posterior thalamic nuclei have cerebral cortical connections, neurones excited by cutaneous noxious stimuli have been rarely encountered in microelectrode studies of the cerebral cortex.

Endorphins

The finding, in brain homogenates, of stereospecific binding sites for opiate drugs (Pert and Snyder, 1973) led to the isolation from brain of polypeptides with opiate properties. The first to be so defined were methionine and leucine enkephalins (Hughes et al., 1975). These pentapeptides have effects similar to those of opiates in pharmacological tests using peripheral tissues (Hughes et al., 1975). They compete with opiates for receptor sites in brain homogenates (Simantov et al., 1976) and produce transient analgesia when injected into the cerebral ventricles of rats and mice (Belluzzi et al., 1976).

Antagonism by an opiate antagonist such as naloxone is important evidence relating effects by any substance to activity at opiate receptors. All of these pharmacological effects of the enkephalins are antagonised by naloxone.

The amino acid sequence of methionine enkephalin occurs at position 61-65 of the pituitary protein β -lipotropin. A C-terminal fragment (61-91) of β -lipotropin also shows opiate activity, and is more potent than the enkephalin in a variety of tests including analgesia (Feldberg and Smyth, 1977). This larger polypeptide has been named β -endorphin and the generic term endorphins has been proposed to cover all polypeptides with opiate activity (Goldstein, 1976).

It was soon proposed that the enkephalins were neurotransmitters and that they might play a role in the regulation of transmission of nociceptive information. Several

investigators have studied the effects of enkephalins, administered from micropipettes, on the firing of central neurones. Methionine enkephalin depressed the firing of neurones in many areas of the central nervous system (Bradley et al., 1976; Hill et al., 1976; Zieglansberger et al., 1976; Duggan et al., 1977), including many neurones not known to receive nociceptive information. Administered in the substantia gelatinosa, methionine enkephalin reduced the excitation of neurones of spinal laminae IV and V by noxious skin stimuli without affecting responses to innocuous stimuli (Duggan et al., 1976, 1977). Such a result is illustrated in figure 2 which also shows the arrangement of micropipettes necessary to inject drugs in lamina II while recording responses of neurones in laminae IV and V. With this cell the selective depression of nociceptive responses following electrophoretic administration of methionine enkephalin amide was rapidly reversed by intravenous naloxone (0.1 mg/kg). This selectivity was not observed when methionine enkephalin was administered near cell bodies, responses to both types of skin stimuli being depressed. In all of the studies quoted the effects of enkephalins on central neurones were antagonised by the opiate antagonist naloxone.

The distribution of the enkephalins and of β -endorphin within the brain has been studied by radioimmunoassay and immunohistochemical techniques. Radioimmunoassay has revealed relatively large amounts of both β -endorphin and enkephalin in the pars intermedia of the pituitary (Rossier et al., 1977) but the levels of these substances differ in other parts of the brain. For example, β -endorphin is absent from the neostriatum, whereas enkephalin levels are high (Rossier et al., 1977). Immunohistochemical studies of the distribution of enkephalin suggest a correspondence between the distribution of enkephalin-containing nerve terminals and of opiate receptors as mapped by the binding of labelled etorphine (Simantov, Kuhar, Uhl and Snyder, unpublished observations). Enkephalin-containing terminals are abundant in the substantia gelatinosa of the spinal cord, the periventricular and periaqueductal areas of the brain stem, dorsomedial thalamus, the basal ganglia and the amygdala. These techniques also show a similarity between the distribution of substance P and enkephalin (Hokfelt et al., 1977), a finding consistent with the suggestion that enkephalin and the opiates reduce the release of transmitter from nociceptive primary afferents (Duggan et al., 1976).

It is an attractive hypothesis that the release of endorphins underlies the various forms of analgesia produced by electrical stimulation at central and peripheral sites. The use of naloxone has however, given only partial support to this proposal. Analgesia produced in the rat by stimulation at midbrain periventricular sites has been reported to be reduced by naloxone (Akil et al., 1976) and to be unaffected by it (Yaksh et al., 1976). Analgesia in humans by stimulation at midbrain and thalamic sites was reduced by naloxone (Adams, 1976; Hosobuchi et al., 1977). Also in humans, analgesia by acupuncture was partially reduced by naloxone (Mayer et al., 1977) but in animals reports are conflicting (Pomeranz and Chiu, 1976; McLennan et al., 1977). Thus, the physiological role of the endorphins is still uncertain. Whether

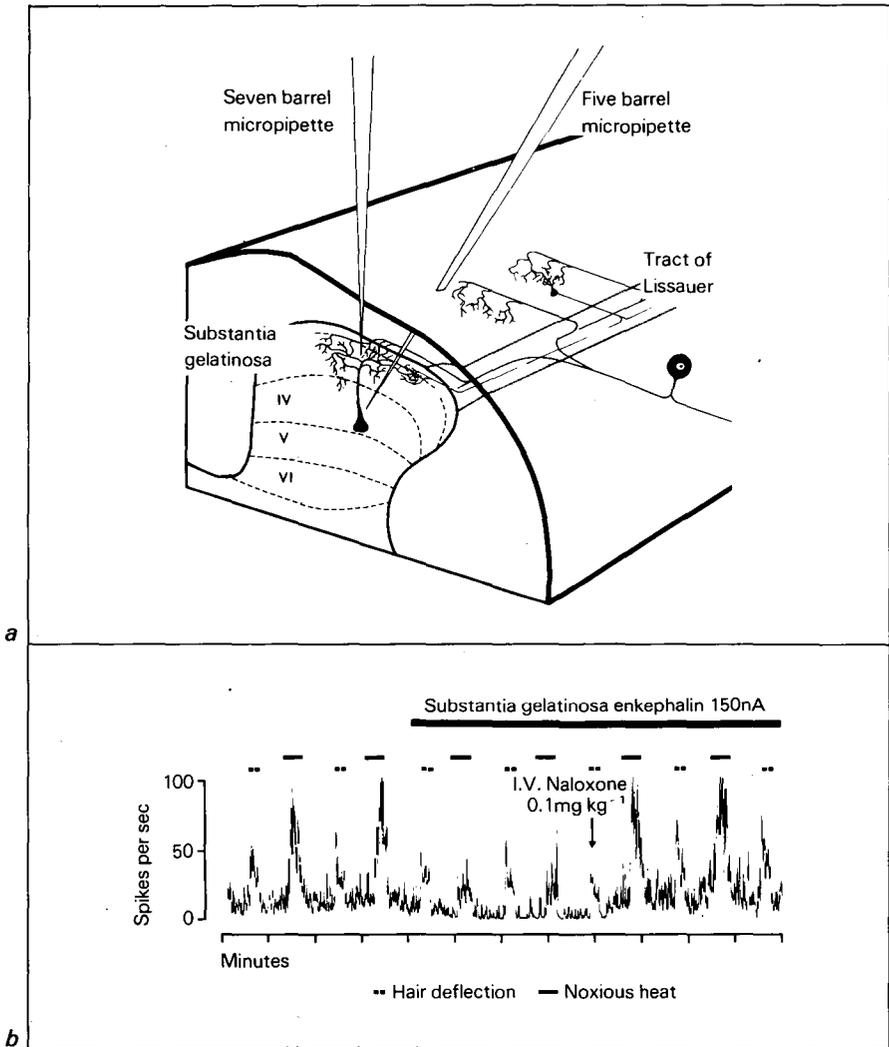


Fig. 2. Reduction of the nociceptive responses of a lamina IV neurone by methionine enkephalin administered electrophoretically in the substantia gelatinosa and the reversal of this effect by intravenous naloxone.

a) Diagrammatic representation of the arrangements of micropipettes. A seven barrel micropipette was positioned in the substantia gelatinosa. A five barrel micropipette, inclined at 18° to the vertical, recorded the firing of a lamina IV or V neurone, separated by a known distance from the tip of the drug administering pipette.

b) Ratemeter records of the alternate excitation of a lamina IV neurone by noxious and non-noxious skin stimuli. The separation between recording and drug-administering micropipettes was 220µm. Methionine enkephalin amide was injected electrophoretically with a current of 150nA for the time indicated by the continuous bar.

the release of these substances from nerve terminals can be brought about as a useful therapeutic measure is also uncertain. Potent enkephalins which induce analgesia when administered intravenously or orally have been developed (Roemer et al., 1977), but it is unlikely that these substances will behave as non-addictable analgesics. Thus, when methionine enkephalin was administered chronically to mice by intracerebroventricular cannula, the signs of withdrawal produced by administration of naloxone (precipitated abstinence) were similar to those observed in animals chronically receiving morphine (Wei and Loh, 1976).

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A Review of Some Aspects of the Pharmacology of Levodopa

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Many of the properties of levodopa (L-dopa) reflect the fact that it is not a drug in the sense of an introduced substance which is foreign to the body, but a natural constituent of both plant and animal cells. Like most amino acids, it has the basic structure shown in figure 1. The central carbon atom (designated the α -carbon) has 4 different groups around it, one being a carboxyl group, another an amino group. Amino acids with this configuration can occur in two forms, one being the mirror image of the other. These two forms have similar physical and chemical properties but rotate polarised light in different directions. These are called dextro- and laevo-rotating isomers. Transport systems and enzymes involved in the metabolism of amino acids are stereo-specific. Only the laevo-rotating form of amino acids is commonly found in animal tissues. In the case of levodopa, the side chain (R) comprises a benzene ring (see fig. 2) making this an aromatic amino acid. Having one amino and one carboxylic group, it is a neutral monoamino-monocarboxylic amino acid. Its full chemical name is L-3,4-dihydroxyphenylalanine.

The structure of levodopa was first determined by Guggenheim in 1913. He extracted it from the pods and beans of *Vicia faba*. He was probably the first person to experience the emetic effect of levodopa, as his curiosity led him to swallow 2.5g of the substance. In 1938, Holtz, Heise and Ludtke identified an enzyme in the kidney which catalysed the conversion of levodopa to the amine, dopamine. A year later, Blaschko suggested that levodopa and dopamine formed part of a synthetic chain beginning with L-phenylalanine and ending in the pharmacologically active

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catecholamines, noradrenaline and adrenaline. Dopamine continued to be thought of as being important only as a precursor of noradrenaline and adrenaline until 1959, when Carlsson demonstrated that in animal brains dopamine and noradrenaline, though present in roughly equal concentrations overall, had different distributions. The corpus striatum had high concentrations of dopamine but only traces of noradrenaline. The hypothalamus had high concentrations of noradrenaline but very little dopamine. Carlsson suggested on this basis that dopamine might be a transmitter substance in its own right. In his brief review, Carlsson anticipated events over the next 20 years when, on the basis of his studies of the recently introduced tranquilliser, reserpine, he speculated that Parkinson's disease might be due to a deficiency of dopamine in the corpus striatum and that levodopa might ameliorate this condition. In 1960, Ehringer and Hornykiewicz confirmed that the concentration of dopamine in the corpus striatum of patients suffering from Parkinson's disease was reduced compared with controls. Initial trials with low doses of levodopa were unsuccessful but in 1967 Cotzias and his colleagues reported that when 16 patients were given up to what was then regarded as an heroic dose of 16g of levodopa, half of them improved substantially. In his study, Cotzias (1967) economised by giving the racemate of dopa and 4 patients developed granulocytopenia. Presumably, this was an effect of D-dopa on bone marrow, for it is not seen when L-dopa is given alone.

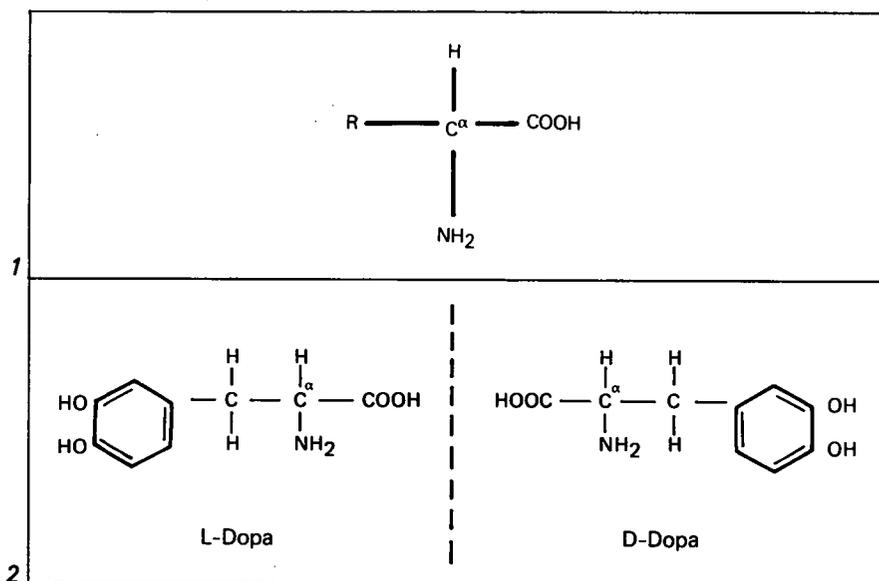
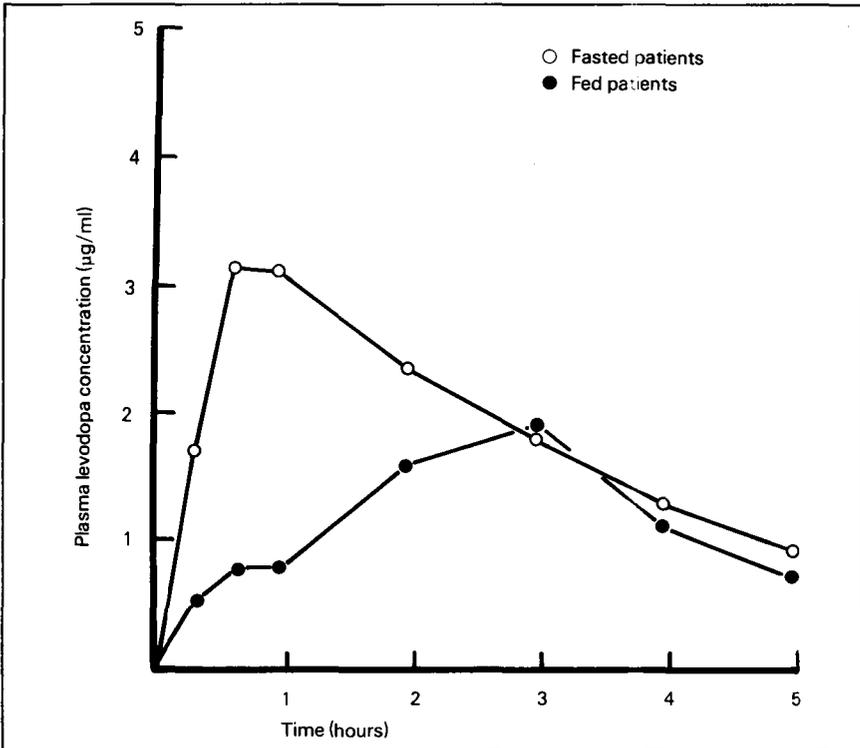
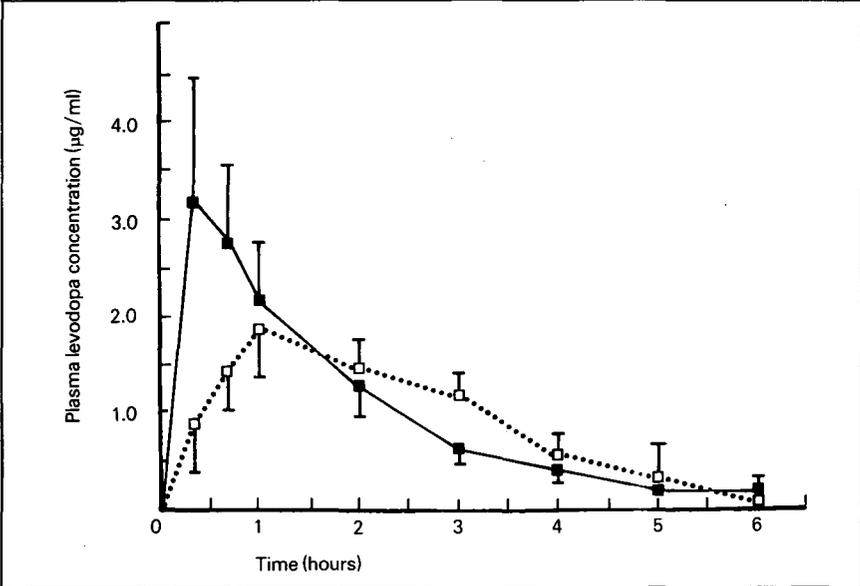


Fig. 1. Basic structure of amino acids.

Fig. 2. Optical isomers of dopa.



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These then are some of the salient steps which led to the introduction of levodopa for the treatment of Parkinson's disease. In the remainder of this review, I shall discuss those aspects of the pharmacology of levodopa which seem relevant to the proper use of the agent in practice or provide insight into its mode of action.

Absorption of Levodopa

Until 1951, it was thought that the absorption of amino acids by the gut was a passive process. At that time, Gibson and Wiseman showed that the L-isomers of alanine, phenylalanine and histidine were absorbed more rapidly from rat small intestine than the D-isomers. This suggested that an active transport system preferentially carried the L-isomers into the mucosal cells. Subsequent research has shown that L-amino acids can be transported across the gut wall against a concentration gradient. This system is dependent upon an adequate supply of oxygen, has an optimum pH and is saturable. Several different transport systems have been described:

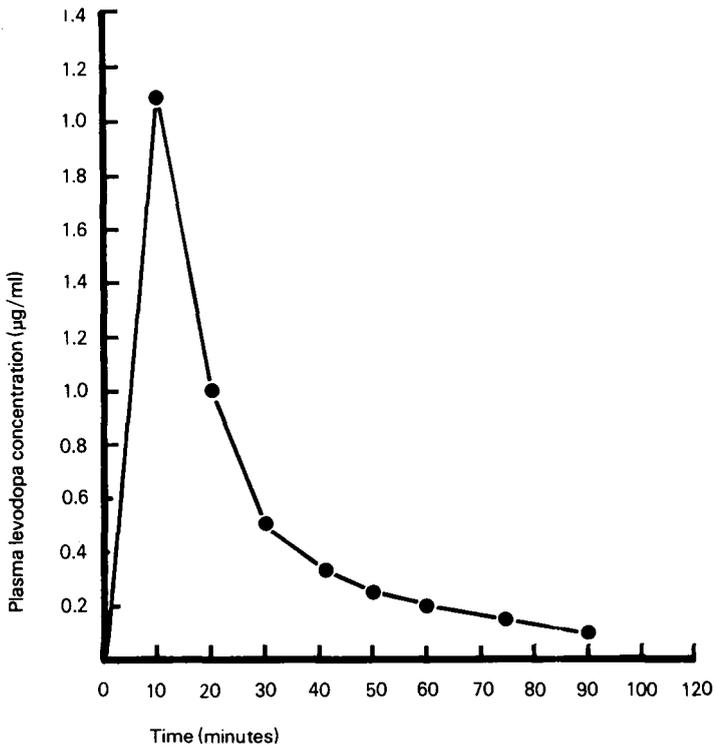
- 1) One shared by monoamino monocarboxylic acids (e.g. phenylalanine, tyrosine, tryptophan and histidine)
- 2) One shared by the diamino acids (e.g. ornithine, arginine and lysine)
- 3) One shared by proline and hydroxyproline
- 4) One for glycine.

Within each group, one amino acid competes for transport with another; Matthews and Laster (1965) have reviewed this subject. Active transport of amino acids is confined to the small bowel (Cordero and Wilson, 1961). Amino acids are almost entirely absorbed in the duodenum and upper 100cm of the jejunum (Borgstrom et al., 1957).

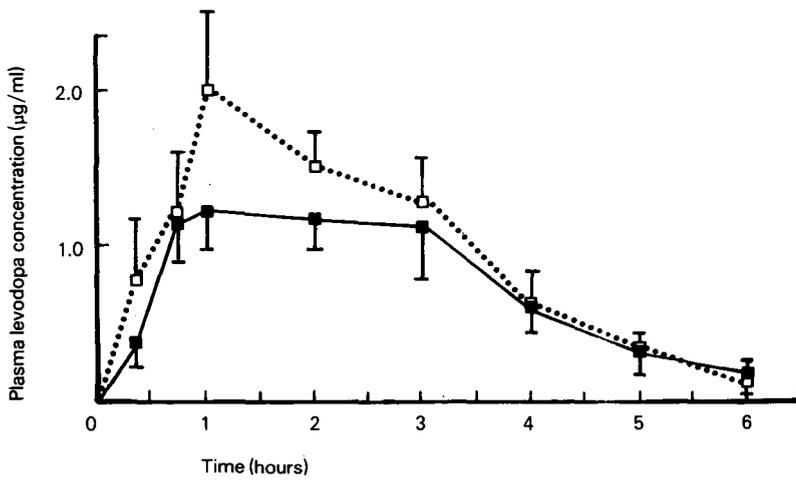
Levodopa is also actively absorbed from the small intestine (Wade et al., 1973). It probably shares the same carrier as the other monoamino monocarboxylic acids for it competes with L-phenylalanine for absorption (Granerus et al., 1971). Like other amino acids, levodopa is probably not absorbed from the stomach. Factors such as food, which slow the rate of gastric emptying, delay the absorption of levodopa (fig. 3) [Morris, 1976]. Metoclopramide, a drug which increases the rate of gastric emptying, hastens levodopa absorption (fig. 4) [Morris et al., 1976]. Levodopa is probably

Fig. 3. Mean plasma levodopa concentrations following an oral dose of 15mg/kg of 'Larodopa' in 9 fasted patients and in 11 patients who had an unbuttered bun and a cup of coffee before taking the drug.

Fig. 4. Mean plasma levodopa concentrations of 10 subjects after taking 'Larodopa' (15mg/kg) (□) and after taking the same dose with 10mg of metoclopramide (■) SEM is also shown.



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absorbed maximally from the duodenum. As shown in figure 5, when a suspension of levodopa plus benserazide was infused directly into the second part of the duodenum of the author, the peak concentration of levodopa in the plasma occurred 10 minutes later.

Since levodopa is an amino acid which is absorbed actively in the proximal part of the small intestine there are several consequences of interest to the prescriber. Firstly, factors which alter the rate of gastric emptying (e.g. anxiety, nausea, food, anticholinergic drugs or metoclopramide) may affect the rate of absorption of levodopa and thereby the clinical response. Secondly, amino acids formed as digestion products of a protein meal may reduce the amount of levodopa absorbed. Thirdly, levodopa is metabolised by enzymes, mainly L-amino acid decarboxylase, in the gastric and gut mucosa (Rivera-Calimlim et al., 1971). The longer levodopa stays in the stomach and small intestine, the more it is metabolised. Finally, it has proved difficult to find an effective sustained release preparation of levodopa. One such preparation ('Brocadopa Temtabs') which *in vitro* dissolved over a period of 2.5 hours, far from producing sustained plasma levodopa concentrations, behaved more as a poorly absorbed preparation (fig. 6). One explanation for this finding is that a slowly dissolving preparation is exposed to a larger area of gut over a longer period and is metabolised to a greater extent than a fast dissolving tablet. However, administering the 'Temtabs' with a decarboxylase inhibitor also failed to produce sustained plasma concentrations of levodopa (fig. 7). It seems possible from these findings that not only is levodopa normally absorbed from the most proximal segment of the small bowel but its absorption is confined to this segment. Slowly dissolving preparations of levodopa fail because the drug released after the tablet has passed through the proximal small bowel is not absorbed (Morris et al., 1976) (fig. 8).

Distribution and Metabolism of Levodopa

It will be apparent from figures 4 to 8 that following the oral administration of levodopa under a variety of conditions, the amino acid can only be detected in the plasma for about 6 hours. It is distributed, metabolised and excreted with great rapidity. Following intravenous infusion, its plasma half-life is of the order of 40 minutes (Coutinho et al., 1971). In the blood, it enters red cells but is probably not

Fig. 5. Plasma levodopa concentrations in one subject following infusion of a suspension of 100/10 'Madopar' into the second part of the duodenum.

Fig. 6. Mean plasma levodopa concentration of 11 subjects after taking 'Larodopa' (15mg/kg) (□) and after taking the same dose of 'Brocadopa Temtabs' (■) SEM is also shown.

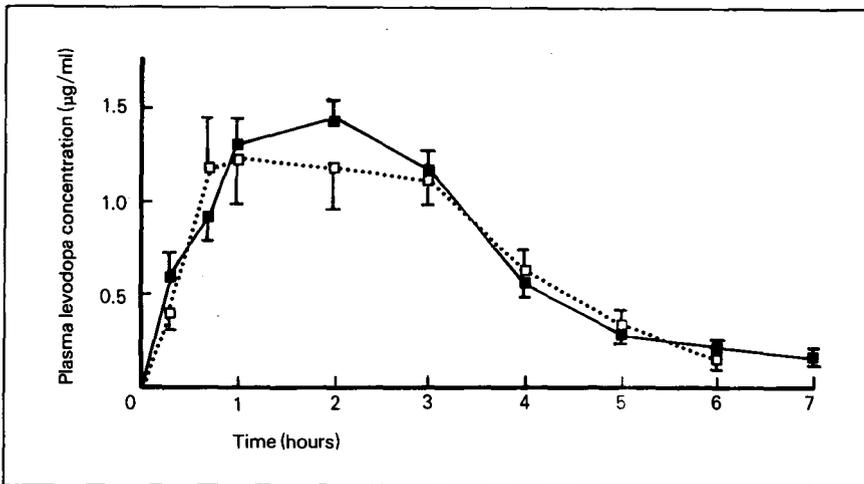


Fig. 7. Mean and SEM plasma levodopa concentrations of 8 subjects after taking 'Brocadopa Temtabs' (15mg/kg) (□) and 'Brocadopa Temtabs' (5mg/kg) with carbidopa (■).

metabolised therein (Mearrick, 1975). It penetrates most organs of the body — particularly liver, kidney, pancreas and skin (Long, 1970). Active transport of levodopa from blood into brain has been demonstrated (Guroff and Udenfriend, 1962; Wade and Katzman, 1975). It also enters, but is not metabolised by, muscle (Mearrick, 1975).

80 to 90% of an oral dose of $2\text{-}^{14}\text{C-L-dopa}$ is absorbed after oral administration. Levodopa appearing in the plasma, however, represents only 20 to 40% of the labelled compounds absorbed. Thus levodopa is extensively metabolised in its first passage through the small intestine and liver (Coutinho et al., 1971; Abrams et al., 1971).

The major metabolic pathway for levodopa metabolism involves enzymic decarboxylation to dopamine by L-aromatic amino acid decarboxylase (Sandler and Ruthven, 1969). This enzyme is widely distributed in the body, its activity being greatest in the kidney, liver and small intestine (Davis and Awapara, 1960). Its presence in cerebral capillaries provides an enzyme component to the blood-brain barrier for levodopa (Bertler et al., 1966). The enzyme catalyses the decarboxylation of several amino acids (Lovenberg et al., 1961). This is of theoretical interest for it follows that levodopa can be decarboxylated in a variety of neurones, for example, in serotonergic neurones as well as dopaminergic and noradrenergic neurones.

Dopamine is catabolised by the actions of two main enzymes: monoamine oxidase and catechol-O-methyl transferase (Calne and Sandler, 1970). 90% of the radioactivity found in the plasma 1 to 2 hours after an oral dose of labelled levodopa is due to the phenolcarboxylic acids, 3,4-dihydroxyphenylacetic acid (DOPAC) and

homovanillic acid (HVA), according to Peaston and Bianchine (1970). While studies of this type give information about the quantitatively most important pathways of metabolism of levodopa they tell little about its metabolism in individual neurones. In adrenergic cells, for example, dopamine is probably β -hydroxylated to noradrenaline though this diversion is not reflected in a large increase in the urinary excretion of vanilmandelic acid (Calne et al., 1969). The main metabolites appearing in the brain stem after intravenous ingestion of levodopa in rabbits are also HVA and DOPAC (Carlsson and Hillarp, 1962). This probably reflects metabolism within the brain stem since these acids do not readily cross the blood-brain barrier (Bartholini et al., 1966). The concentration of HVA in the cerebrospinal fluid also rises during levodopa therapy. Much of this probably derives from metabolism of levodopa in the cerebral capillaries as the concentration falls when benserazide, a peripheral decarboxylase inhibitor, is given with equivalent doses of levodopa (Rinne et al., 1973).

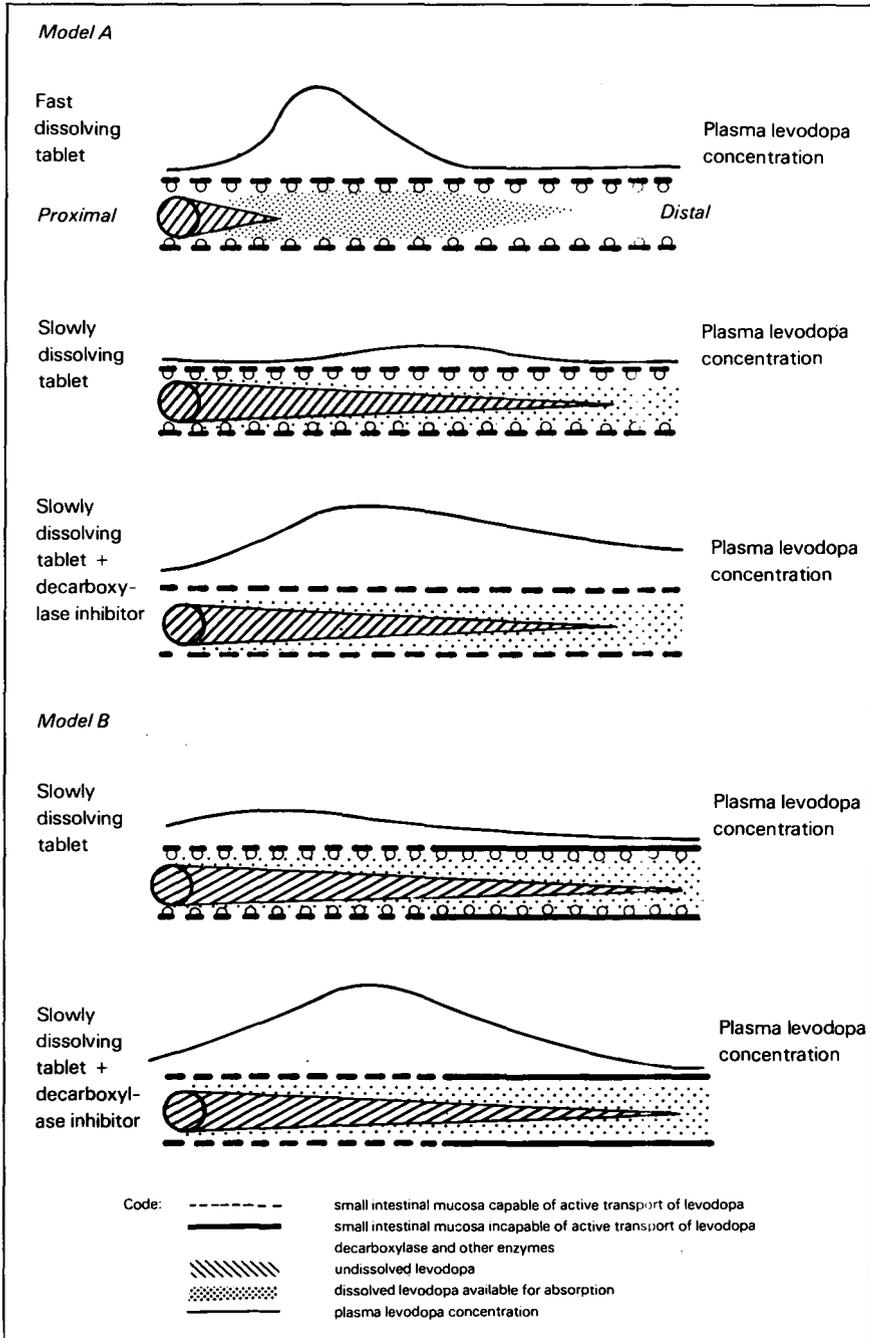
The main route of metabolism of levodopa is thus to dopamine and its degradation products. Levodopa itself is pharmacologically inert. An elegant demonstration of this was provided by Goldberg and Whitsett (1970). In anaesthetised dogs, intravenous injection of dopamine produced an immediate increase in cardiac contractile force and blood pressure. Levodopa also increased cardiac contractile force but this effect developed gradually over a period of about 10 minutes. D-dopa, which is not decarboxylated, had no effect. When levodopa was given with the decarboxylase inhibitor, α -methyl dopa, again there was no effect. Levodopa depended for its action in this study on conversion to dopamine. The pharmacological activity of levodopa thus depends on that of its metabolites, principally dopamine.

Pharmacology of Dopamine

So diverse are the effects of this amine that it is convenient to subdivide them according to the system involved.

Cardiovascular Effects

Dopamine is normally found in small quantities in the adrenal medulla and sympathetic nerves and ganglia where it is a precursor of noradrenaline and adrenaline (Vogt, 1973). Some of the effects of administered levodopa may therefore be due to increased formation of noradrenaline and adrenaline. The increase in the force of contraction of the heart, already described following an intravenous infusion of dopamine, probably depends on β -receptor stimulation for it is completely blocked by propranolol (McDonald and Goldberg, 1963). Small intravenous doses of dopamine cause dilatation of renal arterioles (McNay et al., 1965). This effect is thought to be due to the presence of specific dopaminergic receptors in these vessels as it is not blocked by α - or β -adrenergic blocking agents. This dilatation is diminished by



haloperidol (Yeh et al., 1969), a drug which also blocks the effects of dopamine within the brain. Because it raises blood pressure and at the same time increases renal blood flow, intravenous dopamine has proved to be a useful agent in the treatment of shock (Talley et al., 1969). With very large doses of intravenous dopamine, a generalised vasoconstriction and thereby a rise in blood pressure occur. These effects are probably due to stimulation of α -adrenergic receptors as they are blocked by phenolamine or phenoxybenzamine (McDonald and Goldberg, 1963). These then are the immediate effects of dopamine on the cardiovascular system.

In Parkinsonian patients on long term treatment with high doses of levodopa, the main effect of the amino acid is to induce postural hypotension. It has been suggested that dopamine may replace noradrenaline in peripheral sympathetic nerves and act as a false transmitter, its effect on α -receptors being much weaker than that of noradrenaline. However, peripheral sympathetic nerves do not appear to take up dopamine unless dopamine β -hydroxylase is inhibited (Thoenen et al., 1967). The hypotensive effect of levodopa probably depends in part on its conversion to dopamine within the brain. When levodopa is injected into the cerebral circulation of a dog with neural but no vascular connections between head and trunk, the blood pressure in the trunk falls (Kaplan et al., 1972). Calne has suggested that postural hypotension induced by levodopa may also depend in part on a peripheral effect of dopamine. Reflex vasoconstriction in response to the Valsalva manoeuvre is impaired by levodopa. This effect is blocked by a peripheral decarboxylase inhibitor. Reduction in supine blood pressure induced by levodopa is unaffected by peripheral decarboxylase inhibition (Calne et al., 1973).

Perhaps the most potentially dangerous effect of levodopa on the cardiovascular system is the precipitation in elderly patients of ventricular arrhythmias by the stimulation of β -adrenergic receptors. The risk of this occurring is greatest in patients receiving cyclopropane or halothane anaesthetic agents or sympathomimetic drugs for asthma and in those with coronary artery disease (Goldberg and Whitsett, 1970). The combination of levodopa with a peripheral decarboxylase inhibitor reduces the risk (Mars and Krall, 1971).

In summary, the effects of dopamine on the cardiovascular system are complex. Dopamine stimulates α - and β -adrenergic receptors and probably specific dopamine receptors in the renal vessels. Its precursor, levodopa, lowers supine blood pressure by a central effect. A peripherally mediated hypotensive effect is described. Postural hypotension may be a dose-limiting side effect. Cardiac arrhythmias are an unusual complication if simple precautions are taken (Klawans and Bergen, 1975).

Fig. 8. Two suggested models to account for the failure of a slowly dissolving preparation of levodopa to produce sustained plasma concentrations.

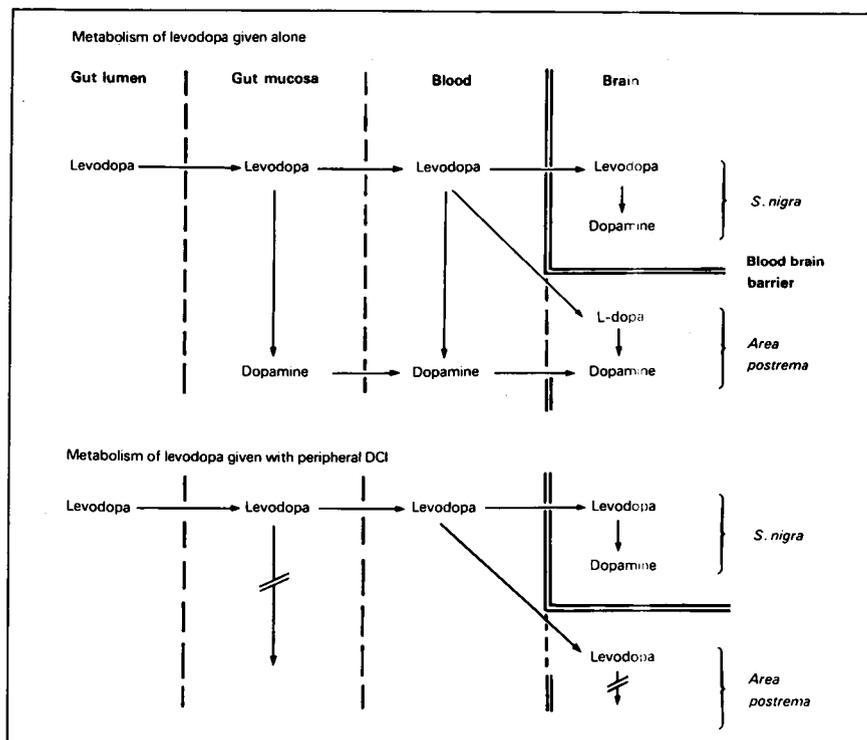


Fig. 9. Prevention of nausea by dopa decarboxylase inhibitors (DCI).

Nausea and Vomiting

Nausea is probably the commonest early side effect of levodopa therapy. It occurs usually within an hour of taking the dose. The act of vomiting relieves the nausea completely but temporarily. Nausea is less if levodopa is taken with food. With continued treatment, the dose needed to induce nausea increases. The incidence and severity of nausea are markedly reduced by peripheral decarboxylase inhibitors. This would suggest that the receptors involved in the production of nausea lie outside the brain — perhaps in the gut. This seems unlikely, however, for levodopa also induces nausea when it is administered intravenously (Degwitz et al., 1960). Levodopa and dopamine are 50 times more potent in causing vomiting in animals when infused into the fourth ventricle than when they are given intravenously (Clark and Lotti, 1970). Nausea probably results from the action of dopamine on cells in the area postrema. This is a collection of glial cells, neurones and venous sinusoids which bulges into the fourth ventricle from the lateral roof in the medulla. Ablation of this area prevents vomiting induced by apomorphine (a centrally acting emetic) but not

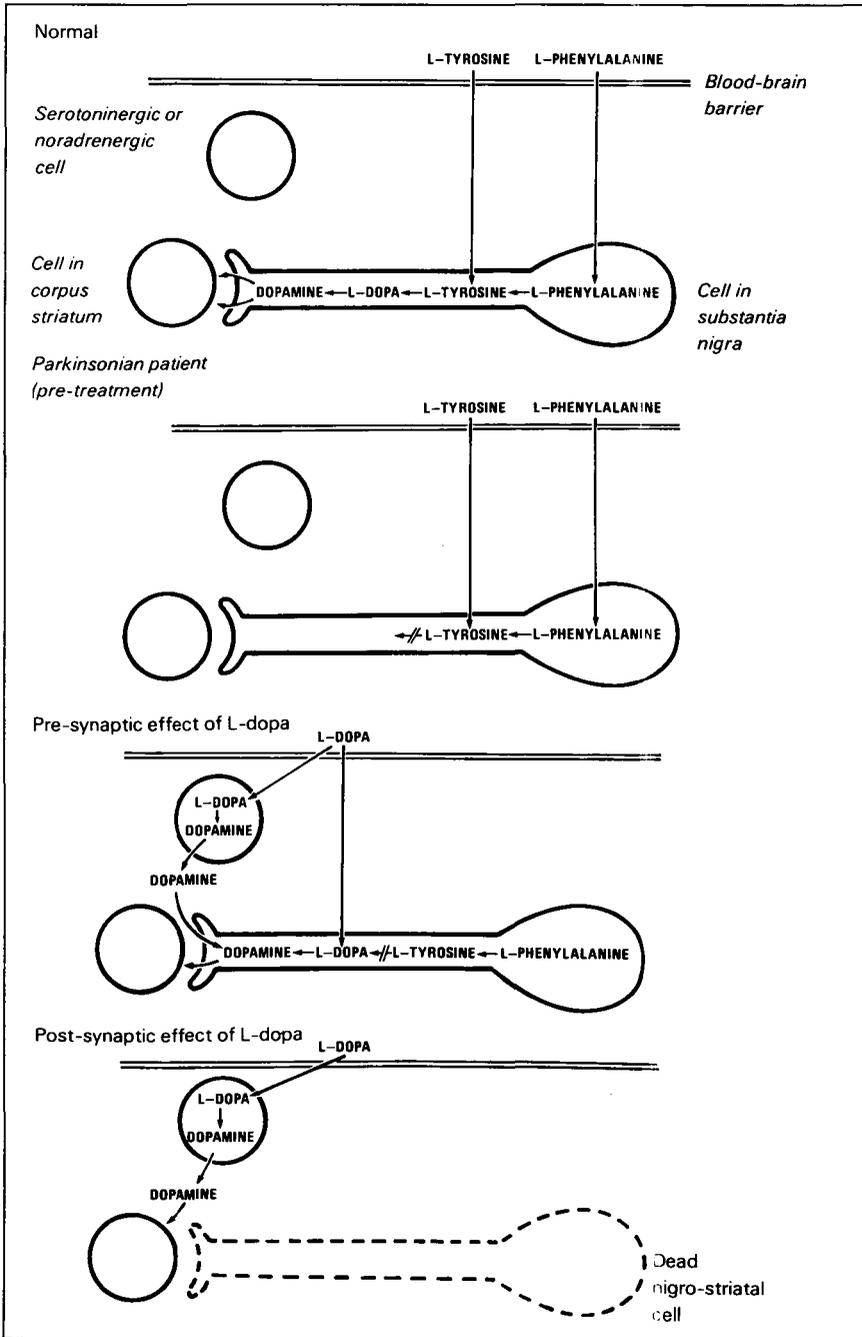
by copper sulphate, an emetic whose action is largely dependent upon an intact innervated gut (Borison and Wang, 1953). Apomorphine is a dopamine agonist (Ernst, 1967). Ablation of the area postrema also abolishes the emetic response to levodopa in dogs (Peng, 1963). The area postrema lies outside the blood-brain barrier (Dobbing, 1961). Neurones containing dopamine have been demonstrated in this region (Fuxe and Owman, 1965).

Thus nausea occurring during levodopa therapy is probably due to an action of dopamine in the plasma and formed locally on neurones in the area postrema. Peripheral decarboxylase inhibitors reduce the formation of dopamine in the area postrema, and lower its concentration in the plasma (fig. 9).

The Nigro-striatal Tract

Much evidence has accumulated over the last 20 years that Parkinson's disease is due to degeneration of the dopaminergic neurones of the nigro-striatal tract. As this was the rationale for giving levodopa to these patients, it may be pertinent to review the salient pieces of evidence for this hypothesis. The most consistent pathological lesion in Parkinson's disease is loss of pigmentation and degeneration of neurones of the substantia nigra (Foix and Nicolesco, 1925). Lesions placed in the substantia nigra of the cat produced the histological picture of degenerating nerve endings in the corpus striatum (Nauta and Mehler, 1969). Cell bodies in the substantia nigra and nerve endings in the striatum have been shown by a histochemical fluorescent technique to contain large amounts of dopamine (Falck, 1962; Falck et al., 1962; Carlsson et al., 1962). Experimental lesions placed in the substantia nigra of monkeys reduce the concentrations of dopamine in the striatum (Poirier and Sourkes, 1965). Electrical stimulation of the substantia nigra produced inhibition of neurones in the caudate nucleus (Conner, 1968), and an increase in the output of dopamine in the effluent obtained by irrigating the putamen with a push-pull cannula (McLennan, 1965). Micro-electrophoretic application of dopamine in one series of experiments led to inhibition of 60% of the neurones tested in the caudate nucleus (McLennan and York, 1967). As described in the introduction, the concentration of dopamine is reduced in the basal ganglia of patients suffering from Parkinson's disease. Catecholamines do not cross the blood-brain barrier (Axelrod et al., 1959; Bertler et al., 1966). In order to increase the concentration of dopamine in the basal ganglia, it was therefore necessary to give an amino acid precursor. For this purpose, the immediate precursor of dopamine, levodopa, was chosen.

That levodopa ameliorates the symptoms and signs of Parkinson's disease is beyond dispute. How it works is not yet fully understood. Assuming that the active metabolite of levodopa is dopamine (other possible substances are mentioned below), two modes of action may be considered: presynaptic and postsynaptic (fig. 10).



Presynaptic Model

In Parkinson's disease, neurones of the nigro-striatal tract degenerate and die. Levodopa can have no beneficial effect on dead cells or surviving normal cells of the nigro-striatal tract. It must therefore work on cells which, though alive, can no longer form dopamine. A failure on the part of the cell to make one of the enzymes in the chain from L-phenylalanine to dopamine could produce such a situation. An obvious possibility is tyrosine hydroxylase. This enzyme is more or less saturated by normal tissue concentrations of its substrate L-tyrosine (Udenfriend, 1966). A failure to make adequate amounts of this enzyme would have a profound effect on the formation of levodopa and thereby dopamine. By giving levodopa, this step would be bypassed. On the basis of this model, cells which could no longer make tyrosine hydroxylase in adequate amounts might still be able to make aromatic amino acid decarboxylase. As degeneration of the cells continued, they would eventually fail to make decarboxylase and levodopa therapy would then cease to be effective. The eventual deterioration which is seen in most patients taking levodopa could be explained in this way. However it is conceivable that levodopa could be effective even if cells of the nigro-striatal tract failed to make both tyrosine hydroxylase and decarboxylase. It has been mentioned earlier that decarboxylase is a non-specific enzyme found in a variety of cells. Levodopa might be decarboxylated to dopamine by other cells, for example serotonergic cells, in the region of the synaptic cleft. It is a property of adrenergic and dopaminergic presynaptic terminals to take up amines released into the synaptic cleft and re-release them (Iversen, 1971; Hellman et al., 1971). Thus function might be restored to a nigro-striatal cell which had lost the enzyme machinery necessary for the production of dopamine but which could still take up dopamine and release it.

Postsynaptic Model

Another possibility is that dopamine, formed by glial cells, serotonergic cells or noradrenergic cells in the striatum, diffuses into the synaptic cleft and acts directly on the dopaminergic receptors without intervention by neurones of the nigro-striatal tract. Evidence that this may occur comes from an animal model of Parkinson's disease. Unilateral injection of 6-hydroxydopamine into the substantia nigra of rats induces a selective degeneration of the entire nigro-striatal tract (Ungerstedt, 1968). This degeneration is complete after 48 hours. The rat now deviates in its movements and posture towards the lesioned side due to the unopposed action of the intact contralateral nigro-striatal tract. Drugs such as amphetamine and amantadine which release endogenous stores of dopamine affect only the intact nigro-striatal tract and

the animal actively rotates towards the lesioned side (Ungerstedt, 1976). These rotations can easily be recorded. Levodopa induces a rotation towards the non-lesioned side. Thus although it presumably reaches both striata, it has a greater effect on the denervated side. This effect is blocked by decarboxylase inhibition showing that, as with the heart, levodopa has to be converted to dopamine to be active (Ungerstedt, 1971). That dopamine has more effect on the denervated than on the intact side could be due to an alteration in the sensitivity of the dopamine receptors as a result of denervation. This 'denervation hypersensitivity' is well recognised in cholinergic neuromuscular junctions (Mountcastle, 1974). Another factor is that dopamine, formed on the denervated side by glial cells or non-dopaminergic neurones, cannot be removed by uptake into nigro-striatal terminal fibres, as these have degenerated. It therefore has a more persistent effect on the postsynaptic dopamine receptors. This model has been used extensively to study the effects of different drugs on striatal dopamine receptors. Apomorphine has been found to have a similar effect to levodopa. Bromocriptine also causes the animal to rotate towards the non-lesioned side (Johnson et al., 1976). These drugs act directly on 'hypersensitive' dopamine receptors on the denervated side. Cocaine, a drug which blocks the re-uptake of dopamine, as might be expected acts only on the intact side causing the animal to rotate towards the lesioned side (Ungerstedt, 1976). Of great interest in the context of current therapy for Parkinson's disease is the finding that benztropine and other anticholinergic drugs also cause the animal to rotate towards the lesioned side. Benztropine, like cocaine, inhibits the uptake of dopamine into dopaminergic terminals (Hamberger, 1967). Thus some of the benefit derived from anticholinergic drugs, particularly in combination with levodopa (Hughes et al., 1971), may be due to this mechanism rather than due to an effect on cholinergic neurones of the striatum (Calne, 1970).

Of the drugs mentioned, apomorphine has been found to produce a transient improvement in Parkinsonian patients though its emetic effects and the fact that it has to be injected have limited its usefulness (Cotzias et al., 1970). Bromocriptine, by contrast, has become established as an effective treatment of Parkinson's disease (Calne et al., 1974).

These observations on the effect of various drugs on the 6-hydroxydopamine animal model have led to the view that dopamine agonists, like apomorphine and bromocriptine, produce their beneficial effect on Parkinsonian patients by a direct action on dopamine receptors in the striatum. The suggestion has been made that in this way, the degenerating cells of the nigro-striatal tract can be bypassed and that patients who lack the enzymes necessary to convert dopa to dopamine may benefit from bromocriptine (Calne et al., 1974).

This point of view may be criticised on two grounds. Firstly, it must not be forgotten that neurotransmitters are a means by which one cell can have an effect, whether excitatory or inhibitory, on another. One would no more expect improvement in a disturbance of function as complex as that of akinesia by directly stimulat-

ing dopamine receptors in the basal ganglia than one would expect to improve power in the denervated muscles of a patient suffering from motor neurone disease by flooding his neuromuscular junctions with acetyl choline. Secondly, the syndrome induced by 6-hydroxydopamine in rats is dissimilar to Parkinson's disease in man and the turning movements induced by dopamine agonists can hardly be regarded as an improvement in function. These involuntary stereotyped movements are more akin to the dyskinesia induced by dopamine agonists than to an improvement in Parkinsonism. Dyskinesia is the major dose-limiting side effect of levodopa in the long term. Beginning with a tendency to invert or plantar flex the foot repeatedly, it may progress to facial grimacing, tongue protrusion and eventually generalised restless writhing and jerking movements of the limbs. It is dose-dependent, occurs often in clear relationship to the last dose of levodopa and, with continued treatment, appears at progressively lower doses of levodopa. It does not occur when levodopa is given to normal subjects.

In summary, it is suggested that the effects of dopamine on the nigro-striatal system are both presynaptic and postsynaptic. Dopamine release in a controlled fashion from the presynaptic nigro-striatal neurone results in improvement of Parkinsonian symptoms. Direct action on receptors in the striatum by dopamine released in an uncontrolled fashion by other cells in the vicinity of the synapse may result in dyskinesia. The beneficial effect of bromocriptine is unlikely to be due to a direct effect on dopamine receptors in the striatum.

Other Effects of Dopamine

Dopaminergic pathways have now been identified in the olfactory tubercles, nucleus accumbens, central amygdaloid nucleus and all parts of the limbic system (Vogt, 1973). In the retina, light stimulation releases dopamine from a layer of neurones between the inner nuclear and inner plexiform layers. Kramer has suggested that this attenuates sensory input (Kramer, 1971). Dopaminergic neurones are also present in the hypothalamus (Hokfelt et al., 1971). Growth hormone levels in the plasma rise after oral administration of levodopa (Boyd et al., 1970). Dopamine inhibits the release of prolactin (Meites, 1977).

The Dopamine Receptor

Iversen has recently reviewed evidence which suggests that dopamine acts on its receptors in such a way as to activate adenylyl cyclase and thereby release cyclic AMP (Iversen et al., 1975). Low concentrations of dopamine release cyclic AMP in many dopamine-rich areas (e.g. bovine superior cervical ganglia, rat and bovine retina and homogenates of rat basal ganglia). These effects are antagonised by chlorpromazine and haloperidol and mimicked by apomorphine. The enzyme/receptor is probably located mainly on the postsynaptic membrane in the striatum, since the dopamine-

stimulating activity persists unchanged after destruction of the nigro-striatal tract. The activity of proposed dopamine agonists can be assessed in part by their effect on adenylyl cyclase activity. One interesting recent development has been the finding that lergotriole mesylate, a compound which inhibits prolactin release, alleviates Parkinsonism and behaves like a dopamine agonist in animal models, does not increase adenylyl cyclase activity in the rat caudate nucleus (Kebabian et al., 1977). Moreover, this drug blocks the effect of dopamine on striatal adenylyl cyclase activity. This finding suggests that there is more than one type of dopamine receptor. Consistent with this view is the observation that dopamine applied iontophoretically to caudate neurones can cause excitation as well as inhibition of neurones (McLennan and York, 1967). Inhibition and excitation of neurones in *Aplysia* by dopamine is also described (Ascher, 1972).

Summarising the pharmacology of dopamine, it may be said that dopamine responsive cells exist in a number of sites both within the brain and in other tissues. Levodopa has no effect on these cells until it is decarboxylated to dopamine. The response of a particular cell to levodopa and dopamine depends upon its position with respect to the blood-brain barrier and upon the type of dopamine receptor which is stimulated.

Decarboxylase Inhibition

Many of the effects of inhibiting L-aromatic amino acid decarboxylase on the pharmacology of levodopa have already been discussed. The pharmacology (Pinder et al., 1976) and clinical use of decarboxylase inhibitors (Marsden, 1975) have recently been fully reviewed. The main clinical benefits of peripheral decarboxylase inhibitors may be summarised as follows:

- 1) Less levodopa needs to be given to produce a similar therapeutic response
- 2) The incidence of nausea and vomiting is markedly reduced and
- 3) As a result of this, levodopa can be introduced more quickly and the therapeutic response occurs earlier than when levodopa is given alone
- 4) The incidence of levodopa-induced cardiac dysrhythmia is reduced
- 5) Pyridoxine, an essential prosthetic group and cofactor for decarboxylase activity contained in many multi-vitamin preparations, does not reverse the beneficial effect of levodopa in the presence of a peripheral decarboxylase inhibitor.

Of these effects, the most important is the reduction in the incidence of nausea and vomiting. For this reason alone, the treatment of choice in Parkinson's disease is now levodopa combined with benserazide or carbidopa. Dyskinesia occurs with equal or greater frequency in patients taking the combined preparation compared with those taking levodopa alone.

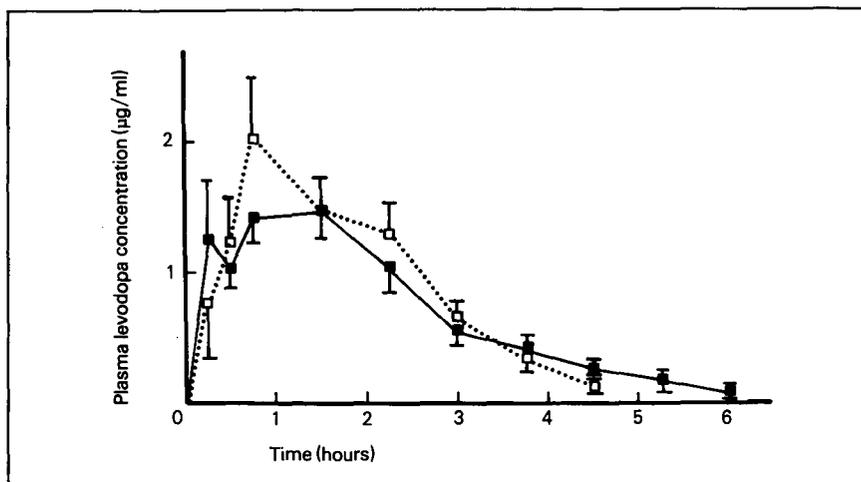


Fig. 11. Mean and SEM plasma levodopa concentrations of 11 subjects after taking 'Larodopa' (15mg/kg) (□) and 'Sinemet' (4mg/kg) (■).

As decarboxylation is the major route of metabolism of levodopa, it might be expected that one effect of peripheral decarboxylase inhibitors would be to prolong its plasma half-life: levodopa might need to be given less frequently throughout the day when given with the decarboxylase inhibitor. This, however, has not been found to be the case. A source of confusion in this context was the finding of Bianchine and his colleagues (1972) that the total plasma radio-activity half-life following oral administration of C^{14} -labelled levodopa in 3 patients was increased from 3 to 15 hours by concurrent administration of carbidopa. As the total radio-activity in the plasma is contributed to by all the metabolites of levodopa as well as by levodopa itself, this gives no information about the half-life of levodopa. Neither benserazide nor carbidopa significantly prolong the half-life of levodopa in the plasma following oral dosage (figs. 11 and 12, Morris et al., 1976). Similar peak concentrations of levodopa are achieved with one quarter to one fifth of the dose of levodopa when it is given with a peripheral decarboxylase inhibitor. These results suggest that the main effect of decarboxylase inhibitors is on decarboxylase in the gut. Inhibition of the enzyme at this site results in a greater proportion of an oral dose reaching the plasma as unchanged levodopa. Once in the plasma, it is removed at the same rate as occurs when it is given alone. That decarboxylase inhibitors have their main effect on the gut is not altogether surprising. The gut is probably the main site of decarboxylation of levodopa (Mearrick et al., 1975). Only 40 to 70% of an oral dose of benserazide and carbidopa are absorbed from the gut (Pinder et al., 1976). Both drugs undergo extensive metabolism within the body, urinary excretion of unchanged labelled carbidopa amounting to only 30% of the total urinary radio-activity (Vickers et al., 1974).

Thus the highest concentrations of unmetabolised carbidopa is achieved in the gut and inhibition of decarboxylation is likely to be maximal in that organ after an oral dose.

Minor Metabolites of Levodopa

Much of the foregoing discussion has assumed that dopamine is the only pharmacologically active metabolite of levodopa apart from adrenaline and noradrenaline. Minor metabolic pathways of levodopa also exist and some of their products are active.

3-O-Methylation

A metabolite of levodopa which has aroused interest is its methylated derivative, 3-O-methyl dopa (fig. 13). Although this accounts for only 2% of the total radioactivity in the plasma 1 to 2 hours after oral administration of labelled levodopa (Bianchine et al., 1971), this proportion rises with continued treatment (Pilling et al., 1975). The reason for this accumulation is that 3-O-methyl dopa has the relatively long half-life of 15 hours (Kuruma et al., 1971). In the presence of a peripheral decarboxylase inhibitor, a higher proportion of levodopa is methylated (Bartholini and Pletscher, 1968). These observations have led to the view that 3-O-methyl dopa may provide a depot for the slow release of levodopa. This, in turn, might account for the

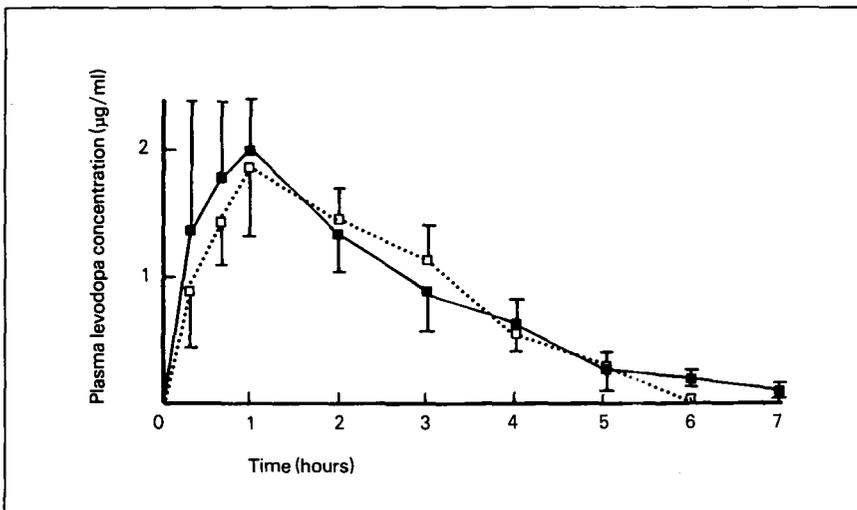


Fig. 12. Mean and SEM plasma levodopa concentrations of 6 subjects after taking 'Larodopa' (15mg/kg) (□) and 'Madopar' (3mg/kg) (■).

fact that deterioration in Parkinsonism following cessation of treatment with levodopa may take several days. In man, however, there is little evidence of demethylation of 3-O-methyl dopa back to levodopa (Curzon, 1973). Moreover, 3-O-methyl dopa has no therapeutic effect on Parkinson's disease (Geissbuhler et al., 1972). To the contrary, there is evidence that the presence of 3-O-methyl dopa in the plasma could reduce the efficacy of levodopa since the two amino acids compete for transport into the brain (Wade and Katzman, 1975).

Alkaloid Products

In 1971, Theodore Sourkes suggested that some of the pharmacological effects of levodopa might be due to the formation of tetrahydroisoquinolines. This group of biologically active alkaloids can be formed by the Pictet-Spengler condensation of amines with an aldehyde. Salsinol, formed by the condensation of dopamine with acetaldehyde, has been detected in the urine of Parkinsonian patients given levodopa and alcohol (Bonham Carter and Sandler, 1973). Salsinol acts as a dopamine agonist in the gut of the mollusc *Tapes wallingi* (Dougan et al., 1975). Tetrahydropapaveroline (THP), formed by the condensation between dopamine and one of its aldehyde metabolites, 3,4-dihydroxyphenylacetaldehyde, has also been detected in the urine of Parkinsonian patients taking levodopa (Bonham Carter and Sandler, 1973). THP possesses hypotensive activity (Holtz et al., 1964). Though structurally similar to the dopamine agonist apomorphine, it antagonises the action of dopamine in some preparations (Dougan et al., 1975). Tetrahydroisoquinolines can be taken up by adrenergic nerve endings and released as false transmitters (Cohen, 1976). That these highly active compounds can be formed during the metabolism of levodopa has been established. Their importance with regard to the beneficial and adverse effects of levodopa is as yet uncertain.

Transamination Products

Trace amounts of levodopa are transaminated to dihydroxyphenylpyruvic acid and dihydroxyphenyllactic acid (fig. 13). 3-O-methyl dopa is also transaminated. When decarboxylation is inhibited, transamination becomes a major pathway (Sandler et al., 1974). There seems little evidence at the present time that any of these metabolites are pharmacologically active.

Bacterial Metabolism

N-tyramine and n-hydroxyphenylacetic acid appear in the urine of patients treated with levodopa. These are probably formed by metabolism of levodopa by micro-organisms, as their concentration falls markedly when the patients are also given neomycin by mouth. Again, the importance of these metabolites of levodopa has not been established (Bakke, 1973).

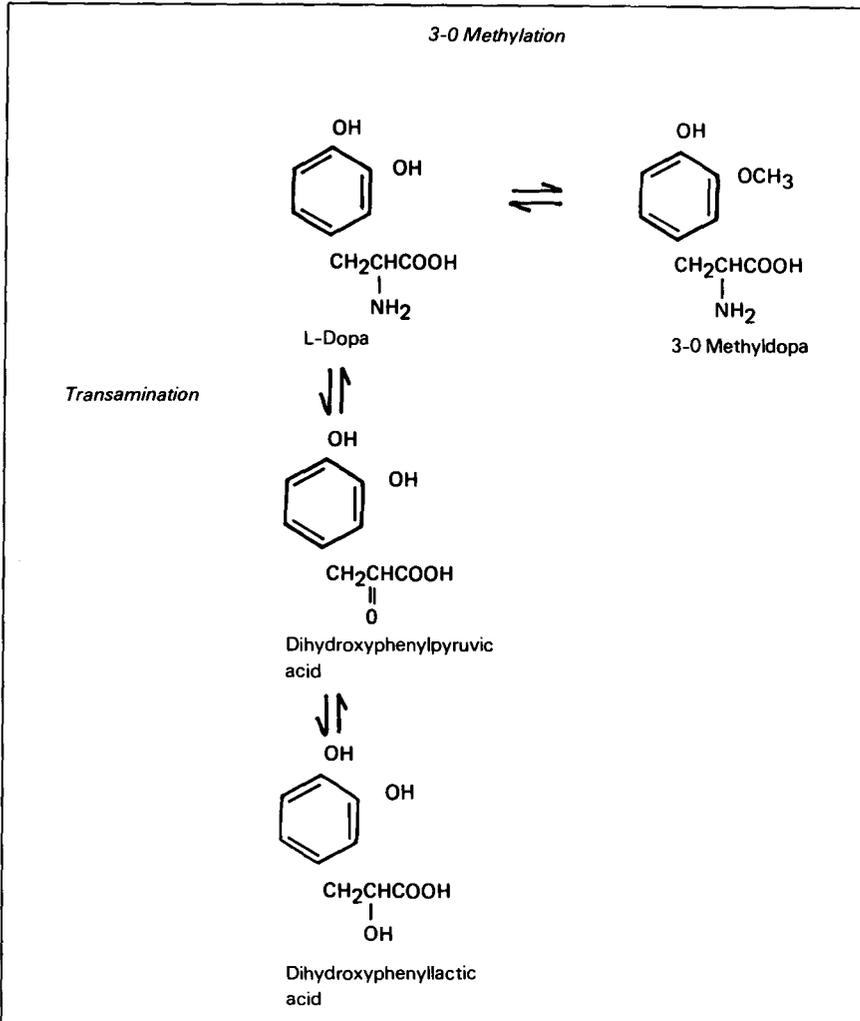


Fig. 13. 3-O-Methylation and transamination of levodopa (L-dopa).

The On-off Phenomenon

Perhaps the most intriguing aspect of levodopa therapy in the long term is the so-called 'on-off' phenomenon. While there is no generally agreed definition the condition is taken here to refer to frequent episodes, of sudden onset, in which the patient's akinesia becomes much worse for an hour or two. Usually, patients have been taking levodopa for at least 1 year before they begin to experience these attacks. In many

patients, there appears to be a relationship in time between their fluctuations and the dosage schedule of levodopa. In its most florid form, the patient swings repeatedly from being akinetic to dyskinetic. Barbeau has defined 4 progressive stages in the 'on-off' phenomenon (Barbeau, 1972). Marsden and Parkes subdivide the fluctuations into 6 types (1976). Theories as to the cause of these fluctuations fall into two groups. The first relates the fluctuations to the plasma levodopa concentrations (Tolosa et al., 1975). Due to its short plasma half-life, when levodopa is given 3 or 4 times daily, there are periods during the day when none is available in the plasma for uptake into the brain. Deterioration in some patients appears to coincide with these periods. Dyskinesia tends to occur at the time of peak concentrations. It is not possible however to relate clinical response to plasma levodopa concentration in all patients who fluctuate (for review see Bianchine and Shaw, 1976). Moreover, increasing the frequency of dosage is often ineffective in preventing fluctuations. There is no convincing evidence that the plasma half-life of levodopa shortens with continued treatment and yet patients do not complain of fluctuations when first treated.

For these reasons, alternative causes for the 'on-off' phenomenon have been sought. One possibility is that with continued treatment increasing amounts of levodopa are diverted into pathways which produce metabolites which block the action of dopamine, such as tetrahydropapaveroline (Dougan et al., 1975).

Investigation of this interesting phenomenon is made difficult by the fact that Parkinsonian patients are prone to brief episodes of worsened tremor or akinesia, or conversely, improved performance, when they are not taking levodopa. A proper understanding of the 'on-off' phenomenon will depend first and foremost on the establishment of clear clinical criteria of what the condition refers to. As yet, this has not been done.

Summary and Conclusions

Levodopa has become established as the treatment of choice in Parkinson's disease. It is absorbed by an active mechanism from the small bowel. Its pharmacological activity depends upon the formation of dopamine and possibly other metabolites. Its beneficial effect in Parkinson's disease probably depends upon temporarily restoring the ability of degenerating nigro-striatal cells to release dopamine. Its main side effect, that of dyskinesia, may reflect a direct action of dopamine on striatal receptors. Peripheral decarboxylase inhibitors reduce the incidence of levodopa-induced nausea, probably by lowering the concentration of dopamine in the area postrema.

The introduction of levodopa in the treatment of Parkinson's disease is generally regarded as one of the uncommon examples in medicine where effective therapy has resulted from systematic research rather than serendipity. As our knowledge of the pharmacology of levodopa grows, we may be forced to admit that perhaps the right drug was chosen for the wrong reasons.

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The Pharmacology of Anticonvulsant Drugs

*M.J. Eadie**

Anticonvulsant pharmacology may be divided into its pharmacodynamic and pharmacokinetic studies. Under the former designation fall those matters pertaining to the actual effects produced by drugs when they reach their sites of action. The term pharmacokinetics takes in those factors which determine the presence of the drugs at their sites of action *viz.* the processes of absorption, distribution and elimination.

Anticonvulsant Pharmacodynamics

The actions of anticonvulsant drugs may be studied at a number of different levels of biological complexity. These levels range in a descending hierarchy from the whole human brain through various animal models of epilepsy to the level of single biological molecules.

The Whole Human Brain

To the physician, the most pertinent criterion of the activity of an anticonvulsant drug is the response of human epilepsy to that drug.

It is known empirically that certain forms of epilepsy in man are likely to respond better to certain anticonvulsants than to others. A correlation between type of epilepsy (based on the Classification of Epileptic Seizures proposed by the Interna-

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Table 1. Correlation between type of epilepsy and potentially effective anticonvulsant drugs. In general drugs are listed in order of diminishing efficacy

Type of epilepsy		Drugs
	Absences	Ethosuximide; clonazepam; valproate Troxidone
Generalised	Absences with myoclonic phenomena	Clonazepam; valproate Nitrazepam; diazepam Ethosuximide; phenobarbitone and congeners ¹ Carbamazepine
	Convulsive seizures	Phenytoin, carbamazepine, phenobarbitone or congeners ¹
Partial, (all varieties — without or with secondary generalisation)		Clonazepam ? Valproate ? Sulthiame

1 Phenobarbitone congeners = methylphenobarbitone and primidone.

tional League against Epilepsy — Gastaut, 1969) and potentially effective drugs is set out in table I. Exceptions to this correlation occur, though some may be explained by:

- 1) Incorrect diagnosis of the type of epilepsy
- 2) Capricious behaviour of the natural history of epilepsy in individual patients, or
- 3) Pharmacokinetic interactions between concurrently taken anticonvulsants such that change in the dose of one drug produces an unrecognised alteration in the plasma level and biological effect of another drug with a different spectrum of anticonvulsant action.

The plasma drug levels that have been associated with the most favourable therapeutic effects in human epilepsy (the therapeutic ranges) are set out in table II.

In the past, the non-epileptic human brain was occasionally used as a model to study anticonvulsant action (Huot et al., 1973), mostly during the course of electroconvulsive therapy in psychiatric patients. Relatively little of importance for human therapeutics seems to have come from such studies.

The Whole Brain of Experimental Animals

A number of animal models of epilepsy have been used to study the actions of anticonvulsant drugs. These experimental preparations have been reviewed by a number of authors e.g. Naquet and Lanoir (1973), Swinyard (1973). In assessing the results of studies on such preparations one needs to consider:

- 1) the appropriateness of the experimental preparation as a model for human epilepsy, and
- 2) the question of whether drug doses have been used which produce anticonvulsant drug concentrations in plasma similar to those which apply when these drugs exert an anti-epilepsy effect in man.

Till quite recently the latter question was often ignored though, in the light of contemporary knowledge, its relevance is obvious.

It would be impractical to attempt a detailed review of all the available data concerning the actions of commonly used anticonvulsant drugs on the various whole animal models of epilepsy, particularly in view of the different criteria that have been used to assess treatment effect. It is perhaps more useful for the purposes of the clinician to attempt to correlate certain types of commonly used experimental preparations with types of human epilepsy, and then to indicate the response of these preparations to the anticonvulsant drugs more commonly used in man.

Correlation Between Experimental Animal Epilepsy and Human Epilepsy

Whole animal models of epilepsy fall into two groups. In the first, the animals have a natural predisposition to epilepsy, though their seizures may be provoked when convenient for the investigator. In the second, the animals are deliberately made epileptic.

Table II. Therapeutic ranges of plasma anticonvulsant levels

Drug	Therapeutic range	
	µg/ml	µmol/L (10 ⁻⁶ mol)
Phenytoin	10-20	40-80
Phenobarbitone	10-30	40-130
Carbamazepine	6-12	25-50
Troxidone (dimethadione)	> 700	> 5500
Ethosuximide	40-100	280-700
Clonazepam	.025-.075	0.08-0.24
Valproate	50-100	350-700
Sulthiame	?	?

Table III. Whole animal models of epilepsy, and their correlation with types of human epilepsy

Type of seizure	Human	Animal model
Generalised	Absences	None
	Absences with myoclonic phenomena	<i>Papio papio</i> Systemically administered chemicals e.g. pentylenetetrazole, penicillin, picrotoxin, thiosemicarbazide, bicuculline, bemegride, procaine, lidocaine, cocaine, strychnine
	Convulsive seizures	Electroshock, applied to the whole head (maximal and minimal)
Partial		Freezing lesions of cortex Locally applied chemicals e.g. penicillin, cobalt, alumina Local electrical stimulation (including 'kindling' model)

Spontaneous Seizures

The spontaneous seizure models include the photosensitive baboon, *Papio papio*, and mice with a tendency to audiogenic seizures. The *Papio papio* model is clearly analogous to the photosensitive type of myoclonic epilepsy that occurs in children. The equivalence between mouse audiogenic seizures and human epilepsy is less clear, as there is some uncertainty about the interpretation of electroencephalographic findings in audiogenic seizures (Naquet and Lanoir, 1973).

Models of Generalised Epilepsy

Seizures in previously normal animals may be provoked in such a way that the animals serve as models of generalised or partial epilepsy. Situations akin to generalised epilepsy may be produced by applying electrical shocks to the whole head, or by the systemic administration of convulsant chemicals (classically pentylenetetrazole). In general pentylenetetrazole and related chemicals produce seizures similar to those of myoclonic generalised epilepsy in man (with or without subsequent convulsions), while the electrogenic seizures on the whole resemble human convulsive generalised epilepsy. However certain patterns of electrical stimulation can produce animal seizures rather more like those of myoclonic generalised epilepsy which subsequently develops into a convulsive seizure. There appears to be no adequate animal model of petit mal absence epilepsy that is in any widespread use. Seizures

provoked by systemically administered pentylenetetrazole are sometimes equated with absence epilepsy, but the affinity seems rather to be with so-called myoclonic petit mal than with pure absence attacks.

Models of Partial Epilepsy

Experimental models of partial epilepsy are produced by applying electrical shocks to restricted volumes of the cerebral cortex, or to certain subcortical structures. Temporary models of partial epilepsy can be produced by local electrical stimulation, or by local application of chemicals with a rapid onset but short duration of convulsant action (e.g. penicillin, strychnine, pentylenetetrazole). More enduring animal epileptic models may also be produced electrically or chemically. The chronic repeated application of electrical shocks to one region of the cortex or subcortex can finally set up a spontaneously discharging focus which may itself initiate mirror focus formation. In many ways this 'kindling' model is the best available analogy to human partial epilepsy (Wada, 1977). Certain chemicals (e.g. cobalt, alumina, tungstic acid), if applied to grey matter can set up a delayed onset, but persisting, epileptic focus.

Anticonvulsants in Experimental Animal Epilepsy

The *Papio papio* Preparation

Drugs effective as anticonvulsants in this preparation include phenobarbitone (Stark et al., 1970; Meldrum et al., 1975), the benzodiazepines clonazepam and, to a lesser extent, diazepam (Stark et al., 1970), and valproate (Patry and Naquet, 1971). Ethosuximide is ineffective and phenytoin and carbamazepine offer protection only when given in doses that are toxic to the animals (Meldrum et al., 1975).

Audiogenic Seizures in Mice

Valproate will protect against these seizures (Simler et al., 1973).

Systemically Administered Chemical Convulsants

Pentylenetetrazole seizures in mice are prevented by phenobarbitone (Swinyard and Castellion, 1966), primidone in the acute situation, before there has been time for phenobarbitone to form from it (Goodman et al., 1953b), troxidone (Goodman et al., 1953a), ethosuximide (Chen et al., 1963), clonazepam (Blum et al., 1973) and valproate (Frey and Loscher, 1976). Phenytoin (Woodbury and Esplin, 1959), carbamazepine (Theobald and Kunz, 1963) and sulthiame (Wirth et al., 1960) are relatively ineffective. In contrast to the above findings Baumel and colleagues (1973) noted that primidone did not confer significant protection against pentylenetetrazole

seizures in rats, and Julien and Hollister (1975) showed that carbamazepine did protect against such seizures in mice, though the workers responsible for the Department of Health Education and Welfare Publication No (NIH) 76-1093 (1976) obtained a contrary finding. Such conflicting findings, even in only a small portion of the available literature, inevitably draw attention to the uncertainties of relating animal findings to the human situation.

Other systemically administered convulsants have not been as widely used as pentylenetetrazole. Strychnine induced seizures may be prevented by phenobarbitone and clonazepam but not by phenytoin (Blum et al., 1973) or carbamazepine (Theobald and Kunz, 1963), and are only weakly prevented by valproate (Frey and Loscher, 1976).

Thiosemicarbazide and 2,4-dimethyl-5-hydroxymethyl pyrimidine seizures may respond to phenobarbitone (Banziger and Hane, 1967) and clonazepam (Blum et al., 1973), but not to phenytoin (Banziger and Hane, 1967). Troxidone offers some protection (Banziger and Hane, 1967).

Seizures produced by systemically administered local anaesthetics (procaine, cocaine, lignocaine) in various species respond to phenobarbitone (Sanders, 1967), troxidone (Sanders, 1967), and clonazepam (Blum et al., 1973), but not to phenytoin (Eidelberg et al., 1965).

Bicuculline induced seizures are not prevented by phenytoin, carbamazepine and troxidone, though the clinical pattern of the seizure is modified (Blum et al., 1973). However, phenobarbitone and clonazepam do protect against these seizures (Blum et al., 1973), and valproate confers some protection (Frey and Loscher, 1976).

Bemegride induced seizures are prevented by clonazepam (Blum et al., 1973) and by valproate (Van Duijn and Beckman, 1975).

From the above findings one gains the impression that phenobarbitone, troxidone, clonazepam and valproate are the most effective drugs against chemically induced generalised seizures of myoclonic pattern in experimental animals. On the whole these conclusions correlate with response of human myoclonic generalised epilepsy to anticonvulsant drugs. Some of the discrepant results in the animal studies may be due to the anticonvulsant drug in certain circumstances acting as a specific chemical antagonist to the agent provoking the seizures (e.g. valproate in the case of bicuculline and picrotoxin seizures) rather than, or as well as, having its general action of interfering with subsequent epileptic events.

Electrically Induced Generalised Convulsions

A number of different techniques have been used for electrically evoking generalised convulsions in experimental animals, and different criteria have been employed for assessing anticonvulsant effects. The most widely used model has been the maximum electroshock seizure.

The following drugs are effective in preventing and/or modifying maximum electroshock seizures in various species of experimental animal (usually mice): phenytoin (Woodbury and Esplin, 1959), phenobarbitone (Goodman et al., 1953b), unmetabolised methylphenobarbitone (Craig and Shideman, 1971), unmetabolised primidone (Goodman et al., 1953b), carbamazepine (Julien and Hollister, 1975), clonazepam (Swinyard and Castellion, 1966) and sulthiame (Wirth et al., 1960). Troxidone (Goodman et al., 1953a), valproate (Frey and Loscher, 1976), and to a small extent ethosuximide (Department of Health Education and Welfare Report, 1976) confer protection against maximum electroshock seizures, but all three drugs are more effective against generalised epilepsy induced by systemically administered chemical convulsants.

The minimum electroshock seizure is a less frequently used model. Phenytoin raises the threshold for this type of seizure (Woodbury and Esplin, 1959), and phenobarbitone, carbamazepine and clonazepam (Blum et al., 1973) protect against it.

It thus appears that drugs useful in preventing generalised convulsive seizures in man, whether these seizures arise primarily or are secondary to partial epilepsy, are those drugs which protect in the electroshock models of generalised epilepsy in experimental animals.

Electrically Induced Partial Epilepsy

At concentrations in the therapeutic range, phenytoin reduces 'kindled' amygdaloid seizures in cats and baboons, though perhaps not in other species (Wada, 1977). Neocortical 'kindled' convulsions are more readily suppressed by the drug than amygdala 'kindled' seizures in several species (Wada, 1977). Carbamazepine has no prophylactic effect against amygdala 'kindled' attacks (Racine et al., 1975). Phenobarbitone suppresses amygdala 'kindled' seizures in rats, even if given in doses that made the animals comatose (Wada, 1977). However it did protect against seizures in this model of partial epilepsy in cats (Wada et al., 1976). Diazepam is an effective anticonvulsant in the amygdala 'kindled' preparation (Tanaka, 1972; Racine et al., 1975).

Chemically Induced Partial Epilepsy

Many chemical models of partial epilepsy have been studied. Only a few of the findings are outlined here. Phenytoin will prevent clinical seizures in cats with a penicillin induced cortical focus (Louis et al., 1968). Carbamazepine has a similar prophylactic effect on seizures from alumina induced foci in the hippocampus or sensori-motor cortex in rhesus monkeys (David and Grewal, 1976), while phenobarbitone prevented seizures from a stropanthin focus in the rabbit cerebral cortex (Petsche, 1972). Clonazepam prevented seizures arising from penicillin-induced cortical foci in rabbits (Blum et al., 1973), and valproate had a protective effect against

seizures beginning in an experimental cobalt focus in the cat hippocampus. Little information is available as to the effects of troxidone and ethosuximide on such models of partial epilepsy.

Thus, on the whole, similar drugs appear useful in human partial epilepsy and in experimental partial epilepsy in animals.

Groups of Neurons in Animals

Epilepsy appears to originate in groups of interconnected neurons. Therefore the neuronal 'pool' is an appropriate model for the study of epileptic phenomena and anti-convulsant drug action. Experimentally, neuronal pools may be brought to a state of heightened excitability by the various techniques described in the previous section, and the effects of anticonvulsant drugs on the local electrical properties of these pools may then be studied. The models approximate to the situation of human partial epilepsy, though it appears reasonable to assume that similar local events would also apply in human generalised epilepsy. Often the same experimental circumstances are used as in whole animal models of partial epilepsy, but the preparations are studied at a more intimate level. Of all the possible neuronal pools which might be investigated, certain ones are more commonly studied because 'epileptic' activity is more readily instigated in these neuronal groups. Thus in man, monkey and cat, post-stimulus after-discharges are more readily instigated in the hippocampus than in the motor cortex, amygdala and basal ganglia. The frontal and occipital cortices have higher after-discharge thresholds, and within the thalamus the nonspecific thalamic nuclei have higher thresholds than the specific ones (Naquet and Lanoir, 1973).

The effects of anticonvulsants on such neuronal pools were reviewed by Krupp and Monnier (1973). The electrical phenomena studied can be divided into four groups:

- 1) Activity at the site of epileptogenesis
- 2) Propagation of activity from the site
- 3) After-discharges at the site, or after-discharges set up at other sites
- 4) Synaptic transmission.

In interpreting such studies, one again needs to consider the question of whether clinically relevant anticonvulsant concentrations were operative.

Activity at the Epileptogenic Site

Spike activity at the experimental epileptogenic site either is not suppressed (Louis et al., 1968) or is only briefly suppressed (Dow et al., 1973) after phenytoin administration. The latter authors found that phenobarbitone increased the frequency and duration of spiking at cobalt cortical foci in rats. Edmonds et al. (1974) found

that phenobarbitone did not alter spike frequency in the rat cortical penicillin focus, but Morrell and colleagues (1959) noted that phenobarbitone caused a modest decrease in spike frequency at a cortical focus produced by local freezing. Carbamazepine to some extent diminished activity at an alumina induced cortical focus (David and Grewal, 1976), but at concentrations below $9\mu\text{g/ml}$ it failed to influence spike activity at penicillin produced cortical foci in cats (Julien and Hollister, 1975). However in this species, Holm et al. (1970) showed that carbamazepine, at concentrations of 5 to $9\mu\text{g/ml}$, rather specifically suppressed activity in the anterior ventral nucleus of the thalamus (a structure thought to be involved in the generalisation of epileptic seizures). Higher carbamazepine levels were required to suppress the centrum medianum, brain stem reticular formation, amygdala, hippocampus, hypothalamus, caudate nucleus and putamen. Ethosuximide did suppress spiking at a cobalt focus in rat cerebral cortex (Dow et al., 1973). Both clonazepam (Giunta et al., 1970; Petsche, 1972), and diazepam (Celesia et al., 1973) did not appear to alter focal spiking in certain chemically induced cortical foci in experimental animals. However valproate did decrease discharge frequency at a cobalt induced hippocampal focus in cats (Mutani et al., 1968).

Thus activity at a cortical spike focus appears to be suppressed by two drugs which are of dubious value in partial epilepsy (ethosuximide and valproate), and is not suppressed by those drugs which are useful in these circumstances in man (phenytoin, phenobarbitone, carbamazepine and clonazepam). However, the selective regional suppression of activity within the thalamus produced by carbamazepine raises the possibility that the other anticonvulsants may also have specific suppressive effects in particular regions.

Propagation of Activity from the Epileptogenic Focus

Despite its relative lack of action at experimental epileptic foci, phenytoin limits the propagation of activity from foci (Musgrave and Purpura, 1963; Louis et al., 1968). Carbamazepine also limited the propagation of focal spike activity (Julien and Hollister, 1975; David and Grewal, 1976), as did clonazepam (Giunta et al., 1970). Morrell and colleagues (1959) showed that troxidone did not alter propagation within the cortex of activity arising from a cortical 'freezing' focus, but tended to prevent such propagated activity spreading into the thalamus.

It thus appears that anticonvulsants useful in human partial epilepsy act in experimental animals with partial seizures by suppressing seizure spread from the epileptic focus, rather than by suppressing events at the focus itself. This accords with the clinical observation that anticonvulsant doses that prevent a patient's partial epilepsy from manifesting itself by a secondary generalisation may not suffice to suppress the epileptic aura, the local manifestations of the discharge in and around the focus.

After-discharges

Following stimulation of neuronal pools, or following propagated spike discharges arising from neuronal pools, residual 'after-discharges' may occur in the neuronal pool, and also in other neuronal pools some distance away. These after-discharges may be regarded as an indication of the neuronal pool's tendency to develop a further epileptogenic discharge. Suppression of after-discharges therefore has an anti-convulsant effect.

Phenytoin can suppress after-discharges induced electrically in various cortical and subcortical neuron pools of experimental animals. The effect varies in different brain regions. Thus Schallek and Kuehn (1963) showed that phenytoin increased the threshold for electrically induced after-discharges to a greater extent in the frontal and parietal cortex than in the thalamus. The drug also decreased the amplitude and duration of any after-discharges that the stimuli produced in these structures. Phenytoin failed to decrease after-discharges from penicillin induced cortical epileptogenic foci in rats (Edmonds et al., 1974) but did reduce the repetitive after-discharges that follow maximum electro-shock seizures in mice (Woodbury and Esplin, 1959).

Phenobarbitone also increased the threshold for after-discharge instigation in the hippocampus and amygdala of cats (Strobo and Spudis, 1960), and in the intralaminar thalamus and neocortex (Schallek and Kuehn, 1963). It failed to decrease after-discharges from a penicillin induced cortical focus (Edmonds et al., 1974).

Carbamazepine increased the threshold for electrical induction of after-discharges in the limbic structures of cats, but not in the lenticular nucleus (Kobayashi et al., 1967). This was in keeping with the earlier finding of Hernandez-Peon (1962), in relation to hippocampal and amygdaloid after-discharges.

Troxidone raised the threshold for the electrical instigation of after-discharges in the intralaminar thalamic nuclei (Schallek and Kuehn, 1963), and in the amygdala, hippocampus and ectosylvian gyrus of cats (Strobo and Spudis, 1960), though it had less effect on neocortical after-discharges (Schallek and Kuehn, 1963).

Clonazepam raised the electrical after-discharge threshold in the cat cortex and thalamus (Schallek, cited by Blum et al., 1973), while diazepam raised the threshold in the thalamus, amygdala and hippocampus, though not in the cortex (Boyer, 1966).

Valproate elevated the threshold for electrical induction of hippocampal after-discharges, and decreased the duration of any after-discharges that developed (Mutani et al., 1968; Mutani and Fariello, 1969).

Thus, apart from the rather refractory after-discharges of the penicillin induced cortical experimental epileptic focus, anticonvulsants seem to suppress after-discharges in a variety of brain regions commonly involved in the initiation and propagation of epileptic activity. There is a degree of relative regional selectivity of suppressant action which seems to vary from drug to drug. These observations can go some way toward explaining the effects of particular anticonvulsants on different

types of human epilepsy, with their different areas of origin and different directions of preferential propagation within the brain.

Synaptic Transmission

The observation, *vide supra*, that many anticonvulsants suppress the spread of experimental seizure activity, rather than its initiation, raises the question of the effect of anticonvulsants on transmission through synapses in monosynaptic and polysynaptic pathways.

Phenytoin profoundly depresses the post-tetanic potentiation of impulse transmission (Esplin, 1957). This effect occurs at phenytoin doses which have no other effect on neural function. Sherwin (1973) has advanced the proposition that phenytoin acts mainly on responses which depend on repetitive activity in polysynaptic circuits. This effect might depend on the effect of the drug on post-tetanic potentiation. Phenobarbitone suppresses monosynaptic and polysynaptic transmission in the spinal cord (Esplin, 1963) but has no clear-cut effect on post-tetanic potentiation (Fromm and Landgren, 1963; Kutt, 1974). Carbamazepine decreases synaptic transmission in the spinal trigeminal nucleus of cats (Fromm and Killain, 1967). In the rabbit spinal cord it was found to decrease slightly post-tetanic potentiation (Krupp, 1969). Further information as to the effect of the drug on post-tetanic potentiation was provided by Julien and Hollister (1975), who showed that the phenomenon was not altered by carbamazepine concentrations of 3.5 to 10.0 µg/ml. However supratherapeutic concentrations (15 to 20 µg/ml) did decrease the potentiation. Troxidone has no effect on post-tetanic potentiation (Esplin and Curto, 1957; Woodbury, 1969). Clonazepam does not alter the phenomenon of post-tetanic potentiation in 'spinal' cats (Swinyard and Castellion, 1966).

Thus among the commonly used anticonvulsants only phenytoin seems to have a significant effect on post-tetanic potentiation. This action of phenytoin could go some way to explain how this drug limits seizure propagation, as it must militate against the rapid transmission of a series of discharges. However other anticonvulsants must utilise different mechanisms to suppress after-discharges and limit the propagation of epileptogenic activity.

Single Neurons

The effects of anticonvulsant drugs on the electrical behaviour of single neurons has been studied in an endeavour to explain the actions of these drugs. Such observations, reviewed by Chalazonitis and Arvanitaki (1973), should be interpreted in the light of explaining the phenomena summarised above concerning the actions of anticonvulsants on neuronal pools. Again, the question of clinically relevant drug concentrations arises, as does the question of the extent to which findings on individual invertebrate neurons will prove applicable to human neurons.

The parameters of neuronal electrical function investigated include:

- 1) The resting membrane potential
- 2) The action potential
- 3) Post-synaptic excitation
- 4) Post-synaptic inhibition.

The Resting Membrane Potential

Phenytoin does not alter the resting potential or conductance across the cell membrane of skeletal muscle, though membrane conductance changes in certain invertebrate neurons without the resting membrane potential altering (Ayala and Johnston, 1977). Earlier, Woodbury (1955) had stated that phenytoin did increase the resting membrane potential.

Phenobarbitone, at concentrations (1 to 2g/L), one or two orders of magnitude above those which are effective as an anticonvulsant in man, produces only a slight resting membrane hyperpolarisation in neurons of the invertebrate *Aplysia* (Chalazonitis and Arvanitaki, 1973).

With the passage of a rapid series of impulses through a synapse, the phenomenon of post-tetanic hyperpolarisation of the axon terminal may occur. Phenytoin reduces such post-tetanic hyperpolarisation in crayfish stretch-receptor neurons (Ayala and Johnston, 1977).

The Action Potential

Phenytoin produces little alteration in the action potential of squid giant axons (Korey, 1951), or in the action potential of muscle (Carnay and Grundfest, 1974). However Ayala and Johnston (1977) stated that the effect of phenytoin on the action potential varied in different experimental neuron preparations. Phenobarbitone alters action potentials only at supratherapeutic concentrations e.g. 5×10^{-2} M (Rosenberg and Bartels, 1967). The therapeutic range for the drug is of the order of 10^{-4} M. Supratherapeutic carbamazepine concentrations (23.6 to 236 μ g/ml) decrease the membrane potential of the squid giant axon.

Post-synaptic Excitation

Phenytoin decreases excitatory post-synaptic potentials in *Aplysia* neurons (Ayala and Johnston, 1977).

Post-synaptic Inhibition

In the invertebrate *Aplysia*, phenytoin has different effects on different post-synaptic inhibitory mechanisms (Ayala and Johnston, 1977). The drug has little effect on

Cl^- dependent inhibitory post-synaptic potentials. Phenytoin considerably prolongs γ -aminobutyrate (GABA) mediated inhibitory post-synaptic potentials in the crayfish stretch-receptor, in which preparation the drug prolongs any induced conductance change in the post-synaptic membrane.

Thus not a great deal of information is available concerning the effects of anti-convulsants on single neurons. To some extent this reflects the technical difficulties inherent in such studies, and the problems of preparing suitable aqueous solutions of some of the relevant drugs. The findings for the effects of phenytoin on post-tetanic hyperpolarisation may correlate with its effect in reducing post-tetanic potentiation. If the invertebrate findings can be transferred to man, the drug may also have an anti-convulsant effect by altering synaptic transmission in other ways.

Biochemical Effects

It seems likely that the action of anticonvulsant drugs at a molecular level would involve changes in the biochemical mechanisms responsible for nerve impulse transmission within the neuron, or changes in the chemical transmission of activity across synapses between neurons. The relevant biochemical mechanisms likely to be involved might include:

- 1) The production of energy, necessary to maintain polarisation of the cell membrane and to permit synthesis of synaptic transmitter molecules
- 2) The ionic concentration gradients across cell membranes
- 3) The formation, release, reuptake, action and inactivation of synaptic transmitter molecules.

In addition there is some suggestion that altered folate metabolism may be involved in anticonvulsant action, as may be altered protein and macromolecule formation.

Effects of Anticonvulsants on Energy Production

Phenytoin: It appears that phenytoin produces some inhibition of certain biochemical reactions which have the final effect of providing energy for various metabolic activities of cells. At concentrations (10^{-4} M) comparable to those which have an anticonvulsant effect in man, the drug inhibits terminal mitochondrial NADH oxidase in beef heart mitochondria (Cowger and Labbe, 1967). Spector (1972) showed that 'therapeutic' concentrations of phenytoin reduced oxygen consumption (a measure of overall metabolic activity) in a microsomal-synaptosomal preparation from rat brain. This decrease in oxidative metabolism was reversed by the addition of noradrenaline or tetrahydrofolate. There are some conflicting findings as to the effects of the drug on Krebs cycle enzymes. Green et al. (1973) found that the drug had no effect on the succinate dehydrogenase activity of chronically isolated cerebral

cortex in the cat. In rats long term phenytoin therapy did not alter cerebellar succinate dehydrogenase activity (Karkos, 1975), nor did the drug decrease the 'resting' levels of redox enzymes in the cortex or spinal cord (La Manna et al., 1977b). In contrast Leznicki and Dymecki (1974) found that long term phenytoin use in animals did diminish succinate dehydrogenase activity.

Phenytoin enhances the conversion of glutamic acid into Krebs cycle intermediates via α -ketoglutaric acid. This action might make available more energy for some process which makes the neuron less excitable (Woodbury, 1969). However the other actions of phenytoin mentioned above would tend to diminish available neuronal energy. There are several ways in which decreased energy availability might alter neuronal function, but it is difficult to see how any one action would have a decisive anticonvulsant effect.

Phenobarbitone: Like phenytoin, phenobarbitone depresses terminal mitochondrial oxidation, though this effect of phenobarbitone occurs at concentrations (10^{-3} M) an order of magnitude above those at which the drug exerts an anticonvulsant effect in man (Cowger and Labbe, 1967). In cats, even in anaesthetic doses, phenobarbitone did not block mitochondrial electron transport between NADH and cytochrome a_1a_3 . However it caused a decrease in NAD^+ in the cerebral cortex, suggesting that there would have been decreased cerebral oxygen consumption (La Manna et al., 1977a). Despite these depressant effects on cerebral metabolism, phenobarbitone facilitates glucose transport from blood to brain. However Bachelard (1976) has noted this effect at drug concentrations (0.25×10^{-3} M) which are somewhat above the therapeutic range in man (0.04 to 0.13×10^{-3} M). In rats phenobarbitone at anticonvulsant concentrations inhibits cytochrome oxidase (Constantinescu et al., 1973). In this species the drug also caused a fall in brain succinate dehydrogenase activity (Leznicki and Dymecki, 1974).

As well as having these actions on the oxidative metabolism of glucose, phenobarbitone inhibits anaerobic glycolysis (Bachelard, 1976). This action would be likely to decrease the amount of pyruvate available to enter the Krebs cycle.

Thus phenobarbitone has effects likely to decrease the availability of energy to cells, but whether these actions are important at therapeutic concentrations of the drug is doubtful, as also is the relation between decreased energy availability and an anticonvulsant effect.

Carbamazepine: No information is available.

Troxidone: While troxidone inhibits the increase in oxygen uptake and in anaerobic glycolysis that occurs in brain slices which are stimulated electrically (Mori, 1974), this finding may not reflect any direct effect of the drug on oxidative metabolism. Instead, it may simply be that an anticonvulsant effect of the drug mediated through an entirely different mechanism reduces the need for increased neuronal

metabolic activity in the stimulated cells. The drug facilitates glucose transport from blood to brain cells (Nahorski, 1972).

Ethosuximide: Chronic administration of ethosuximide to rats decreased succinate dehydrogenase activity (Lenzicki and Dymecki, 1974). The drug facilitates glucose transport from blood to brain cells (Nahorski, 1972).

Clonazepam: No information has been traced bearing on the effect of this drug on oxidative metabolism.

Valproate: While valproate alters the function of enzymes of the so-called GABA shunt, no data have been found suggesting that the drug alters function in the related Krebs cycle.

Thus, while some anticonvulsants may alter oxidative metabolism and energy availability in neurons, this effect does not appear to provide an adequate biochemical basis for the anti-epilepsy actions of these drugs.

Effects of Anticonvulsants on Ionic Concentration Gradients

Sodium Ions

Phenytoin: The effect of phenytoin on Na^+ in excitable tissues has been reviewed in some detail by Ayala and Johnston (1977) and Deupree (1977). The validity of Woodbury's (1955) finding that phenytoin causes a fall in brain intracellular Na^+ concentration seems generally accepted. The mechanisms involved remain controversial. There are two main possibilities:

- 1) There may be an increased active extrusion of Na^+ from within cells
- 2) There may be impaired influx of Na^+ into cells.

If there were increased active extrusion of Na^+ the likely mechanism would be increased function of the Na^+ 'pump', the enzyme Na^+K^+ linked adenosine triphosphatase (Skou, 1965). The published findings regarding the effects of phenytoin on this enzyme have been frankly conflicting. Certain workers have found no evidence of activation of this enzyme by the drug, and in fact have found evidences of inhibition (Pincus and Rawson, 1969; Formby, 1970; Deupree, 1976). Other workers have obtained evidence that phenytoin did activate the enzyme, but only at rather critical, non-physiological, environmental $\text{Na}^+:\text{K}^+$ concentration ratios (Festoff and Appel, 1968; Escueta and Appel, 1971; Siegel and Goodwin, 1972). Escueta and Appel (1972) found that phenytoin activated the enzyme at more physiological $\text{Na}^+:\text{K}^+$ concentration ratios in experimental epileptic cortex (freezing lesion) than in normal cortex. On the whole, opinion appears to be hardening that phenytoin does not activate Na^+K^+ -adenosine triphosphatase (Ayala and Johnston,

1977; Deupree, 1977; La Manna et al., 1977b). However, as Deupree (1977) pointed out, it would be exceedingly difficult to prove experimentally that phenytoin did not increase the efficiency of the enzyme in some way, without activating it. Deupree (1977) attempted to reconcile the discrepant findings regarding Na^+K^+ -adenosine triphosphatase by suggesting that those workers who found activation may have inadvertently allowed K^+ contamination of the reaction medium to occur, because of the difficulty of dissolving phenytoin in a neutral aqueous environment. In Escueta and Appel's (1972) work with freeze-damaged epileptogenic cortex, the injured cells may have released K^+ into the incubation medium. As far as one can judge, on the basis of the data available, phenytoin probably lowers intracellular Na^+ by some means other than activation of the sodium pump.

The studies of Pincus and Rawson (1969), Pincus et al. (1970) and Pincus (1972) were in favour of the possibility that phenytoin restricted the influx of Na^+ into cells. Such an effect would reduce intracellular Na^+ concentration and consequently reduce the stimulus for active extrusion of Na^+ . The phenomenon of post-tetanic hyperpolarisation, believed due to stimulation of active Na^+ extrusion, would therefore be reduced in the presence of phenytoin. As a consequence post-tetanic potentiation would be reduced. Thus the effects of phenytoin on Na^+ conductance would go some way to explain some of the alterations in neuronal electrical function produced by the drug.

Phenobarbitone: According to Bunker and Vandam (1965), phenobarbitone causes decreased Na^+ and K^+ flux across cell membranes. The drug produces decreased intraneuronal Na^+ concentration (Pincus et al., 1970). If these findings are correct they suggest that phenytoin and phenobarbitone may share a common biochemical mechanism of anticonvulsant action, even though their actions at an electrical level do not appear identical.

Formby (1970) found that phenobarbitone did not activate Na^+K^+ -adenosine triphosphatase and, *in vivo*, inhibited the enzyme. However, Iznicki and Dymecki (1974) obtained a contrary result.

Carbamazepine: Schauf et al. (1974) showed that carbamazepine, at a concentration of 0.25 to 1.0M^{-3} (therapeutic range 0.25 to $0.45 \times 10^{-4}\text{M}$) produced a dose-dependent decrease in Na^+ and K^+ conductance in squid giant axon.

Troxidone: Troxidone may produce a fall in intracellular Na^+ concentration in lobster nerve (Pincus et al., 1970). Brink and Freeman (1972) found that troxidone and its metabolite dimethadione both activated Na^+ , K^+ , Mg^{++} -linked adenosine triphosphatase.

Ethosuximide: While no information appears available regarding the effect of ethosuximide on Na^+ itself, Leznicki and Dymecki (1974) found that chronic administration of the drug to rats decreased brain Na^+ , K^+ -adenosine triphosphatase activity.

Clonazepam: No evidence has been traced as to the effect of this benzodiazepine on neural Na^+ concentrations.

Valproate: Similarly, data are not available regarding the effect of valproate on Na^+ levels in neurons, or on enzymes involved in Na^+ transport.

Calcium

Phenytoin: Pincus and Lee (1973) obtained evidence that phenytoin reduced Ca^{++} influx into rat neurons. It seemed possible that the drug might decrease membrane permeability to Ca^{++} . Dretchen et al. (1977), on the basis of their studies on cat soleus nerve, concluded that phenytoin blocked the cyclic nucleotide-mediated influx of Ca^{++} that occurs in association with neurotransmitter release. This Ca^{++} flux controls the slow K^+ current that can contribute to post-tetanic hyperpolarisation. Ferrendelli and Kinscherf (1977) showed that phenytoin, at levels above $20\mu\text{g}/\text{ml}$, increased Ca^{++} but decreased K^+ flux into synaptosomes which had been depolarised. However Sohn and Ferrendelli (1976) had found that phenytoin in $0.8 \times 10^{-4}\text{M}$ concentration (therapeutic range 0.4 to $1.1 \times 10^{-4}\text{M}$), inhibited Ca^{++} influx into depolarised synaptosomes.

There thus seems a consensus that phenytoin does limit Ca^{++} influx. This finding does not appear due to an effect on the enzyme Ca^{++} , Mg^{++} -adenosine triphosphatase, activity of which is not altered by phenytoin (Deupree, 1976). While this change in Ca^{++} flux might contribute to the effect of phenytoin on post-tetanic hyperpolarisation, Ca^{++} mediates other aspects of neuronal function, including neurotransmitter release. These other effects might also contribute toward the anti-convulsant action of the drug.

Phenobarbitone: At a therapeutically relevant concentration ($0.4 \times 10^{-4}\text{M}$), phenobarbitone inhibited Ca^{++} influx into depolarised rabbit neocortex synaptosomes (Sohn and Ferrendelli, 1976). It thus seems that both phenytoin and phenobarbitone may have similar effects on Ca^{++} concentrations, and that this effect may have anti-convulsant consequences.

Other anticonvulsants: Data do not seem to be available regarding the actions on Ca^{++} metabolism of the other anticonvulsants here considered.

Potassium

Phenytoin: Escueta and Appel (1971) found that phenytoin stimulated K^+ transport into synaptosomes under ionic conditions which simulate the depolarised state, but not under other ionic conditions. At environmental K^+ concentrations of $10^{-2}M$, phenytoin increased K^+ uptake by nerve terminals in an experimental epileptic focus produced by cortical freezing (Escueta et al., 1975). However this effect was not seen at the more physiological K^+ concentration of $5 \times 10^{-3}M$.

Whether these effects of phenytoin on K^+ contribute to its anticonvulsant effect is uncertain.

Other anticonvulsants: No information has been traced regarding the effects of these substances on K^+ .

Hydrogen Ions

Dimethadione, the metabolite of troxidone, caused a rise in extraneuronal hydrogen ion concentration, with intraneuronal CO_2 accumulation (Butler et al., 1966). The extent to which this change in pH contributes to the anticonvulsant effect of troxidone is uncertain.

Thus some currently available anticonvulsants alter the concentrations of small monovalent or divalent cations in neurons. These changes at times have effects which can be seen as contributing to the anticonvulsant actions of the drugs in question. However sufficient information is not available to allow the construction of any general hypothesis about the mechanism of anticonvulsant action interpreted in terms of the effects of these drugs on inorganic cations.

Effects of Anticonvulsants on Synaptic Transmitters

Anticonvulsants have been shown to alter the concentrations, release and actions of several known or putative synaptic neurotransmitters. Since a complete knowledge of the distribution of neurotransmitters in the brain is lacking, as is full knowledge of the pathways of propagation of all epileptic discharges, it is impossible to construct a complete interpretation of anticonvulsant effect in terms of altered neurotransmitter function. However in a general way one can see that if a drug alters the function of a transmitter at its various sites of occurrence, thus inhibiting synaptic transmission, this may constitute an anticonvulsant action if the synapses in question were involved in epileptic activity. Such effects would be expected to limit the propagation of epileptic seizures rather than to prevent their initiation. As has been indicated earlier, this appears to be the mode of action of many of the anticonvulsants.

Acetylcholine

Acetylcholine appears to be the synaptic transmitter in certain ascending pathways from the midbrain (Lewis and Shute, 1967; Shute and Lewis, 1967) which may to some extent correspond with the centrencephalic integrating system of Penfield and Jasper (1954). Thus acetylcholine may be a synaptic transmitter in structures relevant to generalised epilepsy. It has been shown that both phenytoin (Woodbury, 1969) and phenobarbitone (Tower and Elliott, 1953) alter acetylcholine release in neural tissue, and the drugs decrease acetylcholine biosynthesis (Mori, 1974). No information has been traced as to the effect of other anticonvulsant drugs on acetylcholine.

Serotonin (5-hydroxytryptamine)

There is some evidence that raised brain serotonin levels are associated with a degree of protection against epilepsy. Anderson et al. (1962) noted a relation between rise in brain serotonin level and protection provided by phenytoin against maximum electroshock seizures in rats. Drugs which reduce central serotonin levels also reduce protection against electrically produced convulsions in mice (Meyer and Frey, 1973). Therapeutic but not subtherapeutic plasma levels of phenytoin and phenobarbitone in man are associated with raised CSF levels of the serotonin metabolite 5-hydroxyindoleacetic acid (Chadwick et al., 1975). This rise in metabolite level is probably due to increased serotonin release, and subsequent degradation.

Phenytoin raises brain serotonin levels (Bonnycastle et al., 1956; Chase et al., 1969), probably by increasing serotonin synthesis (Green and Graham Smith, 1975). Phenobarbitone also raises brain serotonin levels (Bonnycastle et al., 1956), as does clonazepam (Fennessy and Lee, 1972; Jenner et al., 1975). Dominic et al. (1975) found that diazepam decreased serotonin synthesis in the telencephalon and diencephalon of mice.

Activity of monoamine oxidase, the enzyme responsible for serotonin degradation, is inhibited by phenytoin (Azzaro et al., 1973), though Leznicki and Dymecki (1974) failed to obtain evidence of inhibition of the enzyme at only slightly suprathreshold concentrations of the drug. The enzyme in rat brain is not inhibited by phenobarbitone or ethosuximide (Leznicki and Dymecki, 1974).

Noradrenaline

There is rather less evidence that noradrenaline plays a role in anticonvulsant action, though Meyer and Frey (1973) observed that drugs which reduced central noradrenaline levels tend to reduce the protective effect of phenobarbitone against electroshock seizures in mice. Noradrenaline seems required for carbonic anhydrase inhibitors to exert an anticonvulsant action (Gray and Rauh, 1967).

At therapeutic concentrations (10^{-4}M to 10^{-5}M) phenytoin increases noradrenaline uptake by rat cerebral cortex slices (Azzaro et al., 1973), and decreases the oxidative metabolism of this catecholamine. However Weinberger et al. (1976) found that 10^{-4}M to 10^{-5}M phenytoin inhibited noradrenaline uptake into rat brain synaptosomes. These authors also found that phenobarbitone (10^{-3}M to 10^{-4}M) inhibited noradrenaline uptake in this experimental situation. Lidbrink and Farnebo (1973) showed that a wide range of phenobarbitone concentrations did not alter the *in vitro* uptake, retention or release of noradrenaline by rat cerebral cortex. Clonazepam and diazepam raise brain noradrenaline levels (Fennessy and Lee, 1972) and in the rat diazepam reduces noradrenaline turnover in the thalamus, mid-brain, cerebral cortex and cerebellum (Taylor and Laverty, 1969).

Of the enzymes involved in noradrenaline metabolism, monoamine oxidase has already been considered. Brain aldehyde dehydrogenase is inhibited by phenytoin at slightly supratherapeutic concentrations ($K_i = 1.7 \times 10^{-4}\text{M}$), by phenobarbitone at therapeutic concentrations ($K_i = 1.2 \times 10^{-4}\text{M}$), by dimethadione ($K_i = 4.7 \times 10^{-4}\text{M}$) and by ethosuximide at therapeutic levels ($K_i = 5.4 \times 10^{-4}\text{M}$), according to the report of Deitrich and Erwin (1975). If the further metabolism of aldehyde biotransformation products of catecholamines is inhibited (due to inhibition of aldehyde dehydrogenase), it is conceivable that brain catecholamine levels may change, with consequences for the control of epilepsy.

Dopamine

There are intimations that certain anticonvulsants alter brain dopamine levels. The fact that therapeutic but not subtherapeutic plasma concentrations of phenytoin and phenobarbitone are associated with increased CSF homovanillic acid levels in human epileptics, raises the possibility that brain dopamine activity may be related to anticonvulsant action (Chadwick et al., 1975).

Phenytoin is a dopamine antagonist (Mendel et al., 1975), and blocks dopamine uptake into the striatum (Azzaro et al., 1973). Clonazepam, but not diazepam, raises brain dopamine levels (Fennessy and Lee, 1972). Fuxe et al. (1975) showed that diazepam decreases dopamine turnover in the olfactory tubercle, nucleus accumbens and neostriatum.

γ -Aminobutyric acid (GABA)

GABA is an inhibitory synaptic transmitter. GABA deficiency, due to dietary pyridoxine deficiency in infants, is a rare cause of hypsarrhythmia. (Pyridoxal phosphate is the coenzyme for glutamic acid decarboxylase, which catalyses the formation of GABA from glutamate.) Drugs which increase brain GABA levels might be expected to have an anticonvulsant effect.

Phenytoin raises brain GABA, and also glutamine levels (Vernadakis and Woodbury, 1960; Saad et al., 1972; Mori, 1974), and reduces brain glutamate levels (Mori, 1974). Phenytoin ($2 \times 10^{-4}\text{M}$) increases the release of GABA from rat cerebral cortical slices (Tappaz and Pacheco, 1973) but also increases uptake of this aminoacid, and that of glutamate, in rat brain synaptosomes (Weinberger et al., 1976). Since phenytoin does not inhibit mouse brain GABA transaminase, and inhibits succinate semialdehyde dehydrogenase only at 20 or more times therapeutic concentrations, it seems likely that phenytoin raises brain GABA level by increasing the synthesis of this aminoacid.

Phenobarbitone raises GABA levels in mouse brain (Saad et al., 1972). At concentrations of 10^{-3}M to 10^{-4}M (therapeutic range 0.4 to $1.3 \times 10^{-4}\text{M}$) phenobarbitone increases GABA uptake into rat brain synaptosomes (Weinberger et al., 1976). At a supratherapeutic concentration (10^{-3}M) only, phenobarbitone inhibits mouse brain GABA transaminase and succinic semialdehyde dehydrogenase (Sawaya et al., 1975). Ethosuximide, at a concentration of $5 \times 10^{-4}\text{M}$ (therapeutic range 2.1 to $8.5 \times 10^{-4}\text{M}$) increases GABA release from rat cerebral cortical slices (Tappaz and Pacheco, 1973). Concentrations of ethosuximide in the therapeutic range slightly inhibit mouse brain GABA transaminase, but do not affect succinate dehydrogenase (Sawaya et al., 1975). The above authors also found that clonazepam had no effect on these two enzymes which catalyse GABA degradation, though Ostrovskaya et al.

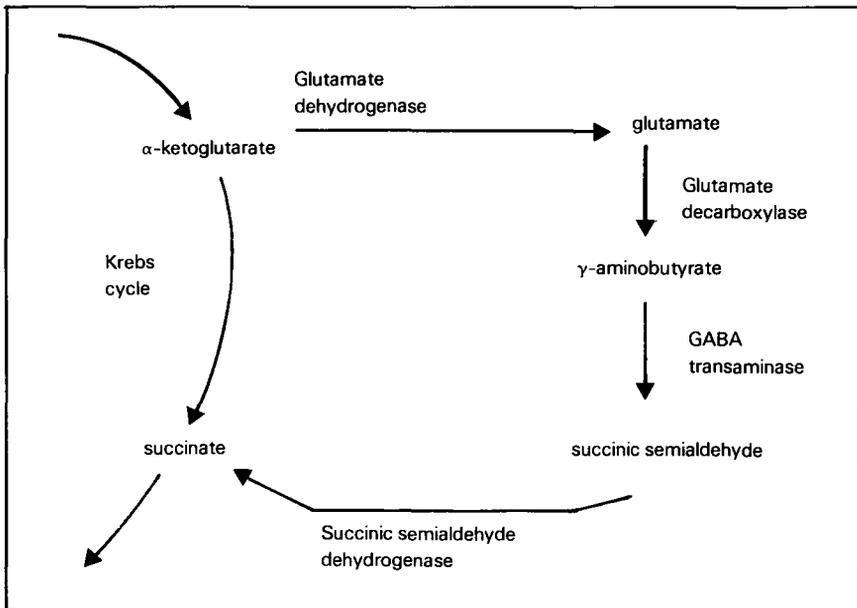


Fig. 1. The GABA shunt.

(1975) found that diazepam inhibited mitochondrial GABA transaminase, and increased brain GABA levels.

It seems widely accepted that valproate acts by raising brain GABA levels. Raised levels of the transmitter have been found by Godin et al., 1969; Simler et al., 1973 and Elazar and Gottesfeld (1975). Kupferberg et al. (1975) showed that the drug raised cerebellar GABA levels and that the time course of the change in these levels paralleled the time-course of the anticonvulsant activity of the drug. However it should be noted that Anlezark et al. (1976) found that valproate would protect against audiogenic seizures in mice without raising brain GABA levels. Godin et al. (1969) and Simler et al. (1973) found that valproate inhibited GABA transaminase. Sawaya et al. (1975) confirmed this finding but noted that, at the therapeutic concentration of 10^{-3} M, the drug was an even more efficient inhibitor of succinic semialdehyde dehydrogenase activity. Godin et al. (1969) found that valproate was a relatively weak inhibitor of glutamate dehydrogenase.

Thus valproate appears to raise brain GABA levels by inhibiting the catabolism of the transmitter, while the other anticonvulsants which raise brain GABA levels probably do so by increasing the formation of GABA.

It would appear that the commonly used anticonvulsants alter brain concentrations of several synaptic transmitters, notably serotonin and GABA. Such changes may contribute to the anticonvulsant effects of these drugs.

Effects of Anticonvulsants on Folates

A number of folate derivatives which form in animals may produce cerebral excitation. Obbens (1973) found that folate administration increased the chances of seizure activity occurring from an experimental epileptic focus produced by cobalt. Hommes et al. (1973) showed that, if large intravenous doses of folate are injected into rats, sufficient folate crosses the blood-brain barrier to cause convulsions. In the rat tetrahydrofolate, dihydrofolate, 5-formyl-tetrahydrofolate and 5-methyl-tetrahydrofolate have all proved to be convulsants (Obbens and Hommes, 1973). Davies and Watkins (1973) found that both folate and folinate administration increased the firing rate of single cortical neurons of cats. In this situation the folates opposed the inhibitory effects of GABA. However, the folate concentrations used were likely to be higher than those which would occur therapeutically.

If folates are cerebral excitants, reduced folate concentrations should have an anticonvulsant effect. In his review of the subject, Reynolds (1976) stated that between 27% and 91% of epileptic patients treated with phenytoin, phenobarbitone or primidone develop reduced serum, red blood cell or CSF folate. There appears to be a special mechanism which determines the relation between CSF and blood folate. Large oral folate doses, given for as long as 3 months, may not correct deficient CSF folate levels. This may explain why oral folate therapy in folate-deficient epileptics may not alter brain function in the presence of continued anticonvulsant intake. Thus

Grant and Stores (1970), Jensen and Olesen (1970), Ralston et al. (1970) and Norris and Pratt (1971) all found that oral folate therapy did not alter behaviour, personality or control of epilepsy in folate-deficient epileptics.

As well as phenytoin, phenobarbitone and primidone (Reynolds, 1976), carbamazepine therapy causes a fall in serum folate levels (Reizenstein and Lund, 1973). There do not appear to be reports of the effects of the other anticonvulsants on folate levels in man.

Mechanisms by which anticonvulsants reduce folate levels may include one or more of the following:

- 1) Interactions between the drug and folate co-enzymes
- 2) Decreased absorption of dietary folate
- 3) Increased demand for folate caused directly by the drug
- 4) Induction of liver enzymes by the drug, creating an increased demand for folate which is a co-enzyme for the induced enzymes (Maxwell et al., 1972).

Some authors have suggested that phenytoin interferes with the absorption of dietary folate (Hoffbrand and Necheles, 1968; Rosenberg et al., 1968), but there is evidence to the contrary (Baugh and Krumdieck, 1969; Fehling et al., 1973). The demand for folate might be increased if its biotransformation (to other biologically active derivatives) were inhibited. Arakawa et al. (1973a) found that phenytoin decreased hepatic histidase activity in rats. A similar inhibition may occur in man. Arakawa et al., (1973b) found that phenytoin treated epileptics excreted increased amounts of formimino-glutamic acid (FIGLU) in urine after an oral histidine load. However Narisawa et al. (1972) showed that phenytoin (50µg/ml) did not inhibit the following rat liver enzymes involved in folate metabolism: histidase, urocanase, formyliminotransferase, N⁵-¹⁰-methylenetetrahydrofolate reductase, formyltetrahydrofolate synthetase, serine hydroxymethylase and glycine cleavage enzyme. Lacy and Smith (1973) found that phenobarbitone inhibited folate reductase, the enzyme catalysing the conversion of folate to folinate.

The mechanisms whereby anticonvulsant intake reduces folate levels remain uncertain. While relative folate deficiency may tend to have an anticonvulsant effect, it seems unlikely that this can be the sole explanation of the action of anticonvulsant drugs. These drugs protect against epilepsy before folate deficiency due to the drugs has time to develop.

Effects of Anticonvulsants on Macromolecules

Both phenytoin and phenobarbitone have been shown to alter the biological synthesis of macromolecules. The relation of these effects to anticonvulsant action is obscure but it seems conceivable that altered protein synthesis might change the properties of cell membranes toward the passage of inorganic cations (Shanes, 1958). If so, this could contribute to anticonvulsant action.

Table IV. Absorption parameters of anticonvulsants

Drug	Mode of administration	Absorption rate	Absorption extent	T _{max} (hours)
Phenytoin	Oral	Slow	Reasonably complete	2-8
	Intramuscular	Very slow	Poor	Variable
Phenobarbitone	Oral	Fairly rapid	Complete	6-18
	Intramuscular	No faster than oral	?	2-3
Methylphenobarbitone	Oral	Rapid	No firm data	< 7
Primidone	Oral	Fairly rapid	?	3
Carbamazepine	Oral	Fairly slow	Marginally complete	3-24
Troxidone	Oral	Rapid	?	0.5
Ethosuximide	Oral	Fairly rapid	Complete	3-7
Clonazepam	Oral	Fairly rapid	Complete	2-4
Diazepam	Oral	Rapid	Complete	1
	Intramuscular	Slower than oral	Complete	1-2
Valproate	Oral	Rapid	Probably complete	1
Sulthiame	Oral	?	?	?

Phenytoin increases the incorporation of orotic acid into ribosenucleic acid (Kemp and Woodbury, 1971). At concentrations of $2-10 \times 10^{-4}M$ it decreases ^{14}C -leucine incorporation into proteins in the brains of immature rats. In plasma concentrations of $10\mu g/ml$ and $28\mu g/ml$ respectively, phenytoin and phenobarbitone decrease the incorporation of leucine into rat cerebral cortical proteins (Jones and Woodbury, 1976). Izquierdo and Nasello (1973) found that phenytoin blocked the increase in hippocampal RNA formation which is produced by afferent stimulation in rats. De Lorenzo et al. (1977) showed that therapeutic concentrations of phenytoin decreased net phosphorylation of two rat brain synaptosomal proteins of MW 60,000 to 63,000 and 49,000 to 52,000. This effect did not depend on adenosine triphosphate concentrations. De Lorenzo and Freedman (1977) raised the hypothesis

that the decreased phosphorylation might alter neurotransmitter release into the synaptic cleft.

Carnay and Grundfest (1974) suggested that phenytoin might exert its anticonvulsant effect by altering the physical properties of cell membranes. Thus the hydrophobic configuration of macromolecules in the resting cell membrane of the frog neuromuscular junction appears to be stabilised by phenytoin, yet the macromolecules can still assume the hydrophilic configuration of the excited membrane.

The known biochemical effects of anticonvulsant drugs are diverse. Some of the findings are difficult to interpret, and some may not relate to the protective action of the drugs against epilepsy. However, it seems likely that the effects of the drugs on the passage of inorganic cations through cell membranes and their effects on synaptic transmitter molecules, notably serotonin and GABA, do contribute to their anticonvulsant actions. Their effects on folate may also add to their ability to protect against seizures.

Anticonvulsant Pharmacokinetics

While the available information about anticonvulsant pharmacodynamics is scattered throughout the literature, the data about anticonvulsant pharmacokinetics have been collected in a number of readily accessible recent reviews and monographs (e.g. Woodbury et al., 1972; Eadie and Tyrer, 1974; Richens, 1976; Hvidberg and

Table V. Distribution parameters of anticonvulsants

Drug	V_D (litres kg^{-1})	Percentage bound to plasma protein
Phenytoin	0.6	90-93
Phenobarbitone	0.7	50
Methylphenobarbitone	1.9	?
Primidone	0.6	0
Carbamazepine	1.0	70-75
Troxidone	Body water	0
Ethosuximide	0.7	0
Clonazepam	2.6	82
Diazepam	1.75	97
Valproate	0.2	84-90
Sulthiame	?	?

Table VI. Elimination parameters of anticonvulsants (approximate values)

Drug	Percent excreted unchanged	Half-life (hours)	Clearance (litres kg ⁻¹ hour ⁻¹)
Phenytoin	5	13-31 ¹	0.02
Phenobarbitone	20	75-100	0.004
Methylphenobarbitone	< 5	32	0.05
Primidone	?	6-10	0.06
Carbamazepine	< 2	30-50	0.02
Troxidone			?
Ethosuximide	17-38	30-60	0.015
Clonazepam	2	19-60	0.05
Diazepam	< 1	20-40	0.03
Valproate	7	9-10	0.02
Sulthiame	32	?	?

1 Strictly speaking, one should not quote a half-life for this drug, the elimination of which follows Michaelis-Menten rather than first order kinetics.

Dam, 1976). Therefore it is proposed to provide little more than a very brief outline in tabular form of the pharmacokinetic parameters of these drugs.

Absorption

Some of the anticonvulsants, particularly phenytoin and carbamazepine, are poorly soluble in water and have only marginally complete absorptions. The remainder appear better absorbed. Values for absorption parameters, and for T_{max} (the time to achieve peak plasma concentrations) which depends on elimination rate as well as absorption rate, are given in table IV.

Distribution

Values for the V_D (apparent volume of distribution) of some anticonvulsants (e.g. clonazepam) are sufficiently high to suggest that the drugs are substantially

bound to tissues. Other drugs (e.g. phenytoin, phenobarbitone) appear to be distributed throughout body water, while valproate has a low enough V_D to suggest that the drug is restricted to extracellular fluid. Some anticonvulsants (e.g. diazepam) are very highly bound to plasma protein; others are less highly bound (e.g. phenobarbitone) and some (e.g. ethosuximide) are unbound. Values of distribution parameters are given in table V.

Elimination

All the anticonvulsants in common use are eliminated chiefly by biotransformation, only a minority of the dose of any of the drugs being excreted unchanged in urine. Biotransformation appears to occur mostly by way of oxidation reactions of various types. While most of the biotransformation products possess less anticonvulsant activity than the parent drugs, phenobarbitone forms from methylphenobarbitone and from primidone, and dimethadione from troxidone, while the 10,11-epoxide of carbamazepine is a known anticonvulsant.

Generally the anticonvulsants considered here have elimination half-times of the order of 24 hours or more, so that in the pharmacokinetic steady-state it is rarely necessary to give the drugs more than once daily to keep plasma drug level fluctuations within acceptable limits. However valproate (half-life around 8 hours) is more rapidly eliminated.

Values for the elimination phase pharmacokinetic parameters of the anticonvulsants are set out in table VI.

Conclusion

In recent years knowledge of anticonvulsant pharmacokinetics has accrued rapidly, and it is now comparatively easy to put together a reasonably comprehensive account of what happens to these drugs in man. However, we have far less extensive and definite knowledge of how these drugs produce their biological effects, despite the rather considerable number of scattered and at times almost disparate observations that can be found in the literature. Now that there are relatively few major deficiencies in our knowledge of anticonvulsant pharmacokinetics, perhaps there will be an increasing interest in the pharmacodynamics of these drugs.

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A Case of Spinal Cysticercosis

*I.T. Lorentz**

Cysticercosis infestation is extremely rare in Australia. A search of the medical records of the Royal Prince Alfred Hospital, Sydney, for the years 1950 to 1977 revealed 3 cases only. Among 9,000 patients seen in consultation for various neurological complaints, 2 individuals were diagnosed as suffering from the condition. Of this total of 5 patients, 3 presented with fits, and 1 had a cyst in the breast. The fifth patient, the present case, suffered from a paraparesis (table I). In 3 patients, the diagnosis was made on finding typical calcification in the muscles; 1 of these patients also had intracranial calcification. Cases 4 and 5 were diagnosed at surgery.

Spinal cysticercosis has not been previously reported in Australia.

Case Report

A 50-year-old Czechoslovakian woman was first seen on the 6th December 1977. Apart from two short trips to Hong Kong and California, she had lived in Sydney, Australia, for the past 30 years. She was a practising Jewess, who never ate pork to the best of her knowledge. She complained of difficulty in walking, ataxia and a cold sensation in both feet for 12 months. She gave a history of numbness in both feet and of some urinary hesitancy for the past 6 months. There had been some upper lumbar backache a few years previously, treated with physiotherapy, but backaches were not a recent feature. For some years she had had a tendency to periodic depression. There was a past history of pleurisy when she was aged 18, probably of tuberculous origin. She had no headaches, visual disturbances, blackouts or symptoms relevant to the upper limbs.

On examination she was a nervous, depressed lady. There was no abnormality in the cranial nerves or in the upper limbs. There was no back tenderness. In the lower limbs there was a moderate degree of

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Table 1. Details of 5 patients with cysticercosis

Patient	Sex	Age	Presentation	Calcification	
				muscles	intracerebral
1	M	60	Fits	+	0
2	M	26	Fits	+	+
3	F	41	Fits	+	0
4	F	22	Breast cyst	0	0
5	F	50	Paraparesis	0	0

spasticity with increased deep reflexes and an extensor plantar response on the right. Both lower limbs were weak. There was diminished sensation to pain and temperature below the first lumbar segment on the right and below the second lumbar segment on the left. Vibration and position sense were diminished at both ankles.

Examination of the blood revealed 14g % haemoglobin, 7,000 leucocytes per mm³, with a normal differential count. The ESR was 7mm/h. A full biochemical screening test showed no abnormality. A chest radiograph and plain radiographs of the thoracic and lumbar spine revealed no abnormality. No tapeworms, ova or cysts were found in the faeces.

Myelography was carried out on two occasions prior to operation. The first one was performed at the Royal Prince Alfred Hospital, and the second at St. Vincent's Hospital, Sydney. The myelograms showed an intradural filling defect at T11 and evidence of arachnoiditis. (fig. 1a-c).

A laminectomy was carried out at St. Vincent's Hospital on the 29th Dec 1977 (Mr K. Bleasel). The findings were as follows: the exploration was first carried out at the level of T9 and 10, and there the spinal cord was pressed back against the dura, but the cord was pulsating and the catheter could be passed upwards freely; however, when passed downwards, an arrest occurred at T11. Further laminectomy was then performed at T11 and here the spinal cord was seen to be involved in an adhesive process, the cord being adherent to the posterior dura, especially on the right side. Incision into the extradural space revealed a cyst. This was quite thinwalled and filled with a milky yellow fluid. The whole cyst slid out of its position in the extradural space leaving a smoothwalled cavity. Macroscopically the cyst was ovoid, measuring 35mm × 15mm, thinwalled and the contents were greyish yellow and semisolid. A few separate fibrous tissue fragments were removed with the cyst. Microscopically the cyst showed a striking maze-like folding of its wall (fig. 2). This appearance is so characteristic as to be accepted as diagnostic of *cysticercus cellulosae*, even when the scolex is not demonstrable. Calcium deposits in the cyst were moderately abundant throughout and quite heavy at some sites (fig. 3). The fibrous tissue fragments (fig. 4) consisted of a zone of acute inflammatory exudate made up of fibrin and a dense infiltrate of neutrophil polymorphs with very occasional eosinophils, a zone of plasma cells and lymphocytes and, along one edge, dense collagenised fibrous tissue. The appearances were consistent with a host-tissue inflammatory reaction to a parasitic cyst.

Discussion

Cysticercosis is due to infestation by the larval stage of the pork tapeworm *Taenia solium*. The adult worm may be present in the small intestine of man, pig or

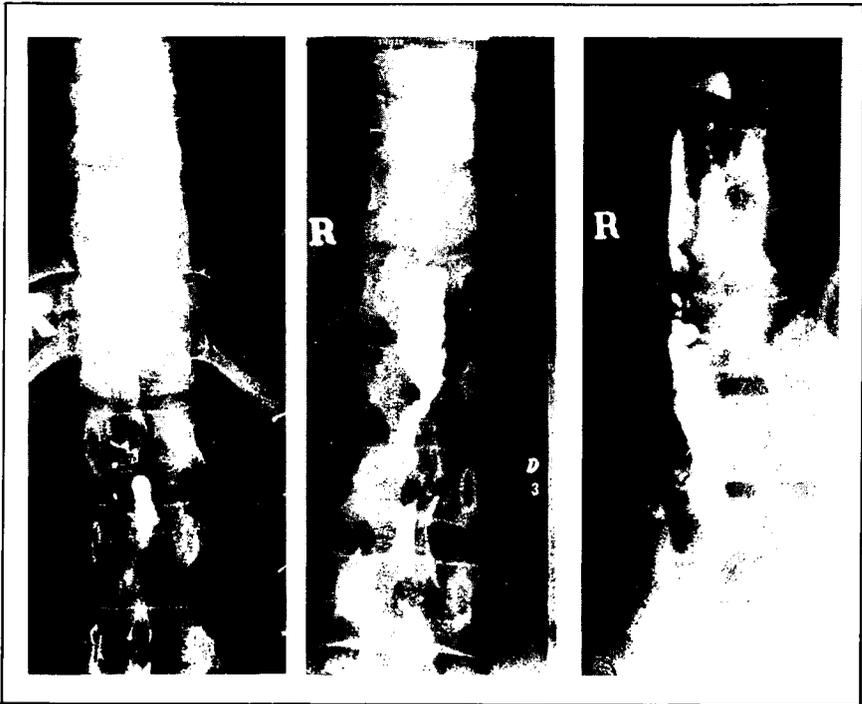


Fig. 1. a) Cisternal myelogram showing intradural filling defect at T11, indicating the upper border of the cyst. b) and c) The same area showing filling defect at T11 and evidence of arachnoiditis.

wild boar, and is usually asymptomatic. The hatched eggs are about 35 microns thick and contain an embryonic oncosphere with 6 hooklets. Man may acquire the infection by eating undercooked 'measly' pork, which contains cysticerci. Infection may also be acquired by eating food contaminated by a carrier. Auto-infection may occur by transferring the eggs from anus to mouth. It is thought unlikely that the eggs can travel in an anti-peristaltic fashion from the small intestine to the upper intestinal tract. The larvae or cysticerci measure 5 to 10mm in diameter. As they die a tissue reaction is provoked and calcification may occur.

Cysticercosis is common in Central and South America, on the Indian Sub-continent, in Asia, in South Africa and in Central and Eastern Europe. In Mexico 2 to 4% of all autopsies showed a larval stage (Faust et al., 1970). In Mexico City, 12% of 1,000 computerised brain scans performed for various causes, showed evidence of cysticercosis (Lombardo and Cifuentes, 1977). Cysticercosis is said to be the most common cause of epilepsy in the Durban African population (Powell et al., 1966 b). The condition is extremely rare in Australia. Migration and increasing international travel from endemic areas should make one aware of the disease. The five cases



2



3



known to me have come from the following countries: one each from Poland, Yugoslavia, Greece, Czechoslovakia and Korea.

The incubation period is usually less than 10 years, and at least 3 patients in the present series were diagnosed within 3 years of their arrival in this country. The subject of the present report arrived in Australia about 30 years ago. It is postulated that she acquired the infection in her country of origin, Czechoslovakia, although she may have been infected on a short trip she took to Hong Kong.

The commonest presentation of cysticercosis is with epilepsy. Other neurological manifestations may include disordered behaviour, intermittent obstructive hydrocephalus, ataxia and failing vision (Bickerstaff, 1955). Cysticerci can be found in the tongue, muscle, brain, eye, heart, liver, peritoneum and the lungs, but they very rarely reach the spinal cord. Spinal cysticercosis has been reported in 1% or less of all cases and is therefore rarely considered in the differential diagnosis of spinal lesions.

Dixon and Lipscomb (1961) collected 450 cases of cysticercosis from the British Army in India. Only 1 of their cases had spinal cord involvement, presenting with a progressive tetraparesis. Cabieses et al. (1959) described 3 patients, 2 with an intramedullary and 1 with an extramedullary spinal cord lesion. In 2 of their patients the condition appeared to be confined to the spinal cord whilst in the third, convulsions and subcutaneous nodules were also apparent. The symptoms were present from 3 to 16 months prior to diagnosis. Singh et al. (1966) reported the case of a 40-year-old strict vegetarian Sikh, with paraparesis, sensory loss and convulsions. He had calcification in the spinal and pectoral muscles as well. Powell et al. (1966b) mentioned 3 African patients with paraparesis and one with tetraparesis in a large series of patients investigated for epilepsy. All of these patients had a positive haemagglutination test for cysticercosis. One of the patients was explored and cysticerci were removed at laminectomy. In another report from South Africa, Cosnett (1965) reported 41 cases of unexplained spastic myelopathy among Bantu patients. It is possible that a small proportion of these cases was due to cysticercosis.

Spinal cysticercosis can be diagnosed with certainty only at surgery. The finding of subcutaneous nodules and calcification in the muscles however, can be suggestive. Plain radiographs of the vertebral column are usually normal. Stool examinations and eosinophil counts are unhelpful as a rule. On myelography single or multiple filling defects may be found. The contrast material may fragment and suggest arachnoiditis (Dorfsman 1966). The differential diagnosis includes metastases, neurofibromatosis, meningioma and arachnoiditis. The cysticercus haemagglutination

Fig. 2. Cyst, showing characteristic folding of its walls (haematoxylin and eosin $\times 25$).

Fig. 3. Calcium deposits stained black (Von Kossa $\times 100$).

Fig. 4. Host tissue inflammatory reaction encapsulating cyst (haematoxylin and eosin $\times 25$).

test is said to be positive in 85 % of proven cases of cysticercosis. In appropriate cases it may prove to be a useful diagnostic tool (Powell et al., 1966a). This test was not carried out on any of the patients mentioned in the present paper.

The treatment of cysticercosis is by excision when possible. Specific chemotherapy for the larval stage does not exist. Steroids may be useful where oedema accompanies parasitic infiltration, e.g. in the muscles (Sawnkey et al., 1976). To my knowledge steroids have not been tried in spinal cases. Anticonvulsant medication should be given where epilepsy is a problem. The prognosis in cases involving the central nervous system and the spine is uncertain, but cure often follows surgical removal.

Better hygiene and more stringent public health measures will no doubt diminish the incidence of this disease in the underdeveloped world. However increasing international travel is likely to lead to patients presenting in countries where in the past this disease has been very rare.

In Australia the diagnosis of cysticercosis should be considered in patients who have lived in endemic areas such as Central and South America, Asia, Africa, India and certain parts of Southern, Eastern and Central Europe. In such patients radiographs of the thighs and possibly a haemagglutination test for cysticercosis may be useful. Spinal cysticercosis in non-endemic areas will probably remain rare and require myelography and surgery for diagnosis.

Acknowledgements

Thanks are due to Dr John Hallinan and Dr Gerald Lim for performing the myelograms, to Mr Kevin Bleasel for the laminectomy, and to Dr Mary Ralston for the pathological diagnosis and helpful discussion.

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Parasitic Diseases of the Nervous System in Thailand

*A. Vejjajiva**

Among a number of human parasites that are prevalent in Thailand only 3 commonly invade the nervous system. *Gnathostoma spinigerum* may be considered to be a Thai parasite since the study of its lifecycle and the clinical syndromes it produces have been reported mostly from Thailand. The second parasite, *Angiostrongylus cantonensis*, is better known in the South Asian region and the tropics. *Cysticercus cellulosae*, caused by *Taenia solium*, has a worldwide distribution.

Gnathostomiasis

The tissue nematode, *Gnathostoma spinigerum*, was first isolated from the tumour of a tiger's stomach at the London Zoo by Sir Richard Owen in 1836. In 1889 Levinsen removed this species of worm from the breast abscess of a girl from Bangkok. The parasite was then known as *Gnathostoma siamense*. Its lifecycle was later worked out by two Thai pathologists (Prommas and Daengsvang, 1934). By 1945 several patients with gnathostomiasis had been reported, including isolated cases from Malaysia, the Philippines, India, Japan and Australia. In the last country, in 1929, Heydon reported a North Queensland patient with a creeping skin eruption from presumed *Gnathostoma spinigerum* infestation (Chitanondh, 1963).

The lifecycle of the parasite is as follows: the adult worms inhabit the stomach wall of cats, dogs and tigers: the mature female worms produce fertilised ova which

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are excreted with the host's faeces and are flushed by rain into ponds, canals and rivers where they hatch into the first stage larvae which are then ingested by small crustaceans of genus *Cyclops*, the first intermediate host. There the larvae develop into the second stage. Infected *Cyclops* are eaten by fish, frogs and eels and the larvae penetrate the intestines of these second intermediate hosts to become encysted in their flesh or viscera and develop into third stage larvae which are infective. Thai people of all income groups are very fond of eating undercooked or even raw fresh water fish. Thus it is not surprising that infestation by *Gnathostoma* is highly prevalent in Thailand. The third stage larvae which may be ingested by man migrate and soon transform into immature worms, each of about 1 cm in length.

Most of the clinical manifestations of human gnathostomiasis are due to the high motility of the immature worms. These commonly cause painless migratory subcutaneous swellings which usually last for a few days and subside spontaneously. The swellings may recur several times a year and the disease may last several years. Migration of the worms into the eye, the lung and pleura, the intestine, the urinary tract and the uterus has been reported. Involvement of the central nervous system had been suspected for some time but was never proven until 1967, when an immature worm was identified in the spinal cord of a fatal case of ascending myelitis (Rosen and Chitanondh, 1967). Further clinicopathological and epidemiological studies of this human parasitic infestation have led to the recognition of a neurological entity (Punyagupta et al., 1968).

The presenting symptom is usually severe, sharp, agonising pain in the trunk or a limb, from irritation of a nerve root. This is often followed within a few days by the sudden onset of paraplegia and urinary retention. In some patients, the disease extends to involve the brain stem resulting in cranial nerve palsies, respiratory failure and impairment of consciousness. The mortality rate is high in these cases. Less frequently, the patient presents with classical features of primary subarachnoid haemorrhage. The presence of moderate to marked eosinophilia, both in the peripheral blood and in the CSF, a history of eating undercooked fresh water fish, and of migratory subcutaneous swellings if present, are helpful in differentiating the disease from ruptured intracranial aneurysm or arterio-venous malformation.

In a recent review of 24 patients with nervous system gnathostomiasis (Boongird et al., 1977) it was found that the commonest clinical syndrome was radiculomyelitis while the purely encephalitic form was the least common.

Case Reports

Case 1

A 64-year-old farmer was admitted to Ramathibodi Hospital with a 3-day history of severe, sharp, burning pain in the right foot which was followed by paralysis of both legs and urinary retention. The CSF contained numerous red cells, 660 white cells/mm³, 75% being eosinophils. 2 weeks after admis-

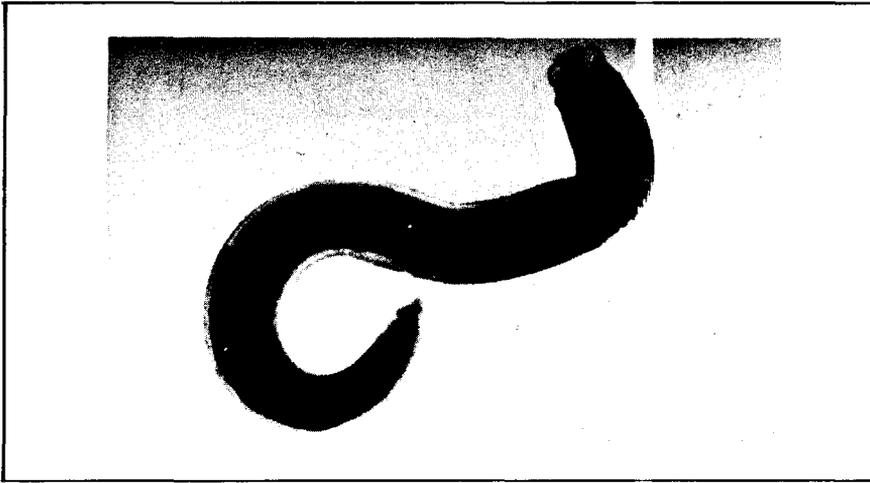


Fig. 1. A male *Gnathostoma spinigerum* removed via small skin incision. (The worm was 8mm long and 1mm in diameter.)

sion, the patient noticed a red swelling over the right buttock with a superficial dark spot in the middle. A male worm (fig. 1) was removed from the swelling via a small skin incision. The patient made a fair recovery from the paraplegia a few weeks later.

Case 2

A 58-year-old man had sudden severe pain in the arm followed by quadriplegia. He had respiratory failure soon after admission. On the 3rd day while on a respirator he had a high fever and became comatose. He died on the 6th day and at autopsy 6 hours later a living *Gnathostoma* was seen moving near the medulla. Multiple haemorrhagic tracks were found in the spinal cord and brain stem (Boongird et al., 1977).

Angiostrongyliasis

The third stage larvae of *Angiostrongylus cantonensis*, the lungworm of rats, were first recovered from the spinal fluid of a Chinese patient who died in Taiwan (Nomura and Lin, 1945). The disease was not well recognised until late 1950's and early 1960's when epidemic outbreaks of eosinophilic meningitis occurred in the Pacific Islands, Vietnam and Thailand. It is now known that man may become host to this parasite by eating raw or undercooked snails or slugs. In Thailand, a large number of cases occur during the rainy season when *Pila* snails breed and are readily available. Most patients, usually traditional Thai of the lower socio-economic groups, give a history of having eaten raw or undercooked *Pila* snails within a month of the onset of their symptoms. It is not uncommon to see several affected patients, a week

or two after they have enjoyed drinking together and having a common meal consisting of raw Pila snails, which they consider to be a great delicacy. Unlike gnathostomiasis, the disease takes a benign and self limiting course, the mortality rate being less than 1%. Those affected usually present with headache. Fever is much less common and, when present, rarely exceeds 38°C and usually last only a few days. Headache, though often present in the occipital area, may sometimes be localised to the retrobulbar and temporal regions. Stabbing pains in the head and paraesthesiae of the scalp are occasionally present. Apart from neck stiffness and a positive Kernig's sign, which are by no means found in all cases, there are no abnormal neurological signs in the majority of patients with angiostrongyliasis. However, blurred vision with swelling of the optic disc and facial palsy are sometimes encountered. Recovery of visual function is usually complete but a case has been reported where the worm had to be removed from the anterior chamber of eye and severe impairment of vision resulted (Prommindaroj et al., 1962). Apart from the clinical features, angiostrongyliasis may be distinguished from gnathostomiasis by examination of the CSF. In angiostrongyliasis, the CSF has a ground-glass appearance or is better described by local physicians as 'like coconut juice'. Eosinophilic pleocytosis is constant, forming up to 70% of total cells which usually range from 500 to 5,000/mm³. In one case report, several male and female living worms, each measuring about 1 cm in length, were recovered from the CSF (Bunnag et al., 1969). Treatment is symptomatic. Repeated lumbar puncture often is necessary for the dramatic relief of headache and most patients recover completely within a month. Long term follow up on those patients has not yet been done. It would be interesting to find out if the parasite is a cause of late-onset epilepsy.

Cysticercosis

Among the various clinical neurological manifestations of cysticercosis in Thailand, epilepsy is perhaps the most common. In our series of almost 100 consecutive Thai patients with late-onset epilepsy studied for a period of 3 years, cysticercosis was the commonest of the known causes, being responsible for about 25% of the epileptic patients. Diagnosis was based on biopsy of palpable subcutaneous nodules, the presence of calcified cysts in radiographs of the limbs or chest, positive complement fixation test on CSF examination and, recently, on evidence from computerised tomography. Less commonly patients presented with symptoms and signs of increased intracranial pressure. These patients could be divided into various types. Those with cysts in the third ventricle causing intermittent obstructive hydrocephalus were usually indistinguishable from patients with colloid cysts or other intraventricular tumours, and the diagnosis of cysticercosis was usually made at operation. Equally common were patients with communicating hydrocephalus who presented with chronic headache, dementia, gait disturbance and, occasionally, epileptic convulsions.

In these cases, we have recently found computerised tomography a most helpful diagnostic procedure.

The diagnostic value of CSF examination should also be mentioned. Surprisingly, eosinophils are not often present and the total cell count is usually not more than 50 to 100/mm³, the majority being lymphocytes. CSF glucose may be reduced, but the protein is not usually markedly increased unless there is spinal subarachnoid block. However, the gamma globulin is nearly always disproportionately increased and the complement fixation test utilising cysticercus antigen yields positive results in a high proportion of patients, particularly in those with acute symptoms.

Case Reports

Case 1

A 76-year-old male presented with a 3-day history of difficulty in walking, urinary incontinence and progressive mental deterioration. 3 years previously the patient had had an epileptic seizure and had been seen by a physician. No abnormal clinical signs were noted and the patient was treated with phenobarbitone. Computerised tomography showed markedly dilated lateral ventricles and a few high density nodules which were believed to be calcified cysticercus cysts in the cerebral parenchyma. Ventriculo-atrial shunt improved his neurological condition and computerised tomography repeated a few weeks later showed ventricles which were smaller in size.

Case 2

A 28-year-old woman had headache and papilloedema for 2 years. She was first treated at a hospital in Bangkok with antituberculous drugs and corticosteroids after bilateral carotid angiograms and an air study were found to be normal. A theco-peritoneal shunt performed at the Ramathibodi Hospital gave some relief of symptoms for a few months before she suddenly collapsed at home and was brought to hospital in coma. She died a few hours after admission. Autopsy revealed cysticercosis affecting both cerebral hemispheres.

Case 3

A 38-year-old man presented with backache and leg weakness. Cisternal myelogram showed narrowing of the contrast medium with two round movable filling defects at L2 and complete obstruction at L3 level. Such findings enabled a correct diagnosis of cysticercosis to be made before operation.

Conclusion

Of the 3 parasitic diseases mentioned, gnathostomiasis and angiostrongyliasis are perhaps not likely to be encountered in Australia. On the other hand, cysticercosis occurs and may cause problems in diagnosis (Gubbay and Matz, 1975). With international air travel and the steady flow of migrants from Asia to Australia, it is likely that more cases of cysticercosis will be encountered. Persons who have never left Australia may be infected by migrant food handlers who acquired tapeworms from their homelands.

Summary

In Thailand there are 3 parasites that commonly cause neurological diseases in man.

1) In gnathostomiasis man becomes an accidental host by eating infected undercooked fresh water fish. The tissue nematode involved, *Gnathostoma spinigerum*, because of its high motility, may cause widespread damage in the spinal cord and brain stem. The common presenting neurological symptoms are severe nerve root pain, paralysis of limbs and urinary retention. Less frequently seen are cranial nerve palsies and symptoms of subarachnoid haemorrhage. The disease has significant morbidity and mortality.

2) Eosinophilic meningitis caused by *Angiostrongylus cantonensis*, the lungworm of rats, has a more benign, self limiting course. It occurs in Thai people of lower socio-economic groups who acquire the parasite by eating infected raw Pila snails.

3) *Cysticercus cellulosae*, caused by *Taenia solium*, commonly results in epilepsy, and sometimes increased intracranial pressure from intraventricular obstruction or from basal arachnoiditis. Spinal cord and cauda equina involvement occurs much less frequently. *Cysticercus* complement fixation tests on the CSF and computerised axial tomography have been found to be of great diagnostic value.

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Vertebral Metastases and Spinal Cord Compression

B.A. Kakulas, C.G. Harper, K. Shibasaki and G.M. Bedbrook†*

Compression of the spinal cord or nerve roots is relatively common in patients with vertebral metastases. Previous reports on this subject generally emphasise the clinical aspects (Alexander et al., 1956; Botterell and Fitzgerald, 1959; Kennady and Stern, 1962; Mullan and Evans, 1957; Torma, 1957). Few give detailed descriptions of the metastatic deposits within the spinal column or of the spinal cord pathology (McAlhany and Netsky, 1955).

The purpose of the present study is to describe the exact location of the vertebral and epidural metastases and the associated changes in the spinal cord. In addition the clinical and the neuropathological findings are correlated. This information may influence the future clinical management and operative procedures in relation to vertebral metastases and spinal cord compression.

Clinical Material and Methods

14 cases of spinal cord compression or radiculopathy due to vertebral metastases were examined in the period from November 1975 to December 1976 in the Depart-

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ment of Neuropathology, Royal Perth Hospital. Most of these patients were examined clinically by at least one of the authors (K. Shibasaki or G.M. Bedbrook) whilst they were in the Royal Perth (Rehabilitation) Hospital.

The greater number of the spinal specimens were fixed within an hour of death by the injection of 50 to 100ml of 10% formol-saline into the spinal theca. Later, at formal necropsy, the vertebral column was removed *in toto*. After a further period of fixation the vertebral laminae were removed and the spinal cord examined *in situ* within the canal. Careful examination of the meninges, spinal cord, nerve roots, and blood vessels was made and photographs and radiographs were taken where appropriate. The spinal cord within its dural sheath was then removed and the vertebral canal inspected. The bony column was sectioned vertically in the sagittal plane. In several instances vertebrae were sectioned in the horizontal plane in order to examine

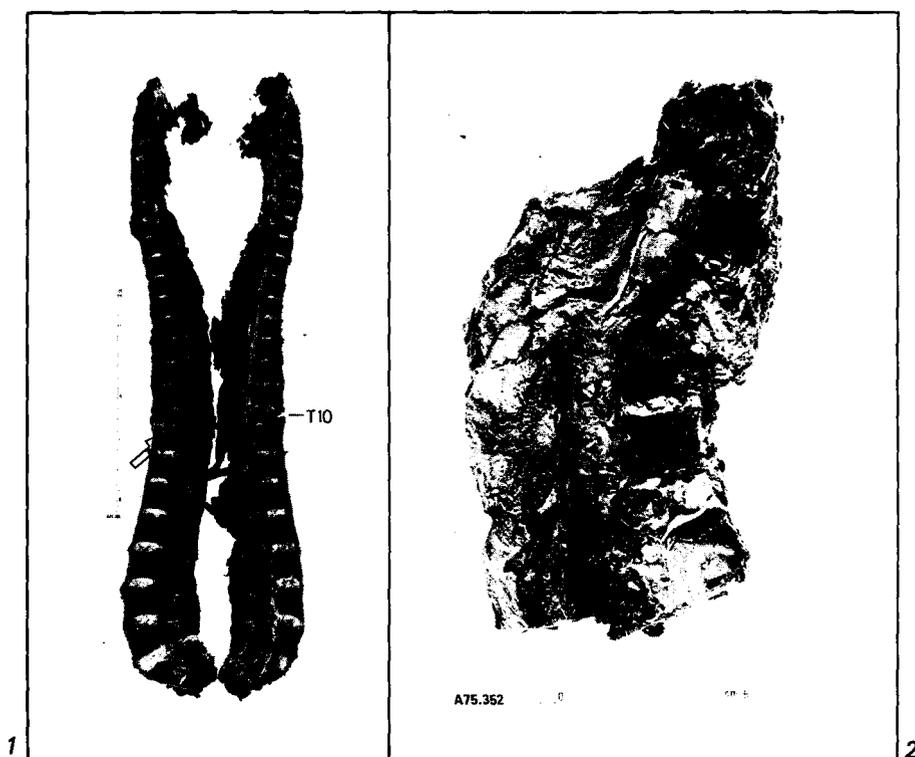


Fig. 1. Case 2: Sagittal section of vertebral column. Note the numerous metastases in the vertebral bodies. T10 vertebra has collapsed causing an incomplete paraplegia below T11.

Fig. 2. Case 1: T2 and T3 vertebral bodies are completely replaced by tumour and have collapsed. There is anterior dislocation of the adjacent vertebrae causing spinal cord compression.

Table 1. Clinical details of 14 patients with spinal cord compression or radiculopathy

Case No.	Sex	Age	Presenting symp. Duration	Neurological signs	Mode of onset	Site of primary carcinoma	Vertebrae affected	Surgery	Survival after onset/surgery (weeks.)
1	F	52	Weakness and paraesthesia in both legs	Incomplete paraplegia below T4	Sudden	Cervix	T2 & T3	—	17
2	F	48	Back pain (1 w)	Incomplete paraplegia below T11	1 week	Breast	Multiple — largest at T10	Laminectomy (T8-11)	8
3	F	67	Neck pain (1 yr)	Transient quadriplegia below C2	Sudden	Breast	C2	—	16
4	M	50	Midthoracic pain (15 min)	Complete paraplegia below T3	Sudden	Lung	T2-T5, T11 & T12	Laminectomy (T2-5)	22
5	F	79	Buttock pain	Complete paraplegia below T12	Several days	Stomach	Multiple — largest from T10-T12	—	2
6	M	49	Subjective paraesthesia in both hands	Slight muscle weakness in both hands	Slow	Larynx	Nil — leptomeningeal carcinoma	—	12
7	F	53	Pain in both legs (1 yr)	Complete paraplegia below T8	4 days	Multiple myeloma	Multiple — largest at T8	—	16
8	M	19	Pain in both legs	Incomplete paraplegia below T6	1 week	Osteosarcoma	Multiple — largest at T6, T12 & L3	—	4
9	F	76	Paraesthesia and numbness in both legs	Caudal symptoms	Slow	Colon	C5, T2 & L4	—	6
10	M	31	Back pain (3 w)	Complete paraplegia below T3	Several days	Lung	T2 & T3	Laminectomy (T1-4)	6
11	F	66	Back pain (5 mth)	Complete paraplegia below L1	Sudden	Multiple myeloma	T12 & L4	Laminectomy (T12 & L4) Ant. Surgery (L4)	20
12	M	49	Low back pain	Subjective paraesthesia in both legs	Sudden	Adenocarcinoma	T11 & T12	Laminectomy (T12)	3
13	M	59	Back pain (10 mth)	Incomplete paraplegia below T4	5 days	Colon	C3, T4 & T5	Laminectomy (T4-5)	3
14	M	57	Back pain	Incomplete paraplegia below T4	Slow	Prostate	T4 & T5	Laminectomy (T4-5)	10

the anatomical relationships between epidural and vertebral metastatic deposits more closely. The dura was opened and the spinal cord examined. Transverse sections of the spinal cord were made at numerous levels. Specimens for histological examination were taken from any suspected vertebral or epidural metastases and from many levels of the spinal cord with particular emphasis on the region of the clinically documented paralysis. Both frozen section and paraffin blocks were prepared and staining techniques included haematoxylin and eosin, Nissl, Weil, Martius scarlet blue, oil red O and Marchi stains. Glees and Marsland silver impregnations were also performed. Tabulations were made of the distribution of metastatic tumours in the vertebral column and spinal canal in relation to the spinal cord lesions. Complete records for each case were available for clinico-neuropathological correlation.

Results

Clinical

Table I summarises the clinical data of the 14 patients, 7 males and 7 females. Their ages range from 19 to 79 years although all but 2 were older than 48 years. 10 of the group were paraplegic and 1 had an episode of transient tetraparesis. This recovered after spinal traction. The other 3 patients had radiculopathy (Case 6), cauda equina involvement (Case 9) and low back pain with paraesthesia (Case 12). Of the 10 paraplegic patients, 5 were clinically complete paraplegia and 5 were incomplete. There was no characteristic pattern of sensory or motor disturbance in the cases of incomplete paraplegia. The presenting symptoms were pain in 11 cases and paraesthesia in 3 cases. 4 patients gave no history of symptoms related to their primary tumour when they first presented to hospital.

Table II lists the sites of the primary tumours. The neoplasms most commonly associated with vertebral metastases in this series were carcinoma of lung, breast and colon and multiple myeloma.

The clinical level of spinal cord compression is shown in table III. 10 of the 14 cases had thoracic cord compression and 6 of these were in the upper thoracic region (T1-6). Paraplegia or tetraplegia developed suddenly in 4 cases and within 1 week of the onset of neurological symptoms in 10 of the 11 patients (table IV). Of the 5 patients who developed sudden tetraparesis, 3 were precipitated by minor trauma. 7 patients were subjected to laminectomy. Details of these cases are shown in Table V. Laminectomy was carried out within 24h of the development of paraplegia in only 1 patient. The results of surgery were poor. Only 1 of the 7 patients made a complete recovery (Case 11). She presented as an incomplete paraplegia below L1, but unfortunately 3 months later at the same level she developed complete paraplegia.

The length of survival after the onset of paraplegia was not significantly affected by operative procedures. The mean survival time of about 10 weeks for both groups of patients was similar, as indicated in table VI.

Table II. Site of primary tumour in 14 cases

Site	Number
Lung	2
Breast	2
Colon	2
Prostate	1
Cervix	1
Larynx	1
Stomach	1
Multiple myeloma	2
Osteosarcoma	1
Adenocarcinoma (primary unknown)	1

Table III. Level of spinal cord or root compression in 14 patients

Level	Number
Cervical	2
Upper thoracic	6
Lower thoracic	4
Lumbar	2

Table IV. Mode of onset of clinical symptoms

Onset	Number
Sudden	5 ¹
Slow (1-7 days)	6
Slow (> 7 days)	3

1 Precipitated by minor trauma in 3.

Table V. Summary of the 7 cases submitted to laminectomy

Feature	Number
<i>Symptoms</i>	
Incomplete paraplegia	4
Complete paraplegia	2
Low back pain only	1
<i>Duration of symptoms before surgery</i>	
24 hours	1
2 days	2
7 days	2
> 7 days	2
<i>Results of laminectomy</i>	
Complete recovery	1 ¹
Improvement of sensory function	1
Unchanged	5

1 This patient had a recurrence within 3 months.

Table VI. Comparison of survival times of 14 patients, 7 of whom underwent operation

Survival time (months)	Operation	No operation
1	2	2
2	2	1
3	1	1
> 3	2	3
<i>Mean</i>	10.3 weeks	10.4 weeks

Table VII. Level of largest vertebral metastases found at postmortem in 13 cases

Level	Number
Cervical	1
Upper thoracic (T1-6)	6
Lower thoracic (T7-12)	5
Lumbar	1

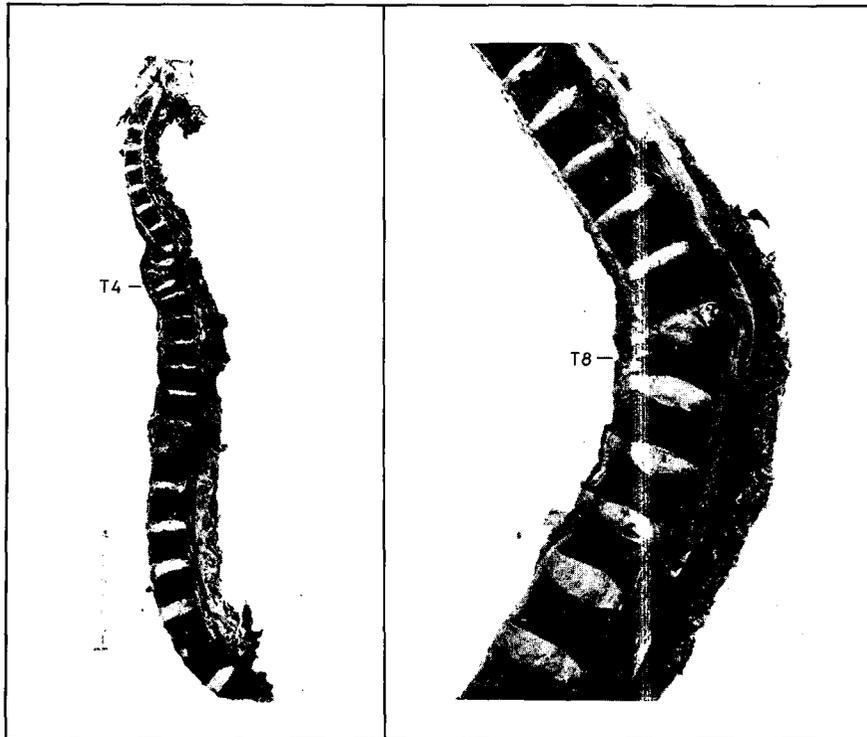


Fig. 3. Case 4: Laminectomy was performed from T2 to T5. There is collapse of the vertebrae and severe instability of the spine at this level.

Fig. 4. Case 7: Collapse of T8 vertebrae causing anterior compression of the spinal cord and a complete paraplegia.

Macroscopic Pathological Findings

The Spinal Column

The largest vertebral metastases were most common in the thoracic spine (table VII). 1 patient (Case 6) presented with lower cervical radiculopathy due to leptomeningeal carcinoma in the absence of vertebral metastases. 12 patients had metastatic foci in 2 or more vertebrae and 4 of these had more than 2 metastases (fig. 1). With regard to other metastatic foci, 9 patients had lung metastases and 2 had cerebral metastases. Table VIII indicates the anatomical localisation of the metastases within the vertebrae at the level of spinal cord or root compression. The vertebral bodies and pedicles were most commonly involved with extension to the posterior

Table VIII. Localisation of vertebral metastases

Site	Number
Vertebral body	13
Pedicle	10
Posterior lamina	5
Epidural deposit	4
Leptomeninges	1

Table IX. Spinal cord pathology

Case no.	Macroscopic findings		Microscopic findings				
	Level of compression	Direction of compression	Focal white matter lesions	Central softening	Wallerian degeneration	Vascular thrombi	Other
1	T2-3	Anterior	T1-T5	T3	+	—	—
2	T11-T12	Anterior	T12	—	+	—	—
3	C2-3	Anterior & posterior	—	—	—	—	Anterior horn cell chromatolysis
4	T2-5	Anterior	T4-T6	—	+	—	—
5	T5-6	Anterior	T5	—	—	+	—
	T11-L1	Anterior	—	T11-L1	—	+	—
6	Nil	—	—	—	—	—	Leptomeningeal carcinomatosis
7	T8	Anterior	T8	—	+	—	—
8	T6	Lateral	T5-T7	T6	+	—	—
9	C5	Lateral (L)	C5	—	+	—	—
	L4	Anterior	—	—	+	—	—
10	T2-3	Anterior	T2-3	—	+	+	—
11	T12	Lateral (L)	T11	—	+	—	—
12	L2	Anterior	L2	—	—	—	—
13	T4	Anterior	T4	—	—	—	—
14	T3	Anterior	T3-4	—	—	+	—

laminae in only 5 cases. It is noteworthy that 3 of the 4 epidural deposits were continuous with vertebral body or pedicle metastases.

At the level of the paraplegia, vertebral bodies were found to be collapsed in 9 cases, and 2 of these were complicated by anterior dislocation of the adjacent vertebrae (fig. 2). There was instability of the vertebral columns at the level of cord involvement. This instability was particularly noticeable in 4 of the patients who had undergone laminectomy (fig. 3). Two other complications were noted in association with laminectomies. Firstly, there were dense meningeal adhesions in all 7 cases and secondly, a cerebrospinal fluid fistula was found in 1 case. The walls of this fistula were infiltrated by carcinoma.

Spinal Cord Changes

The macroscopic and microscopic findings of the spinal cord are detailed in table IX. There was severe softening of the cord adjacent to the compressive lesion in 3 instances. In 10 other cases there was compression with distortion of the spinal cord caused by expansion or collapse of vertebral bodies, pedicles and laminae or epidural deposits. Only 1 of the 4 epidural deposits was a solitary lesion, the others being in



Fig. 5. Peripheral white matter lesions of the spinal cord. Note severe involvement of posterior and lateral columns and relative preservation of anterior columns (haematoxylin and eosin).



Fig. 6. Posterior column showing thrombus within small venule (haematoxylin and eosin).

continuity with vertebral body or pedicle metastases. The epidural deposits were slightly adherent to the dura mater and there was no macroscopic or microscopic evidence of tumour actually infiltrating the dura. One epidural mass was attached to the right C3 nerve root. This was an isolated deposit of adenocarcinoma lying in the epidural space. The spinal cord was macroscopically normal in Case 6 where there was diffuse leptomeningeal carcinomatosis evident histologically.

Of the 3 cases with severe softening of the spinal cord, 2 patients presented with paraplegia of sudden onset following minor trauma. In these cases there was collapse of the adjacent vertebral body. In most cases the anterior surface of the spinal cord was compressed by collapsed vertebral bodies (fig. 4) or by pedicles infiltrated by tumour or by intervertebral malignant masses bulging posteriorly into the spinal canal. 2 cases showed lateral compression. The spinal arteries and veins were carefully examined and they appeared normal.

Microscopic Findings

The vertebral lesions considered macroscopically to be metastases were confirmed histologically. The most interesting finding in this regard was the intimate relationship between the epidural deposits and the metastatic vertebral lesions. 3 of the epidural masses were direct extensions from metastatic tumour within either the body or the pedicles of the vertebrae.

The types of microscopic lesion are listed in Table IX. 12 of the 14 cases showed focal white matter lesions. The lesions tended to be peripheral rather than central

(fig. 5). The central grey matter was generally intact. The lesions were most common in the posterior and lateral columns with relative sparing of the anterior columns. These white matter lesions varied from focal loss of myelin to complete necrosis with destruction of both myelin and axons. The foci were lace-like or vacuolated in appearance. Axon retraction bulbs were present in many of the early lesions and in some instances there were inflammatory infiltrates which were either polymorphonuclear or mononuclear, depending on the age of the lesion. There were foci of different ages in the same transverse section of the spinal cord in several cases. The foci were sometimes wedge-shaped with the base of the wedge lying on the spinal cord surface. In the most severe cases the foci tended to coalesce resulting in a shrunken segment of cord, the lateral and posterior columns showing a spongy vacuolated appearance. The meninges and large blood vessels appeared normal. However, in 3 of the 12 cases with focal white matter lesions, several small blood vessels in the spinal cord contained fibrin thrombi. These thrombi stained specifically with the Martius scarlet blue stain (fig. 6). The thrombi showed no evidence of organisation. The occluded vessels were invariably restricted to the white matter but did not appear to be related anatomically to the focal necrotic or demyelinating lesions. There was no specific pattern of distribution of the thrombi. Meningeal vessels were normal. Of the other 2 cases, 1 patient had diffuse leptomeningeal carcinomatosis (Case 6). There was no evidence of nerve root degeneration in the sections examined. Peripheral nerves were not examined in this case. Patient 3, who suffered a transient tetraparesis and recovered completely, showed chromatolysis of anterior horn cells in the C2-3 transverse sections examined. This was an acute change and could not be related to her original symptomatology.

In 3 cases there was central softening of the spinal cord in addition to the focal white matter lesions which tended to be seen most clearly at the extremities of the central necrotic lesion. These lesions were centred in the grey matter rather than the white matter and extended posteriorly to involve the ventral part of the posterior columns and the posterior horns. There was necrosis of both grey and white matter with central cavitation. There were many lipid filled macrophages within the cavities. Wallerian degeneration of the ascending posterior columns and lateral spinothalamic and spinocerebellar tracts was found in 8 cases. Descending lateral corticospinal tract degeneration was present in 6 cases. The severity of the secondary or Wallerian degeneration was related to the severity of the spinal lesion and the length of survival of the patients after the onset of spinal cord compression.

Discussion

The clinical findings in this series are consistent with previous reports of spinal cord compression and paraplegia due to vertebral metastases (Alexander et al., 1956;

Bansal et al., 1967; Botterell and Fitzgerald, 1959; Brice and McKissock, 1965; Dickson, 1968; Kennady and Stern, 1962; Mullan and Evans, 1957; Perese, 1958; Smith, 1965; Torma, 1957; Wild and Porter, 1963).

The age distribution was in the 4th to 6th decades and the incidence in males and females was the same. Barron et al. in 1959, in a study of 127 cases, found that the commonest primary tumours were carcinomas of the lung and breast, and lymphomas. Our findings were similar with regard to the carcinomas but no cases related to lymphoma occurred in our series. The commonest presenting symptom was pain, usually in the back. Kennady and Stern (1962) stated that a characteristic spinal symptom was pain in almost all of the 103 cases which they studied. The spinal cord or root compression may also be the presenting feature of the primary tumour, as was the case in 3 of our patients.

The acuteness of onset and the rapidity of progression to complete or incomplete paraplegia was notable in this series, and this had been described in previous reports (Arseni et al., 1959; Barron et al., 1959; Kennady and Stern, 1962; Torma, 1957). This rapid progression has been considered to be due to tumour growth and a high incidence of pathological vertebral fractures. Certainly 3 of the 4 patients who developed a sudden paraparesis had suffered a minor back injury and the spinal cord compression was probably related to a collapse fracture.

However, in view of the microscopic finding of fibrin thrombi within small spinal cord blood vessels in 3 cases and the rather unusual peripheral pattern of lesions in the white matter in 12 of the 14 cases, it is suggested that circulatory disturbances play a part in the progression of the neurological signs.

The importance of epidural metastases as a cause of spinal cord compression has been emphasised by many authors. Batson (1942) described the anatomy of the vertebral venous system with its rich, valveless ramifications and connections, and suggested the possibility of retrograde spread of tumour emboli into the epidural space via this pathway. This concept was supported by Dinning (1961), Rogers (1957) and Wild and Porter (1963). They explained the apparent predilection of metastases for the epidural space on this hypothesis.

However, the present study suggests that the epidural metastases are generally in continuity with vertebral metastases. The actual incidence of isolated epidural metastases may be found to be quite low if the entire vertebral column can be examined at autopsy as described in the methodology herein. We noted that there were metastases in the lungs of 9 of these 14 cases. These included 1 case of prostatic adenocarcinoma and 3 intra-abdominal primary carcinomas. This suggests that arterial dissemination of metastases is common and is more important than retrograde spread via the vertebral venous plexus. Nevertheless, it is not denied that metastases may spread via the vertebral venous plexus, particularly from primary carcinomas arising within the pelvis. Experimentally, Coman and DeLong (1951) demonstrated that tumour cell suspensions injected into the femoral veins of rats and rabbits can produce vertebral metastases.

Despite the presence of epidural deposits, there was no direct penetration or invasion of the dura by the tumours. The ease with which epidural metastases can be stripped from the dura mater at operation was emphasised by both Dinning (1961) and Rogers (1957). The exact nature of the protective barrier which the dura mater forms is not understood. It may be that the tumour spreads along lines of least resistance such as within the epidural space. There are venous channels traversing the dura mater but Dinning (1961) suggested that intradural transmission of tumour emboli by this route is unlikely because the intradural venous pressure is higher than the vertebral venous system pressure and flow will be either axial or centrifugal.

Histologically, the most common finding in the spinal cord at the level of compression was focal demyelinating or necrotic lesions which were centred on the white matter columns with relative preservation of the grey matter. These lesions were frequently multifocal and the peripheral areas of the lateral and posterior columns were most severely affected, regardless of the site of maximal compression. The anterior surface of the spinal cord was the most common area of maximal compression. Interestingly, there was relative sparing of the anterior white matter columns.

There was destruction of myelin and subsequently disruption of axons with the formation of axon retraction bulbs. In some instances there was frank necrosis with microcavitation. Despite the relative preservation of the grey matter and the anterior columns, all the cases were clinically transverse spinal cord lesions. This fact is in accord with Barron et al. (1959), who reviewed 127 cases of spinal cord compression by metastatic neoplasms, and pointed out the discrepancies between the clinical symptoms and signs and the morphological changes in the spinal cord. McAlhany and Netsky in 1955 described very similar changes in their study of 19 cases of compression of the spinal cord by extramedullary neoplasms. They stated that the white matter was more severely damaged than the grey matter in each case. Concerning the aetiology of these changes, they attributed the white matter lesions to the mechanical effects of the compression and the secondary collapse of small intramedullary blood vessels. As in our cases, the major arteries and veins were normal both macroscopically and microscopically. However, we noted small fibrin thrombi in the small intramedullary vessels in 3 of the cases. This suggested that thrombosis secondary to continuous compression by epidural masses may be a causative factor in the white matter changes. Similar lesions were shown to occur in spinal phlebitis by Neumayer (1966). McAlhany and Netsky (1955) specifically stated that no thrombi were seen. Sparing of the anterior columns has been observed by other authors. Mair and Druckman (1953) suggested that the white matter lesions were caused by compression of the distal ramifications of the anterior spinal artery, thus sparing the anterior columns. However, this does not explain the preservation of the grey matter. The anterior sulcus may permit greater mobility of this part of the compressed spinal cord and the sulcal vessels may be protected, as was suggested by McAlhany and Netsky (1955).

The cases in which there was severe softening of the spinal cord at the site of compression, with histological evidence of central grey matter necrosis in addition to the peripheral white matter lesions, may represent a different pathological process. These lesions closely resemble those seen in traumatic spinal cord injuries. Kakulas and Bedbrook (1976), in their clinico-pathological study of injuries of the spine and spinal cord, commented that extension and compression or dispersion injuries were more often associated with haemorrhage and necrosis in the spinal grey matter. This group formed the largest number of clinically incomplete lesions in their study of more than 100 cases. It should be noted that Case 1, who had a central type of lesion, presented with a sudden onset of symptoms following minor injuries. The nature of the injury was not ascertained. Vertebral metastases, of course, predispose to pathological fractures, which are usually compression in type and these may have given rise to the traumatic type of spinal cord lesion.

The secondary or Wallerian degeneration of the ascending posterior and lateral spinothalamic and spinocerebellar tracts and the descending degeneration of the lateral corticospinal tracts is identical to that seen in any spinal cord disease which causes interruption of these axonal pathways. This phenomenon is an extremely slow process and histological changes will not be visible until about 3 weeks after the damage occurs. This delay explains the apparent absence of long tract degeneration in several of the cases.

Laminectomy and decompression have been advocated by many authors as the treatment of choice for paraplegia due to vertebral metastases (Botterell and Fitzgerald, 1959; Cole et al., 1969; Kakulas and Bedbrook, 1976; Love et al., 1954; Mullan and Evans, 1957; Smith, 1965; Torma, 1957; Wild and Porter, 1963). However, other authors have disputed the value of laminectomy and have stated that surgery should be directed at relief of pain (Arseni et al., 1959; Rasmussen et al., 1940; Shenkin et al., 1945). In this series, half of the patients were subjected to laminectomy and only 1 of the 7 benefited from the operative procedure. Unfortunately, in only 1 instance was surgery able to be carried out within 24 hours of the onset of paraplegia. As in any situation with spinal cord compression, regardless of the aetiology, the time factor is critical. Barron et al. (1959) suggested certain indications and contraindications for surgery. They stated that patients with a spastic paraplegia have a better prognosis than those with a flaccid paralysis. Patients with metastases from carcinoma of the lung had a uniformly unfavourable prognosis. Other forms of treatment have been suggested and these include laminectomy followed by irradiation (Arseni et al., 1959; Rasmussen et al., 1940; Wild and Porter, 1963). These authors also stated that even minimal neurological improvement is sufficient justification for surgery.

The possible complications of laminectomy must not be overlooked. The most frequent and serious problem following laminectomy in this series was the impaired stability of the spine at the laminectomy site. Bucy (1963) emphasised this problem and described the metal implant used by Krayenbuhl to correct the spinal deformity

and support the vertebral column. Similar techniques have been reported by Halnan and Roberts (1967); Martin and Williamson (1970); Cross et al. (1971) and Wienand (1971). Patient 11 in this series had a very unstable spine after laminectomy, but stability was obtained by resecting the collapsed vertebral body and replacing this with acrylic bone cement. This technique was previously reported by Silverstein in 1971. The anterior approach, as described by Halnan and Roberts (1967) should perhaps be considered more often as the spine retains greater stability.

Summary

Clinical interest in spinal compression and resultant paraplegia due to metastases has mounted in recent years. This has stimulated attention to the neuropathology of the condition. 14 cases of spinal cord compression due to vertebral metastases are compared with over 100 traumatic cases. In the traumatic lesions there is central haemorrhagic necrosis leading to cavitation and gliosis with nerve root regeneration in the late stages. In the metastatic cases, lesions are often peripheral, pie-shaped and are related to vascular factors. The neuropathology of cord necrosis due to metastatic spinal disease is therefore different from that caused by trauma. These observations have clinical importance in planning treatment.

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Wernicke-Korsakov Syndrome Lesions in Coronial Necropsies

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The clinical and pathological features of the Wernicke-Korsakov syndrome have become well known since the first cases in 2 alcoholics and 1 non-alcoholic were described by Wernicke in 1881 (Brody and Wilkins, 1968). Wernicke's disease is characterised by nystagmus, gaze palsies, gait ataxia and mental confusion, and is frequently associated with Korsakov's psychosis. In this latter condition memory is impaired out of proportion to other cognitive functions in an otherwise alert patient. The characteristic vascular lesions and the parenchymatous changes of the Wernicke-Korsakov syndrome occur in the nuclei related to the third and fourth ventricles. Involvement of the medial thalamus appears to be associated with the Korsakov amnesia (Victor et al., 1971).

Although Adams and Victor (1977) found the lesions of the Wernicke-Korsakov syndrome in 2.7% of 1459 consecutive adult necropsies at the Cleveland Metropolitan General Hospital, the lesions seem to be seldom recognised in necropsies carried out by order of the coroner in persons with unexplained coma or who have been found dead. In this report of 12 cases we describe the findings in 3 alcoholics whose brains were referred for study in 1974 to 1976 and in 9 coroner's necropsies in the year between January 1977 and January 1978. These 9 cases represented 5.3% of 169 coroner's necropsies in Hobart in cases of unexpected, non-violent death in that period.

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Case Reports

Case 1

DJO, a male aged 52 years, was a former unsuccessful pugilist who died in the Royal Derwent Hospital. He was probably Tasmania's most recidivistic alcoholic with approximately 400 court appearances on charges associated with the consumption of alcohol. He had previously suffered a fractured skull and fits.

Necropsy showed severe pulmonary emphysema. The liver appeared normal. There was an old healed fracture of the right temporal bone.

The brain (1100g) showed extensive old traumatic destruction of the cortex in both frontal and temporal lobes. The superior cerebellar vermis was markedly atrophied (fig. 1). Slicing of the cerebrum showed appreciable grey and white matter destruction in both inferior frontal lobes.

Histologically there were nerve cell changes, capillary congestion and haemorrhages in the mammillary bodies, fornix, dorsomedial thalamus, hypothalamic nuclei, around the aqueduct, in the trochlear nuclei, locus caeruleus, dorsal motor vagus and vestibular nuclei, the dorsomedial segments of the inferior olives and dentate nuclei. There was a loss of granule cells and Purkinje cells most marked in the superior cerebellar vermis. There was a left Ammon's horn sclerosis.

Case 2

CED, a female aged 26 years, was admitted to the Royal Hobart Hospital confused, hallucinated and febrile. Examination revealed a pulse rate of 140 per minute, blood pressure of 90/60mm Hg, nystag-



Fig. 1. Case 1: Mesial cut surface of left cerebellum showing marked atrophy with shrinkage and separation of folia in the anterior superior vermis.



Fig. 2. Case 2: Discoloration and commencing disintegration in the hypothalamic grey matter around the third ventricle and in the mammillary bodies. There are a few petechial haemorrhages in these areas and in the fornix.

mus and areflexia. The electrocardiogram showed non-specific T wave changes. She was treated with intravenous fluids including 4% dextrose, developed vomiting and diarrhoea and increasing obtundation, finally dying on the sixth day. Her alcoholic history was obtained subsequent to her death.

Necropsy showed a fatty liver and a terminal acute pulmonary oedema.

The fresh brain weighed 1300g. Slicing after fixation showed obvious discoloration and necrosis around the third ventricle and aqueduct and in the mammillary bodies (fig. 2).

Histologically there were nerve cell changes, a marked capillary endothelial proliferation and congestion, small haemorrhages and some astroglial proliferation in the mammillary bodies, periventricular hypothalamic and dorsomedial thalamic nuclei, around the aqueduct, in the inferior colliculi, in the oculomotor, trochlear, dorsal motor vagus and vestibular nuclei, in the locus caeruleus and in the dentate nucleus. There were less severe changes in the caudate nuclei, putamina and inferior olives.

Case 3

LR, a female aged 58 years, was found lying on the floor at home. On admission to the Royal Hobart Hospital she was confused and dishevelled. The pulse rate was 118/minute and the blood pressure 85/35mm Hg. She was areflexic and ataxic. The electrocardiogram showed nonspecific T wave changes.

She had a deep venous thrombosis in one leg and bronchopneumonia. Despite antibiotics and massive vitamin B therapy she died 5 days later with pulmonary oedema and renal failure. She was known to have abused alcohol in the past.

Necropsy showed early renal tubular necrosis, severe bilateral pulmonary oedema but no pneumonia, thrombus in the left calf and thigh veins and a healed gastric ulcer. The liver showed a mild fatty change and an early portal fibrosis without cirrhosis.

The fresh brain weighed 1120g. On slicing when fixed the mammillary bodies appeared discoloured and there was atrophy of the superior cerebellar vermis.

Histologically the mammillary bodies showed a severe nerve cell loss, status spongiosus, capillary endothelial proliferation and congestion, recent small haemorrhages and deposits of haemosiderin, some contained in macrophages indicative of previous old haemorrhage. Recent lesions were noted in the other hypothalamic nuclei, in the periaqueductal grey matter, in the trochlear nucleus and in the locus caeruleus. There was obvious Purkinje cell loss in the superior cerebellar vermis.

Case 4

A WW, a male aged 32 years, was found dead in bed at home. He was last seen alive the previous day and considered then to be drunk. There was a history of alcohol abuse, fits and fractured skull.

Necropsy showed severe bilateral pulmonary congestion and a chronic gastric ulcer 1.2cm in diameter on the posterior wall of the pyloric antrum. There was a chronic subdural haematoma enclosed in a thick fibrous membrane.

The fresh brain weighed 1330g and showed extensive old traumatic lacerations on the undersurfaces of both frontal lobes and on the poles of both temporal lobes. Slicing of the fixed brain showed appreciable

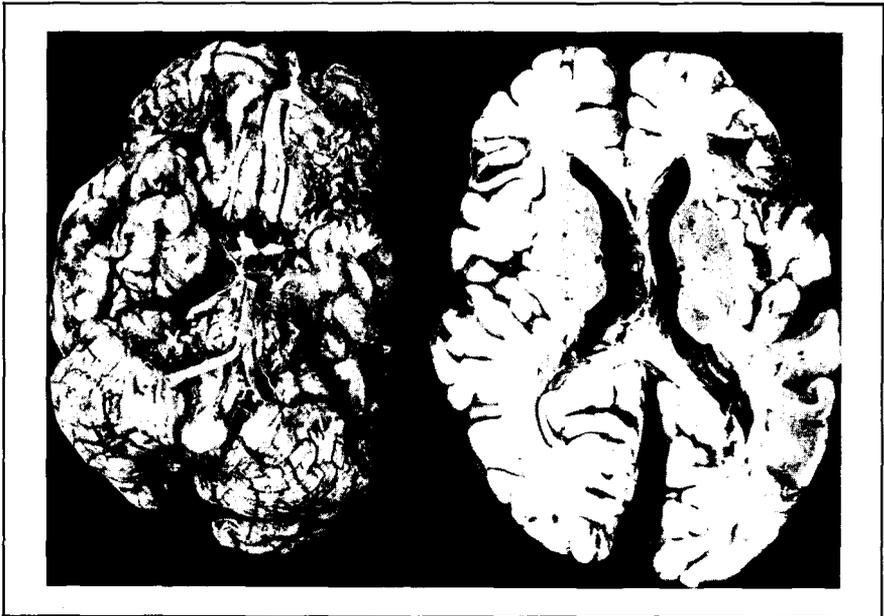


Fig. 3. Case 4: Horizontally sliced brain showing old lacerations on the undersurfaces of both frontal lobes and on the lateral aspect of the left temporal lobe. The cut surface shows appreciable destruction of the underlying white matter.

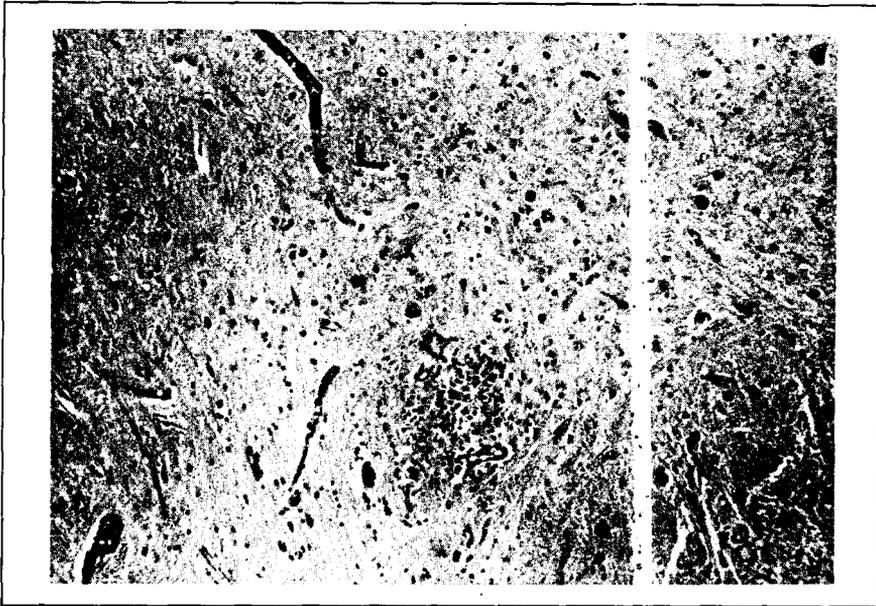


Fig. 4. Case 6: Focus of glial cells, small perivascular cuffs and plump vascular endothelial cells in the dorsal motor vagus nucleus. HE x 75.

white matter destruction in these areas as well (fig. 3). The left hippocampus also was damaged. The superior cerebellar vermis was atrophic.

Histologically there was a left Ammon's horn sclerosis. The hypothalamic nuclei showed status spongiosus and capillary congestion in the mammillary bodies, and small haemorrhages around the third ventricle and in the dorsomedial thalamus. Similar congestion and haemorrhages were seen in the dorsal motor nuclei of the vagus, in the vestibular nuclei, in the locus caeruleus, in the dorsomedial olive and in the dentate nucleus. There was a loss of Purkinje cells and granule cells in the vermis and anterior lateral lobes of the cerebellum.

Case 5

VDR, a female aged 63 years, was found dead on a sofa at home. She was last seen alive two days previously. There was a long history of alcohol abuse, fits and malnutrition. There had been previous surgical evacuation of a subdural haematoma.

At necropsy the severely wasted body weighed only 34kg. The liver was noted to be normal. On the left side of the skull vault there were old scar-filled burr holes. There was an old healed left chronic subdural haematoma scar.

The fresh brain weighed 1230g and showed old traumatic lacerations on the undersurfaces of both frontal lobes and over the pole of the left temporal lobe. There was an old infarct involving the left superior parietal lobule and the underlying white matter down to the lateral ventricle.

Histologically there were minimal nerve cell changes but an intense capillary congestion with haemorrhages in the mammillary bodies, and in the hypothalamic, dorsomedial thalamic, dorsal motor vagal and vestibular nuclei.



Fig. 5. Case 9: An area in the massa intermedia with haemorrhages, endothelial proliferation and status spongiosus. HE x 100.

Case 6

CHL, a male aged 59 years, was a chronic alcoholic who also consumed considerable quantities of methylated spirits. He was found dead on a toilet floor near his night shelter. Facial trauma, a lacerated scalp, brachial plexus injury, fractured ribs and a fractured thoracic vertebra had been sustained on previous separate occasions whilst he was drunk.

Necropsy revealed an enlarged heart (430g), chronic bronchitis and emphysema, diverticulosis coli and an enlarged fatty liver. The kidneys showed a mild hypertensive nephrosclerosis.

The brain weighed 1230g and showed old lacerations on the undersurfaces of both frontal lobes and on the lateral aspect of the right temporal lobe.

Histologically there were glial foci and perivascular cuffing as well as capillary changes and recent haemorrhages in the mammillary bodies and dorsomedial thalamic, dorsal motor vagal (fig. 4) and dentate nuclei. Capillary changes and recent haemorrhages only were seen in the other hypothalamic and periaqueductal nuclei and in the locus caeruleus and inferior olives.

Case 7

LFD, a female aged 57 years, was found dead in bed. Her alcoholic husband said she had complained of headache shortly before death. There was a history of asthma and heavy alcohol consumption.

Necropsy revealed bilateral pulmonary emphysema and right and left ventricular hypertrophy with right-sided dilatation of the 490g heart. The liver was enlarged (2240g) and showed a diffuse fatty change and moderate portal fibrosis without cirrhosis.

The brain weighed 1450g and appeared somewhat swollen but no lesions were seen macroscopically. Histologically there was a small old paravascular scar in the wall of the third ventricle suggestive of a focal destructive lesion. There were nerve cell changes, intense capillary congestion and a

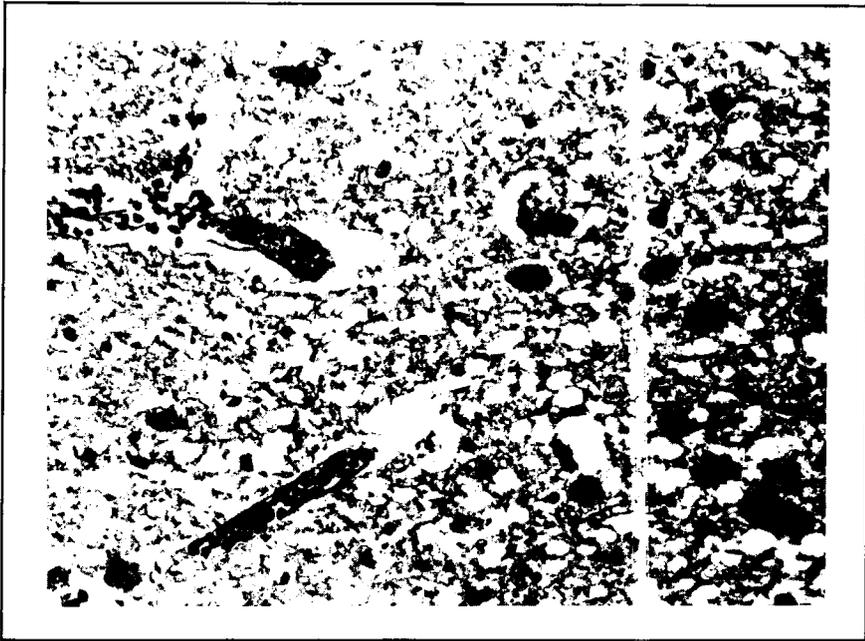


Fig. 6. Case 10: Nerve cell degeneration, status spongiosus and haemorrhage in sixth nerve nucleus. HE x 240.

few recent haemorrhages in the mammillary bodies and in the hypothalamic, vestibular, inferior olivary and dentate nuclei.

Case 8

TJN, a male aged 47 years, was found dead in the caravan in which he lived. There was a history of epilepsy and alcoholism.

Necropsy revealed chronic bronchitis and emphysema with right ventricular hypertrophy and dilatation. The liver (2070g) was enlarged and fatty.

The 1500g brain showed extensive old brown coloured lacerations and contusions over the undersurfaces of both frontal lobes, over both temporal lobes and on the lateral aspect of the left occipital lobe. Slicing after fixation showed a cavity communicating with the lateral ventricle beneath the left frontal laceration. There was some atrophy of the superior cerebellar vermis.

Histologically there was a left Ammon's horn sclerosis. There were nerve cell changes with prominent congested capillaries in the nuclei in the floor of the fourth ventricle, in the mammillary bodies and in the periventricular hypothalamic nuclei where there were also numerous haemorrhages.

Case 9

JT, a female aged 27 years, had had pre-eclamptic toxæmia associated with poor renal function in 1973. A renal biopsy in 1974 showed chronic pyelonephritis. In February 1977 she complained of anorexia for 2 weeks and on examination she had ataxia, mental changes, paralysis of upward gaze and bilateral ptosis. Serum creatinine was 6.6mg. In March 1977 the blood pressure was 190/130mm Hg and she was hypocalcaemic, hyperphosphataemic and anaemic. By May she had become more disorientated

and incoordinated. Serum creatinine was 7.5mg. She then developed fits and papilloedema and was admitted in coma to the Royal Hobart Hospital. A radionuclide brain scan indicated increased perfusion in the right frontal lobe and a right frontal lobe abscess was suspected but this was not confirmed on brain needling. She developed pulmonary oedema, bizarre cardiac rhythms and died 5 days after admission.

At necropsy the kidneys were small (35g each) and were granular and contracted with coarse irregular scarring. Histology showed a severe chronic pyelonephritis.

The brain weighed 1110g and was swollen with flattening of the gyri and narrowing of the sulci with a right frontal needle opening. Slicing after fixation showed needle tracks into the white matter and the right caudate and lenticular nuclei. There were recent pale infarcts in the right frontal and parietal lobes and several focal haemorrhagic infarcts of the left cerebellar cortex. There were obvious petechial haemorrhages around the third and fourth ventricles and aqueduct.

Histologically there were extensive areas of status spongiosus and nerve cell loss, a marked endothelial proliferation and haemorrhages around the third ventricle (fig. 5), the aqueduct and fourth ventricle as well as in the inferior olives. Much of the tegmental pons was severely affected but haemorrhages were not numerous in the areas with the most florid endothelial reaction.

Case 10

ST, a female aged 57 years, was found dead beside her bed. There was a history of tuberculosis, gastric ulcer, emaciation, drug abuse, numerous falls, hypotension, symptoms indicative of Korsakov's

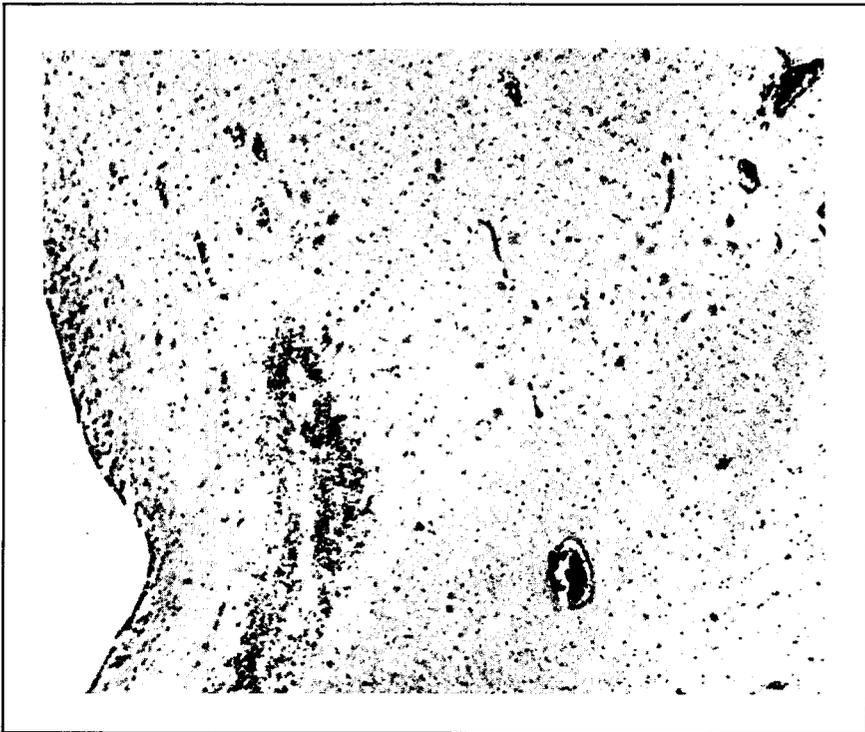


Fig. 7. Case 11: Capillary congestion and haemorrhage adjacent to third ventricle. HE x 30.



Fig. 8. Case 12: Coronal slice of fixed brain showing marked pigmentation in mammillary bodies and discoloration around third ventricle. There is obvious haemorrhage in the left dorsomedial thalamus.

psychosis and a macrocytic anaemia associated with low serum folate. There had been frequent episodes of anorexia, nausea, vomiting and diarrhoea. She had denied significant alcohol consumption.

Necropsy showed right ventricular hypertrophy due to chronic bronchitis and emphysema and mild polycystic disease of the kidneys. There was an extensive but thin right chronic subdural haematoma.

The brain (1200g) showed an old right occipital scar and a parietal lobe infarct which on slicing was seen to extend deeply in the white matter to the lateral ventricle.

Histologically there was status spongiosus, an increase in glial cells and capillary changes in the mammillary bodies, around the third ventricle including the dorsomedial thalamus, in the substantia nigra and around the fourth ventricle (fig. 6) with micro-haemorrhages related to some of these lesions.

Case 11

RD, a male aged 55 years, was found dead in his room at a boarding house. There was a history of tuberculosis, barbiturate overdosage and heavy alcohol consumption.

At necropsy the heart was somewhat enlarged (450g) and showed dilatation of the left ventricle. The liver (2220g) exhibited a severe diffuse fatty change with some portal fibrosis but no cirrhosis. The brain weighed 1300g and showed slight swelling. On slicing there was discoloration round the third ventricle and a superior cerebellar vermis atrophy.

Histologically there was some nerve cell loss in the mammillary bodies and prominent capillaries and haemorrhages in the periventricular hypothalamus (fig. 7) and dorsomedial thalamus and in the hypoglossal and dorsal motor vagal nuclei. There was an obvious loss of Purkinje cells and granule cells in the cerebellum.

Case 12

LCG, a male aged 51 years, was found dead in long grass by the shack where he lived. When last seen alive two days before, he had complained to his drinking companions of visual difficulties.

At necropsy the liver was enlarged (1550g), firm and showed a gross degree of fatty change without fibrosis. The lungs showed a moderate degree of emphysema.

The fresh brain weighed 1200g. Slicing after fixation showed discoloration of the mammillary bodies and around the third ventricle (fig. 8) and aqueduct. Petechial haemorrhages were obvious around the third ventricle and in the floor of the fourth ventricle. There was atrophy of the superior cerebellar vermis.

Histologically there was a loss of nerve cells, an increase in glial nuclei and abundant pigment (much of which not iron-containing) in the mammillary bodies, but no astrogliosis and no recent haemorrhage. The periventricular hypothalamic and dorsomedial thalamic nuclei showed capillary endothelial proliferation with some haemorrhages and similar changes were seen in the vestibular nucleus and locus caeruleus. There was nerve cell loss and vascular congestion but no haemorrhage in the hypoglossal and dorsal motor vagal nuclei. In the cerebellar vermis there was a Purkinje cell loss but the granular layer was little reduced.

Comments

The 12 cases were aged from 26 to 63 (mean 48.7) years. 2 patients were in the third decade, 1 each in the fourth and fifth decades, 7 in the sixth decade and 1 in the seventh decade. 6 were male. 3 patients died in the Royal Hobart Hospital a few days after admission in varying states of disordered consciousness, 1 patient died in the Royal Derwent Hospital and the remaining 8 cases were found dead in or near their residences. 8 cases were known alcoholics of whom 4 had been treated for alcoholism and 3 further cases were almost certainly alcoholics. The remaining case, with a recent history of fits, had had renal failure due to chronic pyelonephritis for 4 years. At some stage prior to death 3 patients had shown the clinical features of the Wernicke-Korsakov syndrome. Case 2 is of particular interest because the cause of her gradually developing coma defied elucidation during life but, in retrospect, the clinical course was quite typical of the syndrome although it developed at the early age of 26. This patient, as well as Cases 3 and 10, developed profound hypotension which together with the abnormal electrocardiograms are common findings in Wernicke's disease, reflecting impaired function of the autonomic system rather than beri-beri heart disease.

None of the 12 cases had terminal pneumonia. 1 case was physically wasted. Active or healed gastric ulcers were found in 2 cases. 7 of the 12 cases had a fatty liver in 3 of which there was a portal fibrosis and in 1 alcoholic hepatitis.

The 12 brains weighed from 1100 to 1450g (mean 1256g) and 6 had lesions characteristic of old cerebral trauma in 2 of which there were associated old infarcts. 4 of these 6 cases with old cerebral trauma had epileptic fits. Chronic subdural haematomata were found in 3 cases. The superior cerebellar vermis was atrophied in 6 cases.

In all 12 cases, acute Wernicke-Korsakov syndrome lesions were present histologically and in 6 cases underlying chronic changes were also seen. Focal collections of glial cells were found in 2 of these.

Discussion

In the 42 cases of the Wernicke-Korsakov syndrome reported by Riggs and Boles (1944) 31 (74%) had liver disease. In the larger series of 81 cases studied by Victor et al. (1971) 50 (62%) had liver disease of whom 36 (44%) had cirrhosis, 11 (14%) fatty change and 3 (4%) hepatitis. In the present 12 cases, 7 (58.3%) had liver disease but, remarkably, none had frank portal cirrhosis.

These cases demonstrate the variable severity of the brain lesions in the Wernicke-Korsakov syndrome (Victor et al., 1971). Although involvement of the nuclei around the third ventricle, aqueduct and fourth ventricle was a constant feature in the present series, the severity of the lesions varied in the different nuclei in different cases. Prominent capillaries and haemorrhages were present in all cases but in some (Cases 2, 3, 9, 12) endothelial proliferation was marked. The capillary changes are the striking feature in these sites in the Wernicke-Korsakov syndrome. The degree of haemorrhage did not seem related to the severity of the capillary changes. Rosenblum and Feigin (1965) described very large haemorrhages in 2 alcoholics with Wernicke's disease, but 17 of their 41 cases had no haemorrhages. Victor et al. (1971) found haemorrhages in only 20% of their cases. While Campbell and Biggart (1939) emphasised that periventricular haemorrhages may occur in other disorders they demonstrated tiny haemorrhages in all their cases.

Although the Wernicke-Korsakov syndrome is caused by the specific nutritional deficiency of thiamine, it develops in only a minority of alcoholics and others who have deficient diets (Victor et al., 1971). Except among Western prisoners of war it has been rare in the Orient in those persons consuming diets deficient in thiamine (Van Itallie and Follis, 1974). The thiamine dependent enzyme transketolase which functions in the pentose phosphate pathway has been shown by Blas and Gibson (1977) to be abnormal in fibroblasts cultured from patients with the Wernicke-Korsakov syndrome. These authors have suggested that it is this inborn enzyme abnormality which predisposes to the development of the syndrome when the intake of thiamine is deficient.

The measurement of erythrocyte transketolase activity and the *in vitro* response to added thiamine pyrophosphate has been used as a test (the TPP effect) to measure thiamine deficiency. The recent National Health and Medical Research Council Report (Clements et al., 1978) has indicated an abnormal TPP effect in patients with renal disease as well as in alcoholics. Although the case of Wernicke's disease in chronic renal failure reported by Lopez and Collins (1968) also had had

haemodialysis and renal transplantation, our Case 9 exhibits a similar association between chronic renal failure and the Wernicke-Korsakov syndrome in a non-alcoholic young woman.

In 2 of the 12 cases of Campbell and Biggart (1939) the brain lesions were not recognised macroscopically. Grunnet (1969) reported that in 7 of her 24 cases, the brain was grossly normal and the diagnosis was determined only after histological examination. An earlier study of 42 cases, also from the Philadelphia General Hospital (Riggs and Boles, 1944), emphasised that the clinical features were of little value for diagnosis which was almost invariably made at necropsy. The lesions were recognised macroscopically in only 5 of our 12 cases. We suggest that the lesions of the Wernicke-Korsakov syndrome should be specifically excluded by microscopic examination of the brain in all patients in whom there is a history of chronic alcoholism or unexplained coma.

Summary

The clinical and pathological features of the Wernicke-Korsakov syndrome are described in 12 cases in which the syndrome had not been recognised before death. In a 1 year period there were 9 cases (5.3%) among 169 necropsies ordered by the coroner in unexpected or unexplained non-violent death. The characteristic brain lesions were grossly apparent in 5 cases and identified only histologically in 7 cases.

The findings suggest that in cases of coma or patients found dead who might have been alcoholics, adequate postmortem examination of the brain is likely to demonstrate the lesions of the Wernicke-Korsakov syndrome in a significant number.

Acknowledgements

We are grateful to Drs. C.H. Kelland, E.T. Cusick, T.J. Brain and Dr. D.R. Challis for referring the brains and making available their necropsy findings in Cases 1, 2, 3 and 12 respectively. Dr. R.V. Parton kindly supplied clinical details about Case 1. We thank Mr. H. Eastwood, Mr. R. Rainbow and Mr. B. Dance for preparing the histological material, Mr. B. McPherson for the gross photographs and Mr. D. Lees for making the prints.

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Association of Central Nervous System Sarcoma with Familial Polyposis Coli

*P.M. Williamson and K.V. Smith**

Familial polyposis is an hereditary disorder characterised by the development of multiple discrete adenomatous polyps in the colon and rectum. Extension above the ileo-caecal valve is rare. Although polypoid disease of the colon had been recognised earlier, Cripps in 1882 first drew attention to the familial nature of the disease (Shiffman, 1962). Genetically, familial polyposis is an autosomal dominant with almost total penetrance. At birth the patient is normal and no polyps are demonstrable but at puberty or shortly after, numerous benign polyps appear in the colon. The characteristic of familial polyposis is the frequency with which adenocarcinoma occurs in the polyp laden colon and the unusually early age at which cancer supervenes. Such malignant change may have multicentric origin. Unless colectomy is performed, half of the patients who have polyps develop carcinoma of the colon by the time they are 30 years of age and practically all are dead by the age of 50 (Laberge et al., 1957).

Of recent years an association has been discovered between familial polyposis and other body tumours. These tumours, which may be benign or malignant, are usually of connective tissue origin in either soft or hard tissues (Miller and Sweet, 1937; Gardner and Richards, 1953; O'Brien and Wels, 1955; Weiner and Cooper, 1955; Collins, 1959; Shiffman, 1962). The association of familial polyposis, osteomas and superficial soft tissue tumours is commonly referred to as Gardner's syndrome (Shiffman, 1962). Cases have been reported where the manifestations of

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extracolonic lesions have appeared before the bowel polyps (Gumpel and Carballo, 1956).

In 1958 two siblings were reported who suffered from familial polyposis and who died from malignant central nervous system tumours (Turcot et al., 1959). One patient had extensive invasion of the spinal cord by a medulloblastoma and the other had a glioblastoma of the left frontal lobe.

This report concerns a patient who had familial polyposis and who died of a sarcomatous central nervous system tumour.

Case Report

The patient was a man aged 35 years when he first presented. His father had had polyposis coli. His own disease was diagnosed at the age of 15 when he had a total colectomy with the rectal stump being retained. 3 years later, as a result of an operation for intestinal obstruction, the ileum was removed and a jejunorectal anastomosis was performed. Because recurrent rectal polyps proved troublesome the rectum was excised at the age of 25, following the establishment of a permanent jejunostomy. Pathological studies on excised tissues showed hyperplastic benign adenomatous polyps in the colon and rectum.

The patient's neurological disease started with unsteadiness of gait followed in 6 months by horizontal diplopia which he had had for a month prior to his admission. Examination then revealed bilateral horizontal nystagmus, partial left 6th nerve palsy and mild ataxia of gait. There was a functioning jejunostomy. Investigations, including skull radiography, EEG, radionuclide brain scan, pneumoencephalogram, full blood count and ESR were normal. CSF was obtained under normal pressure and showed protein of 110mg% and glucose of 25mg% while the coincidental blood glucose was 101mg%. Other CSF studies were normal.

During the following 6 months the patient developed progressive dysarthria and dysphagia with palatal weakness, a depressed pharyngeal reflex and right hyper-reflexia. Repeated CSF examinations showed continuing protein elevation and low glucose and at no stage was there any abnormality of the cells. Because of the possibility of sarcoidosis, the patient was treated with corticosteroids but no improvement resulted. Recurrent episodes of food aspiration necessitated gastrostomy and tracheostomy. Death occurred from respiratory failure and cachexia 6 months after presentation.

Autopsy Report

The body was emaciated and showed evidence of jejunostomy, gastrostomy and tracheostomy. The lungs, heart and major arteries were normal. The large bowel had been resected.

The brain appeared normal to external examination. Macroscopic sectioning of the pons and medulla showed slight distortion on the ventral surface. The cerebral vessels and spinal cord appeared normal.

Microscopic study of brain sections showed a tumour in the substance of the midbrain and cerebellum. Additionally it extended along the subarachnoid space from the upper brain stem to the spinal cord below the level of the cervical enlargement. In some areas the tumour was related to blood vessels. It was composed of elongated nuclei staining darkly with haematoxylin accompanied by little visible cytoplasm (fig. 1). The cells had produced little, if any, reticulin.

The sections were shown to several neuropathologists. Professor Hume Adams of Glasgow, Scotland, considered the tumour was atypical microgliomatosis (reticulum cell sarcoma) of the brain. The late Dr. Brian Turner reported that the tumour was a sarcoma 'as that term is used by Professor Rubinstein'. The latter has recently classified such tumours as 'reticulum cell sarcoma — microglioma' (Rubinstein, 1972).

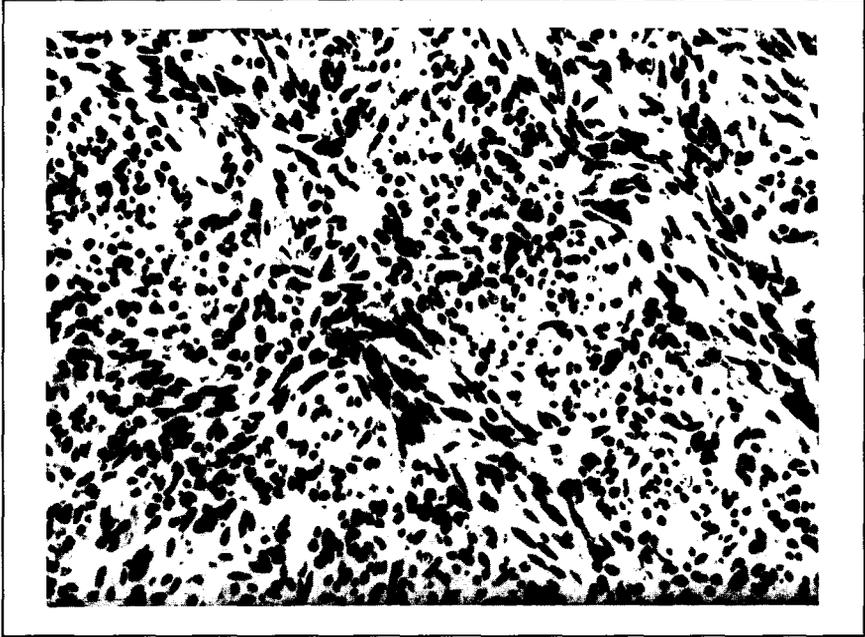


Fig. 1. A high-power view of the tumour showing the elongated nuclei and lack of visible cytoplasm.

Comment

The association of abnormal extracolonic growths with familial polyposis does not appear to be simply fortuitous. In considering this it is interesting to contrast the rarity of malignant change in the Peutz-Jeghers syndrome. In this syndrome diffuse polyposis occurs mainly in the small intestine and melanin spots are present in the buccal mucosa and lips (Bartholomew et al., 1957).

The significance of associated tumours in familial polyposis is unknown at present. It might be the manifestation of a single pleiotropic gene or a genetic linkage between two dominants. It could be argued that the case reported here represents a chance association between a central nervous system tumour and familial polyposis. While the authors admit this possibility, failure to document this case would have denied the pleas of earlier writers who requested such reports in order to establish more firmly the correlation between the two processes (Laberge et al., 1957).

Summary

Familial polyposis of the colon is associated with an increased incidence in other parts of the body of benign and malignant, soft and hard connective tissue tumours.

Clinical details and autopsy findings are reported in a 35-year-old man with familial polyposis who died from reticulum cell sarcoma (microglioma) involving his brain stem and upper spinal cord. While other central nervous system malignancy has been reported in association with familial polyposis, a sarcomatous tumour has not been previously described. In the clinical assessment of patients with familial polyposis the possibility should be considered of associated tumours in extracolonic sites, including the central nervous system.

Acknowledgements

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Preliminary Observations on the Pharmacokinetics of Methylphenobarbitone

*M.J. Eadie, F. Bochner, W.D. Hooper and J.H. Tyrer**

N-methylphenobarbitone is a barbiturate anticonvulsant, which is perhaps more widely used in Australia than elsewhere. It is believed to be less soporific than phenobarbitone, which is its main known metabolite in man. There is evidence that methylphenobarbitone has anticonvulsant properties in its own right (Craig and Shideman, 1971). The pharmacokinetics of phenobarbitone are reasonably well documented, but those of methylphenobarbitone have received little attention to date (Eadie and Tyrer, 1974).

In the present preliminary investigation, data were obtained regarding the following:

- 1) For patients receiving chronic methylphenobarbitone medication:
 - a) the relationship between plasma methylphenobarbitone concentration and methylphenobarbitone dose
 - b) the relationship between plasma phenobarbitone concentration and methylphenobarbitone dose
- 2) For subjects receiving single doses of methylphenobarbitone:
 - a) the kinetics of methylphenobarbitone and derived phenobarbitone in normal volunteers, and in epileptic patients
 - b) the effects of pretreatment with barbiturates, benzodiazepines or hydantoins on the kinetics of methylphenobarbitone and phenobarbitone

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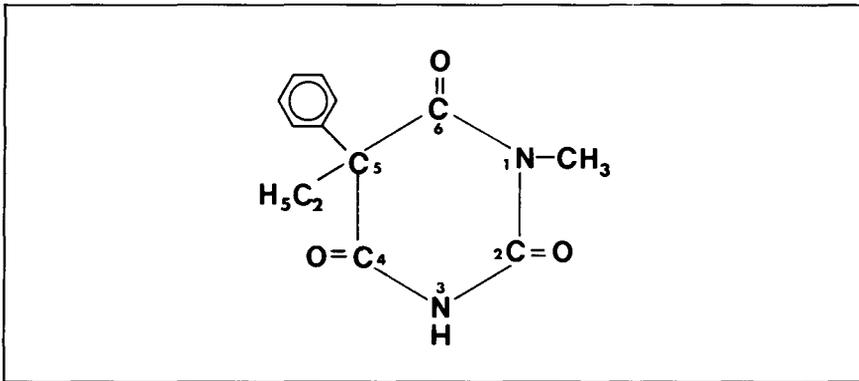


Fig. 1. Methylphenobarbitone.

Materials and Methods

Methylphenobarbitone and phenobarbitone concentrations were measured in plasma and urine as butyl derivatives by a gas liquid chromatographic method (Hooper et al., 1975).

Patients Receiving Chronic Medication

Plasma and urine methylphenobarbitone and phenobarbitone levels were measured in 77 epileptic patients who had taken methylphenobarbitone in constant dosage for at least 1 month, and who were therefore presumed to be in a steady-state as regards the drug at the time of measurement. The patients were collected from a number of sources; there was no evidence suggesting inadequate compliance.

Single Dose Studies

8 subjects were studied. 2 were healthy volunteers and the other 6 were patients with epilepsy in whom treatment with methylphenobarbitone was indicated on clinical grounds. Details of the subjects, and of any concurrent therapy they were taking, are given in table I. All subjects (except subject 8) received an initial single oral dose of methylphenobarbitone as indicated in table I, and plasma levels of this drug, and the phenobarbitone derived from it, were then measured at intervals over several days. Subject 4 was given a second dose of methylphenobarbitone (600mg) 6 days after his first dose (400mg), and the series of plasma level measurements was then repeated. Subject 8 first received a single oral dose of 240mg of phenobarbitone and plasma levels of that drug were followed for 8 days. He then received 800mg methylphenobarbitone by mouth and plasma levels of drug and metabolite were

Table 1. Demographic data

Subject	Sex	Age	Diagnosis	Methylphenobarbitone dose (mg)	Concurrent or previous medication
1	M	35	Healthy volunteer	600	Nil
2	M	30	Healthy volunteer	800	Nil
3	M	62	Cerebrovascular disease	600	Nil
4	M	52	Post-traumatic epilepsy	400, 600	Nil
5	M	56	Cerebrovascular disease	200	Diazepam; phenoperidine; dexamethasone; prochlorperazine; atropine; phenobarbitone
6	F	62	Cerebrovascular disease	600	phenytoin; diazepam; nitrazepam; aspirin; clonidine
7	M	19	Idiopathic epilepsy	600	phenytoin; carbamazepine; clonazepam, methylphenobarbitone
8	M	62	Temporal lobe epilepsy	800	phenobarbitone ¹

¹ See text for explanation.

followed for another 8 days. In subjects 1, 2, and 7 urinary excretions of methylphenobarbitone and phenobarbitone after methylphenobarbitone administration were measured.

Plasma level data appeared to fit a one compartment open model (Gibaldi and Perrier, 1975), and were analysed in terms of the parameters of this model for which

$$C_t = \frac{k_{abs}FX_0}{(k_{abs}-k)V_D} (e^{-kt}-e^{-kt_{abs}})$$

where

- C_t = plasma drug concentration at time t
 k_{abs} = absorption rate constant
 k = elimination rate constant
 x_0 = dose
 F = fraction of dose absorbed
 V_D = apparent volume of distribution

Post-absorption phase plasma level data were analysed by least squares linear regression analysis after semi-logarithmic transformation. A Hewlett-Packard programmable calculator was used to derive a value for k , from which the elimination half-life ($T_{1/2}$) was calculated, using the relationship

$$T_{1/2} = \frac{\log_e 2}{k}$$

Areas under the plasma level curves (AUC) over the durations of the measurements were determined by trapezoidal rule integration. Areas under the curves, from the last measurement to infinity, were determined from the formula (Gibaldi and Perrier, 1975)

$$AUC_t^\infty = \frac{C_t}{k}$$

Clearances were determined from the relationship

$$\text{clearance} = \frac{x_0 F}{AUC_0^\infty}$$

taking into consideration individual body weights (where known) and assuming that F had a value of 1, i.e. the drug was completely bioavailable. Apparent volumes of distribution (V_D) were calculated on the basis of the equation

$$V_D = \frac{\text{clearance}}{k}$$

Because of the length of the study in each subject, and the consequent desire to carry out as few venepunctures as possible, it was impossible to obtain sufficient data points soon after drug intake to permit accurate calculation of absorption parameters. The time at which the peak plasma methylphenobarbitone level occurred was read from the plasma level time curve. Time to attain maximum plasma level of derived

phenobarbitone was determined from the experimental data, and the approximate time of appearance of derived phenobarbitone was determined by visual fitting of a back-extrapolation of the rising phase of the plasma phenobarbitone level data to the time axis. The apparent elimination rate of the derived phenobarbitone was calculated by least squares linear regression after semi-logarithmic transformation of the data. However, the elimination rate constants calculated are likely to be lower than the true figures, because phenobarbitone may have still been forming from traces of methylphenobarbitone during the apparent elimination phase.

In the case of subject 8, after the initial oral administration of 240mg of phenobarbitone, absorption, distribution and elimination parameters were calculated.

Results

Steady-state Methylphenobarbitone and Phenobarbitone Data

Steady-state plasma methylphenobarbitone levels for 77 patients are plotted against methylphenobarbitone dose in figure 2. The linear regression line is statistically significant, with a coefficient of determination of .127. However, when plasma phenobarbitone level is plotted against methylphenobarbitone dose in the same 77 persons (fig. 2), the fit of the points to the regression is better (coefficient of determination = .475). Thus plasma phenobarbitone levels correlate better with methylphenobarbitone dose than do plasma levels of methylphenobarbitone itself.

Plasma phenobarbitone levels are plotted against methylphenobarbitone levels in figure 3. The relation between the two is better fitted by a parabolic regression with a coefficient of determination of .362 than by a linear regression ($r^2 = .302$). Over the range of plasma phenobarbitone levels of 10 to 20 μ g/ml, plasma phenobarbitone:methylphenobarbitone levels tend to be in the ratio 10:1 to 7:1.

A multiple variable linear regression analysis showed no statistically significant effect of phenytoin, carbamazepine or sulthiame dosage on the relation between steady state plasma methylphenobarbitone level and methylphenobarbitone dose, nor on the relation between steady state plasma phenobarbitone level and methylphenobarbitone dose. The following values were obtained for the coefficients of multiple variable linear regression equations of the form,

$$y = a + bx_1 + cx_2 + dx_3 + ex_4$$

- where y = plasma methylphenobarbitone, or plasma phenobarbitone, level in μ g/ml
- x_1 = methylphenobarbitone dose, in mg/kg/day
- x_2 = phenytoin dose, in mg/kg/day
- x_3 = carbamazepine dose, in mg/kg/day
- x_4 = sulthiame dose, in mg/kg/day

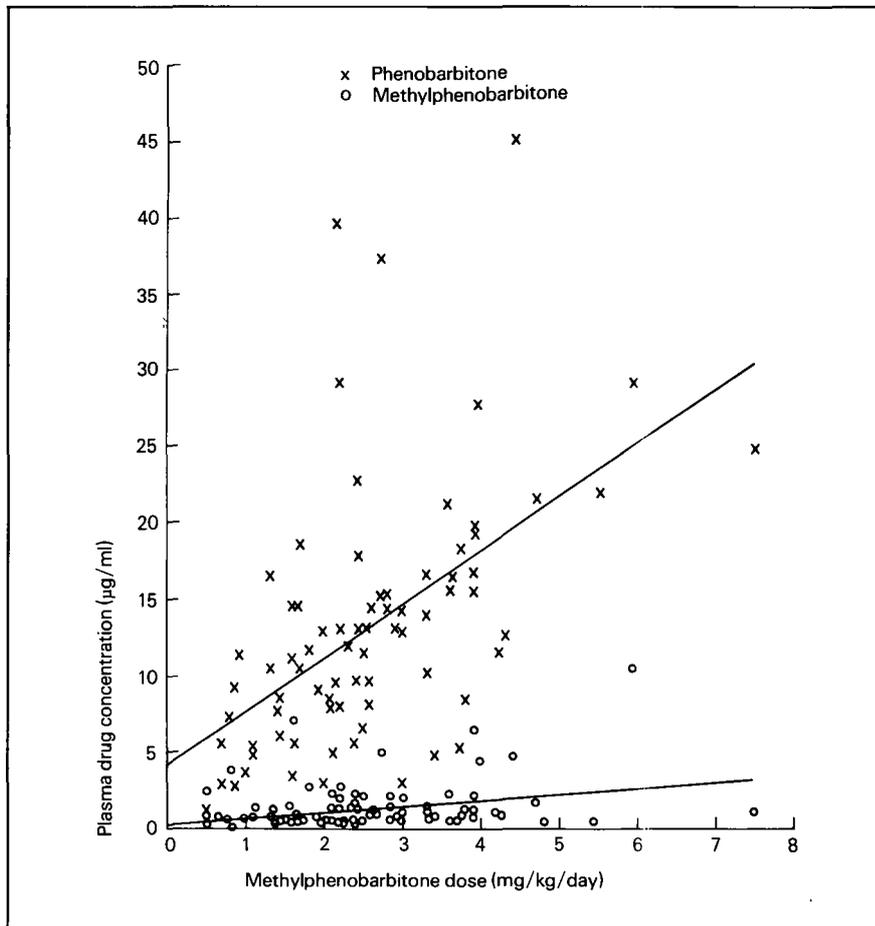


Fig. 2. Linear regressions for the relation between steady-state plasma levels of methylphenobarbitone and phenobarbitone, and methylphenobarbitone dose, in 77 subjects.

For plasma methylphenobarbitone levels

	r	P
a = 1.884	—	—
b = 0.239	.277	< .05
c = -0.194	-.230	N.S.
d = -0.037	-.011	N.S.
e = -0.049	-.149	N.S.

and for plasma phenobarbitone levels

	r	P
a = 9.754	—	—
b = 3.066	.580	< .001
c = -0.759	-.105	N.S.
d = -0.281	.090	N.S.
e = -0.205	-.153	N.S.

Single Dose Studies

For clarity of presentation, the subjects have been divided into two groups — those who had no medication immediately prior to the present study, and those who had been taking other drugs (table I). Subject 4 appears twice in the table because he

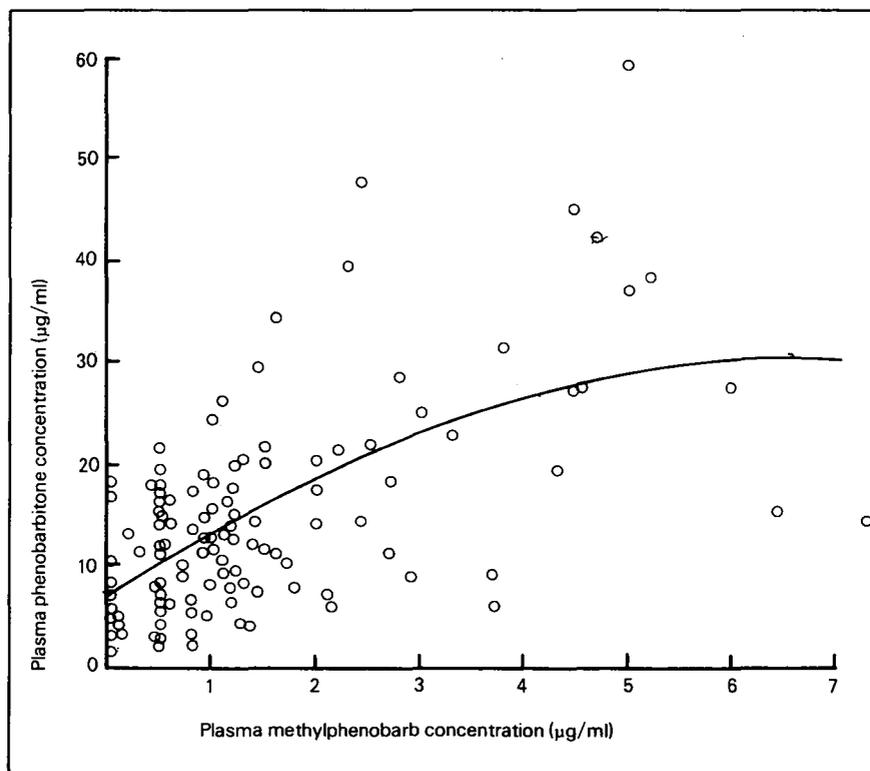


Fig. 3. Correlation between simultaneous steady-state plasma levels of methylphenobarbitone and phenobarbitone.

Table II. Calculated pharmacokinetic parameters

Subject	Methylphenobarbitone						Derived phenobarbitone			
	T _{max}	k (h ⁻¹)	T _{1/2} (h)	V _D (L)	Cl (L ⁻¹ h)	AUC ¹ (mg L ⁻¹ h)	Appearance time (h) ²	T _{max}	K (h ⁻¹)	T _{1/2} (h)
1	26.5	.0091	76.3	144.7	1.32	0.759	24	103	.0054	127.3
2	7.0	.0151	46.0	87.8	1.33	0.754	15	87	.0048	143.5
3	3.0	.0181	38.3	106.8	1.93	0.517	6	71	.0042	166.1
4a	4.5	.0197	35.2	142.4	2.81	0.356	18	—	—	—
<i>Mean</i>	10.3	.0155	49.0	120.4	1.85	0.597	15.8	87	.0048	145.6
<i>SD</i>	11.0	.0047	18.8	27.8	.70	0.196	7.5	16	.0006	19.5
4b	3.5	.0371	18.7	96.7	3.59	0.279	—	72	.0072	96.1
5	3.0	.0408	17.0	48.6	1.98	0.504	—	—	—	—
6	7.0	.0279	24.8	149.5	4.17	0.240	0	55	.0103	67.3
7	4.5	.0531	13.1	163.4	8.67	0.115	3	49	—	—
8	2.5	0.0284	24.4	245.7	6.98	0.143	12	172	0.273	25.4
<i>Mean</i>	4.1	0.0375	19.6	140.8	5.08	0.256	5.0	87	.0149	62.9
<i>SD</i>	1.8	0.0104	5.0	74.2	2.70	0.154	6.2	57	.0108	35.6
<i>Comparison of means</i>										
't'	1.256	3.893	3.400	0.514	2.302	2.927	2.003	0.0000	1.619	3.533
p	> 0.20	< 0.01	< 0.02	> 0.60	> 0.05	< 0.05	> 0.05	—	> 0.20	< 0.025

1 AUC normalised for dose.
2 Graphically determined as described in text.

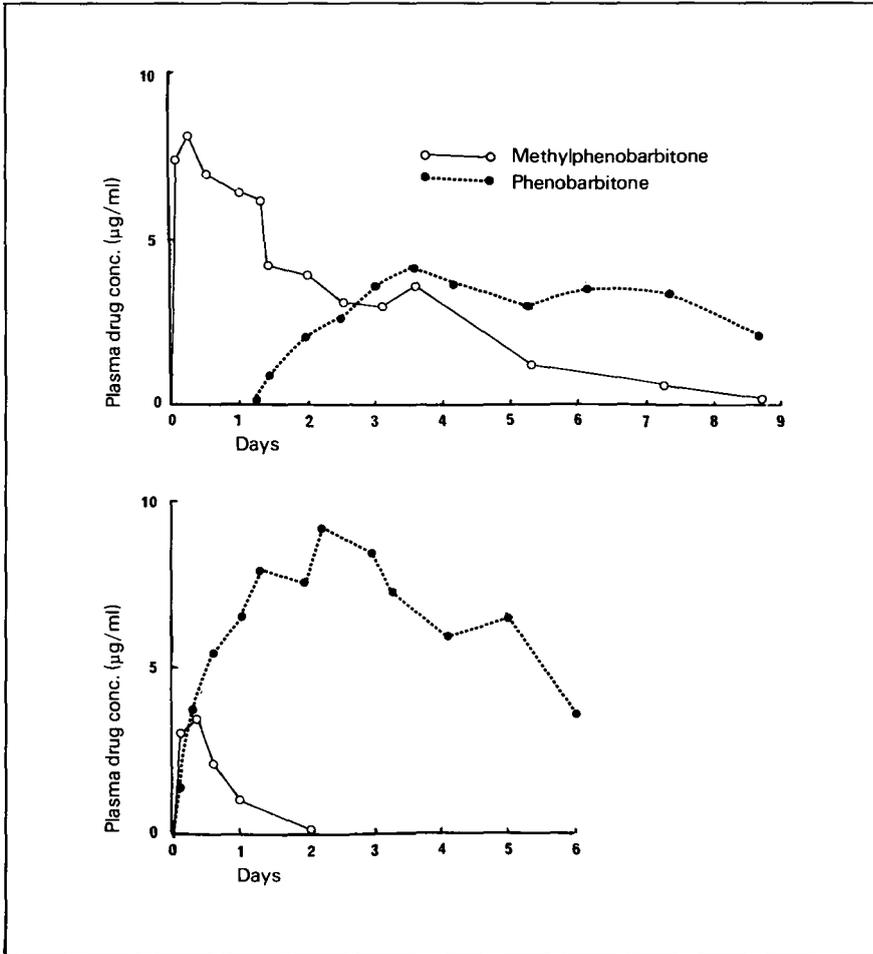


Fig. 4. Time courses of methylphenobarbitone and phenobarbitone plasma levels for subject 2 (no pretreatment) and subject 6 (pretreated).

had no medication prior to the initial dose of methylphenobarbitone (4a), but was obviously pretreated in relation to the second dose (4b). Similarly subject 8 falls into the pretreated category because of the prior administration of phenobarbitone. The plasma level-time courses for a subject from each group are shown in figure 4. The derived pharmacokinetic parameters for subjects 1 to 8 are shown in table II. The principal differences between the two groups are:

- 1) The faster elimination of methylphenobarbitone in pretreated patients ($p < 0.05$)

- 2) The greater clearance of methylphenobarbitone in pretreated patients ($0.05 < p < 0.1$), in the presence of similar values for V_D
- 3) The tendency to earlier appearance of derived phenobarbitone in pretreated patients ($0.05 < p < 0.1$).

Studies on Subject 8

The time course of plasma drug levels in this subject is set out in figure 5. Because of the sequence in which phenobarbitone and methylphenobarbitone were given, it was possible to calculate pharmacokinetic parameters for both drugs in this subject. The elimination of directly administered phenobarbitone was slower than that for methylphenobarbitone ($T_{1/2}$ values 48.7 hours and 24.4 hours respectively), its apparent volume of distribution was lower (25.9 litres to 246 litres), and its clearance less (0.37 to 6.98L/h). In this subject sufficient data were available to allow calculation of absorption kinetics of phenobarbitone, which showed an absorption half-life of 1.4 hours. When 240mg of phenobarbitone were administered, the AUC_0^∞ was 565mg/litres/h. The AUC_0^∞ of phenobarbitone following 800mg methylphenobarbitone was 975mg/litres/h. Thus in this instance there was an apparent formation of approximately 52mg of phenobarbitone from each 100mg of methylphenobarbitone administered.

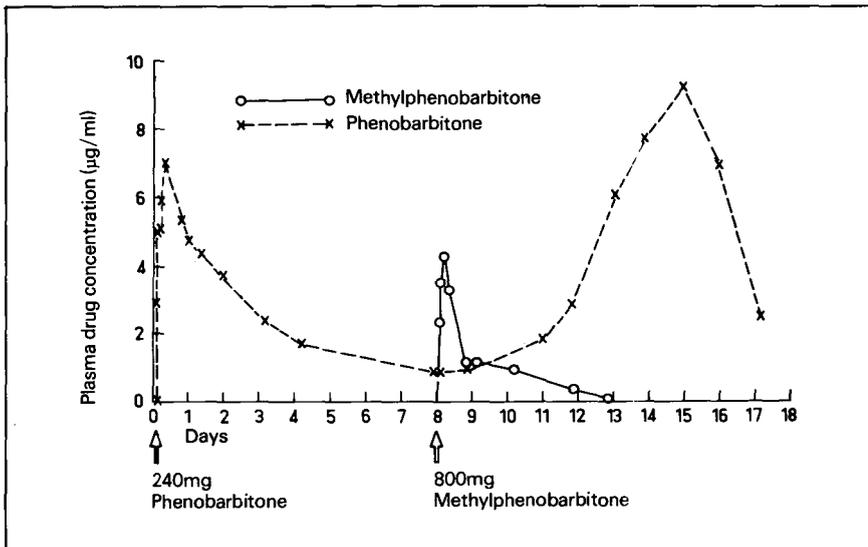


Fig. 5. Time courses of plasma concentrations of methylphenobarbitone and phenobarbitone in subject 8 who, on day 0, took 240mg phenobarbitone, and on day 8 took 800mg methylphenobarbitone.

Table III. Urinary excretions of methylphenobarbitone and phenobarbitone

Subject	Methylpheno- barbitone dose (mg)	Duration of study (h)	Cumulative urine excretion (mg)	
			Methylpheno- barbitone	Pheno- barbitone
1	600	200	18	52
2	800	200	20	90
7	600	75	10	145

Urine Excretion Data

Urine excretion of methylphenobarbitone and phenobarbitone was measured in subjects 1, 2 and 7. The results are summarised in table III. It may be seen that excretion of unchanged drug, together with its major known metabolite, accounted for (respectively) a minimum of 2%, 14%, and 25% of the total elimination of methylphenobarbitone (assuming complete bioavailability of the latter).

Discussion

The single dose studies have led to a number of conclusions, some of which must be regarded as tentative in view of the small number of subjects and the underlying assumptions inevitable in a clinical opportunistic study of this nature. Perhaps the most interesting observation was the differences in the clearance and elimination rate of methylphenobarbitone between the pretreated and untreated patient groups. It would appear that pretreatment with anticonvulsants or sedatives was associated with an increased clearance of methylphenobarbitone and a more rapid appearance of phenobarbitone. An attractive postulate to explain this observation is that pretreatment has resulted in induction of hepatic drug metabolising enzymes. Although there seems to have been little study of induction of demethylation pathways, there is evidence that diazepam, which is extensively N-demethylated, can induce the enzymes responsible for its own metabolism (Kanto et al., 1974). Such induction may account for the high clearance and more rapid appearances of phenobarbitone in the patients pretreated with diazepam. The induction of other metabolic pathways (e.g. aromatic hydroxylation) may also in part explain the increased clearance of methylphenobarbitone. Subject 8 who was pretreated with phenobarbitone only, showed the greater clearance of methylphenobarbitone which characterised the pretreated group. For a more adequate understanding of the metabolism of methylphenobarbitone, it would be necessary to measure the urinary excretion of p-hydroxyphenobarbitone and the

presumptive metabolite, p-hydroxymethylphenobarbitone. The low urinary recovery of methylphenobarbitone and phenobarbitone in persons receiving methylphenobarbitone (table III) also highlights the need to measure other metabolites in urine.

There was no appreciable difference between the two groups as regards apparent volumes of distribution. This further strengthens the hypothesis that the increased clearance of methylphenobarbitone in the pretreated group was due to enhanced elimination, as is evident in the difference in elimination half-life (49h in untreated compared with 20h in treated group). Only in subject 8 was it possible to calculate the volume of distribution for phenobarbitone. His volume of distribution of methylphenobarbitone was some 10 times that of phenobarbitone (if it be assumed that their bioavailabilities were equivalent). It is known that methylphenobarbitone is more lipid soluble than phenobarbitone (Brodie et al., 1960). Possibly methylphenobarbitone is accumulated in body lipid, including myelin. This may result in methylphenobarbitone having a higher brain to plasma level ratio than phenobarbitone.

The mean ratio of phenobarbitone to methylphenobarbitone plasma levels at steady-state (7 to 10:1; fig. 3) is probably largely a reflection of the different distribution volumes and elimination rates of the two substances. Because the two compounds are simultaneously present in plasma and probably in brain, it is impossible to estimate their relative anticonvulsant efficacies in man.

Data obtained from plasma level measurements in the 77 patients in the steady-state (fig. 2) suggest that to achieve therapeutic concentrations of phenobarbitone, methylphenobarbitone dosage of 3 to 4mg/kg/day is required. This is in contrast to the phenobarbitone dosage of 1 to 2mg/kg/day required to achieve similar phenobarbitone levels (Eadie et al., 1977). Although no data are available concerning the comparative bioavailabilities of the two drugs, this difference in dosage requirement probably reflects the fact that methylphenobarbitone is partly eliminated by processes which do not involve phenobarbitone formation.

There are at least two reasons why phenobarbitone plasma levels correlate better with methylphenobarbitone dose than do methylphenobarbitone levels. Firstly, the half-life of methylphenobarbitone is considerably shorter than that of phenobarbitone. Therefore the interdosage fluctuations of methylphenobarbitone may well be greater than those of phenobarbitone. Thus the time of blood collection may be more important for methylphenobarbitone than for phenobarbitone. Our inability to control the collection of samples in relation to dosing time may have contributed to the greater scatter in the methylphenobarbitone concentrations. The second possibility is the fact that methylphenobarbitone levels were usually only 10 to 15% of simultaneous phenobarbitone levels. It is difficult to arrange assay conditions to achieve comparable relative accuracies for simultaneous measurements which differ by such an order of magnitude. Therefore greater experimental error in measuring methylphenobarbitone levels may explain the relatively better fit of plasma phenobarbitone levels to a regression line.

Although the preliminary kinetic studies described above suggested the possibility that intake of other anticonvulsants might induce the demethylation of methylphenobarbitone, there was no statistical evidence that steady-state plasma methylphenobarbitone or phenobarbitone levels were altered by the concurrent chronic intake of other anticonvulsants. This finding may reflect the possibility that, by the time the steady-state has been reached, methylphenobarbitone (or the phenobarbitone derived from it) has already maximally induced the hepatic drug metabolising enzyme system.

The present study has not elucidated the relative anticonvulsant roles of methylphenobarbitone and phenobarbitone. However, it seems reasonable in the chronic dosing situation to regard methylphenobarbitone as primarily a precursor of phenobarbitone. Thus prescribing recommendations for methylphenobarbitone should largely be based on a knowledge of the plasma concentrations of phenobarbitone.

Summary

The pharmacokinetics of methylphenobarbitone and phenobarbitone were studied following the administration of methylphenobarbitone on a chronic basis in 77 patients, and after a single dose to each of 4 subjects who had received no other drugs and 4 subjects who had been pretreated with various anticonvulsants and other agents.

At steady-state, plasma phenobarbitone concentrations correlated better with methylphenobarbitone dose than did plasma methylphenobarbitone concentrations. In this group the ratio of plasma phenobarbitone level to plasma methylphenobarbitone level was in the range of 7 to 10:1.

In the single dose studies, mean values of elimination rate constant (0.0155h) and clearance (1.85L/h) for untreated subjects were different from those for the pretreated subjects (0.0375h and 5.10L/h), while the apparent volumes of distribution did not differ significantly between the two groups (120.3L vs 140.8L). The data are interpreted as most probably indicating induction of hepatic microsomal enzymes in the pretreated group.

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Sodium Valproate: Dose-Plasma Level Relationships and Interdose Fluctuations

*F.J.E. Vajda, G.W. Mihaly, J.L. Miles, P.M. Morris and P.F. Bladin**

Plasma measurements of anticonvulsant concentrations have become an accepted guide to the management of epileptic patients (Eadie, 1976). These measurements provide a guide to dose adjustments in anti-epileptic therapy, and enable a better definition of the therapeutic range. There is a wide inter-individual variation between the doses required to achieve the same order of plasma concentration of most anticonvulsant drugs. Sodium valproate conforms to this pattern (Loisseau et al., 1975; Klotz, 1977; Wulff et al., 1977; Vajda et al., 1978) but, although inter-individual variations are considerable, dose-plasma level relationships in individual patients treated on a chronic basis have not previously been examined closely.

Anticonvulsants which have a relatively long half-life, such as phenytoin ($T_{1/2}$ 20 to 40 hours) exhibit only minor fluctuations in plasma concentrations between administration of consecutive doses (Wilder et al., 1975). Sodium valproate has a shorter half-life ranging from 4.0 to 10.0 hours in chronically treated epileptics (Loisseau et al., 1975; Richens et al., 1976; Espir et al., 1976). It is of importance to assess the change in plasma concentrations between subsequent doses to establish whether the time of sampling and the size of the dose have a major bearing on the plasma levels. If the fluctuation in plasma levels is considerable, then the range of levels regarded as therapeutic needs to be defined in terms of minimum levels measured immediately before the next dose.

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Table 1. Patient details and concomitantly administered anticonvulsants in 14 chronic epileptics treated with sodium valproate

Patient number	Age	Weight (kg)	Sex	Other medication(s)
1	31	63	F	—
2	8	28	F	Phenytoin, clonazepam
3	31	75	F	Phenytoin
4	32	66	M	—
5	16	65	F	—
6	46	65	M	—
7	18	80	M	Phenytoin, carbamazepine
8	24	61	M	Phenytoin
9	31	70	M	Phenytoin, carbamazepine
10	27	81	M	Phenytoin, diazepam
11	23	67	M	Carbamazepine, diazepam
12	35	75	M	Phenytoin, clonazepam
13	41	74	M	Phenytoin, clonazepam
14	20	80	M	Carbamazepine

Materials and Methods

Dose-Plasma Level Relationships

14 chronic epileptic patients comprising 9 males and 5 females of mean age 27.4 (\pm 2.6 SEM) years were treated with sodium valproate and received doses ranging from 400 to 4000mg/day in divided doses. Each patient's dose was adjusted in an attempt to produce plasma levels in the desirable therapeutic range of 50 to 100 μ g/ml (Loisseau et al., 1975). 10 of the 14 patients also received one or more of the following anticonvulsants: phenytoin, carbamazepine, diazepam or clonazepam (table I).

Blood samples from each patient were taken for plasma sodium valproate determinations, in the outpatient department of a general hospital, before the start of sodium valproate therapy; the procedure was repeated, preceding the midday dose, at regular intervals. A minimum period of 4 days was allowed to elapse after the last change in a patient's dose of sodium valproate, before a blood sample was taken. This

allowed steady-state plasma levels to be achieved. Subsequently, during the course of therapy, plasma sodium valproate determinations were performed on each patient at several dose levels. Additional pre-dose blood samples were obtained from each patient whilst on the same dose, when they arrived for subsequent outpatient visits. The plasma was separated by centrifugation and stored at -4°C until assayed. Plasma sodium valproate was measured by a modification of Chard's gas chromatographic method (Vajda et al., 1978).

Inter-dose Fluctuations

Plasma levels were measured from samples obtained at hourly intervals after a single dose during chronic treatment, and the results of measurements were plotted to express the fluctuation of plasma valproate concentrations between 2 subsequent doses. Patients were shown to have achieved steady-state plasma levels by daily plasma level monitoring for several days prior to this study being undertaken.

11 of the 14 patients received sodium valproate 4 times a day, at 6-hourly intervals, 2 patients (numbers 3 and 4) were treated on a thrice daily regimen whilst

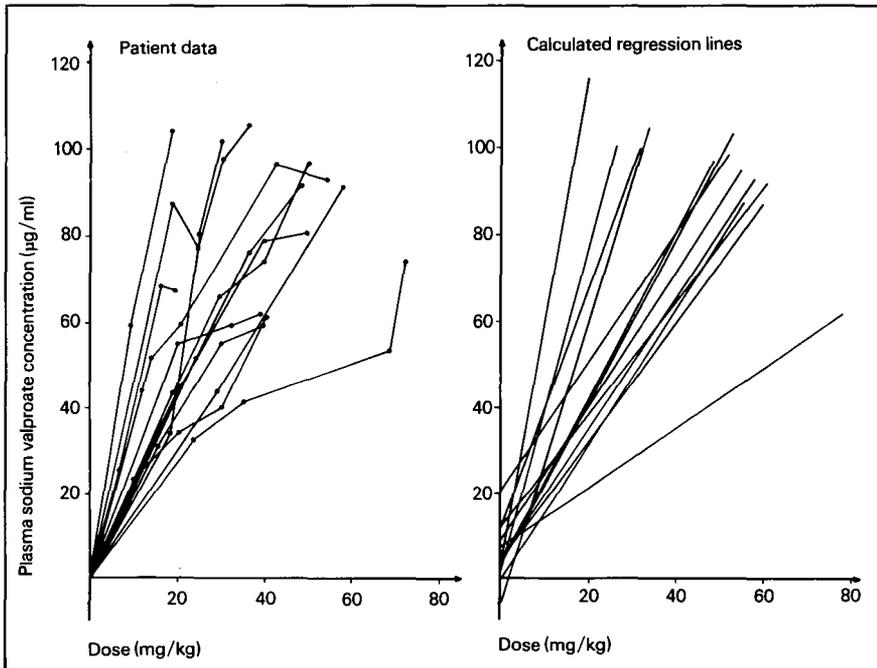


Fig. 1. Individual plasma sodium valproate concentration ($\mu\text{g/ml}$) to dose (mg/kg/day) relationships for the actual patient data and for the calculated regression lines.

Table II. Individual regression line equations for the relationship between plasma level ($\mu\text{g/ml}$) and daily dose (mg/kg). Correlation co-efficient (r), the number of data points in each regression analysis and the levels of statistical significance are also shown

Patient number	$y = A x + B^1$	Correlation coefficient (r)	Number of data points	Significance
1	$y = 3.78 x + 1.45$	0.9869	4	$p < 0.05$
2	$y = 1.60 x - 0.58$	0.9997	3	$p < 0.05$
4	$y = 2.87 x + 11.01$	0.9423	5	$p < 0.05$
5	$y = 5.72 x + 2.25$	0.9972	3	$p < 0.05$
6	$y = 3.32 x - 6.60$	0.9577	4	$p < 0.05$
7	$y = 1.42 x + 3.54$	0.9795	5	$p < 0.01$
8	$y = 1.58 x + 8.42$	0.9164	4	$p < 0.10$
9	$y = 0.86 x + 7.15$	0.9488	5	$p < 0.05$
10	$y = 1.55 x + 4.08$	0.9790	4	$p < 0.05$
11	$y = 1.98 x + 2.07$	0.9963	4	$p < 0.01$
12	$y = 1.31 x + 11.87$	0.9568	6	$p < 0.01$
13	$y = 1.52 x + 20.20$	0.9137	6	$p < 0.05$
14	$y = 1.89 x + 3.10$	0.9930	5	$p < 0.01$

- 1 In the regression line $y = A x + B$ where:
 y : sodium valproate concentration ($\mu\text{g/ml}$)
 A : slope
 x : sodium valproate dose (mg/kg/day)
 B : intercept.

patient number 12 was treated 5 times daily. A venous blood sample was withdrawn just prior to the midday dose, then each patient's usual dose was given and hourly blood samples were taken for the next 6 hours. The scheduled evening dose was administered at the conclusion of the 6 hour collection.

Results

Dose-Plasma Level Relationships

Figure 1 represents the sodium valproate dose (mg/kg/day) and valproate plasma level ($\mu\text{g/ml}$) relationships in individual patients. These are shown as calculated mean plasma levels on each given dose and as computed regression lines utilising the data for each patient. Patient number 3 was excluded from this aspect of the study because of poor attendance as an outpatient and consequently few plasma concentration determinations.

The daily dose of sodium valproate ranged from 6.3mg/kg to 71.4mg/kg whilst mean plasma concentrations ranged from 23.0 μ g/ml to 105.6 μ g/ml. Although there is a wide scatter of calculated regression lines the individual relationships between plasma level and dose are close to linearity. The data point representing zero plasma concentration at zero dose was included in the linear regression analysis because samples were assayed for sodium valproate in each patient before the start of drug therapy.

The calculated equations describing these regression lines are shown in table II. Correlation co-efficients, number of data points in each regression calculation and the level of statistical significance is also contained in table II. Correlation co-efficients

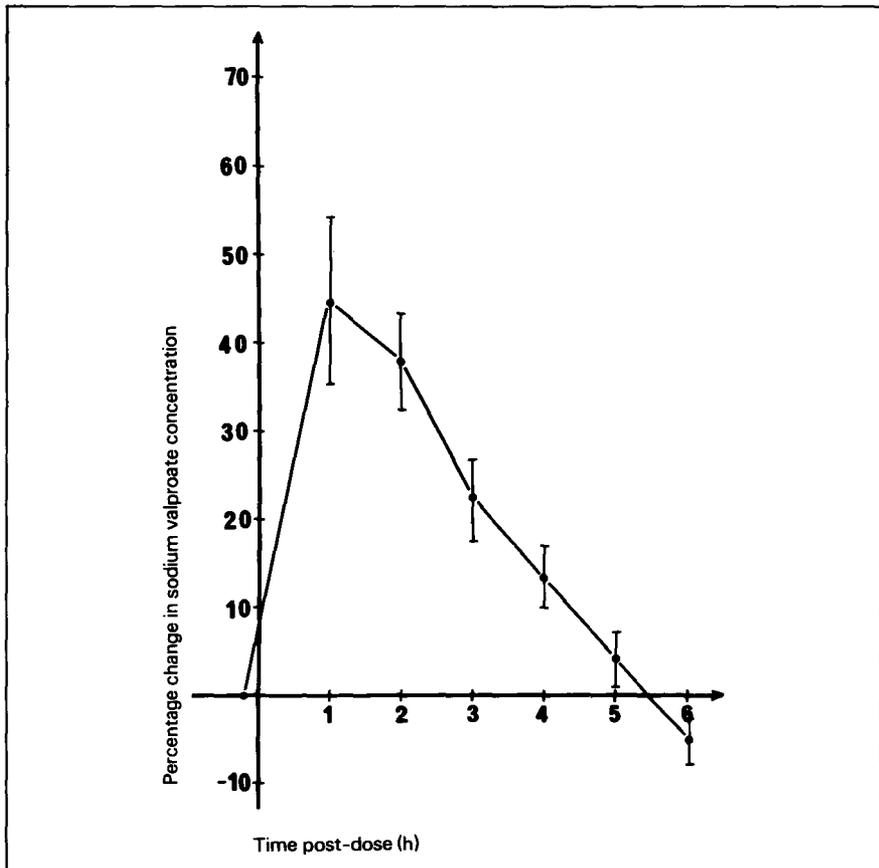


Fig. 2. The mean percentage change in post-dose sodium valproate concentrations (\pm SEM) following a single administration of the usual dose of sodium valproate.

Table III. The hourly percentage change in plasma levels following the administration of the usual sodium valproate dose is listed for each patient. The weight, daily dose, dose at the time of the serial and the pre-dose plasma level is also shown

Patient number	Weight (kg)	Daily dose (mg/kg)	Dose at time of serial study (mg)	Pre-dose plasma valproate level ($\mu\text{g/ml}$)	Change in plasma valproate concentrations (%)						
					Pre-dose	1.0h	2.0h	3.0h	4.0h	5.0h	6.0h
1	63	6.3	100	28.4	0	42.2	29.2	17.3	13.0	2.8	-12.0
2	28	28.6	200	82.0	0	32.1	17.6	10.4	2.6	-4.9	-12.8
3	75	16.0	400	78.8	0	26.6	41.2	20.6	13.6	5.7	9.4
4	66	24.2	400	89.9	0	20.7	19.7	16.0	10.5	1.8	-1.8
5	65	18.5	400	106.2	0	24.9	25.4	25.3	33.3	14.8	12.1
6	65	24.6	400	84.2	0	17.9	29.9	23.9	15.7	14.5	5.0
7	80	20.0	400	32.7	0	153.5	91.1	68.5	40.4	25.1	9.1
8	61	39.3	600	68.5	0	35.3	16.2	-2.6	-7.0	-10.2	-26.7
9	70	34.3	600	42.0	0	57.1	66.2	40.0	27.4	14.5	2.8
10	81	39.5	800	57.0	0	73.7	45.6	32.5	15.6	2.6	-9.0
11	67	47.8	800	89.7	0	31.8	27.8	18.6	6.6	-1.3	-9.5
12	75	53.3	800	84.1	0	37.3	28.4	6.2	-5.4	-12.1	-25.6
13	74	54.1	1000	81.2	0	18.0	57.0	19.1	11.1	5.8	1.5
14	80	50.0	1000	76.6	0	51.8	34.6	14.4	10.3	-1.7	-14.4
<i>Mean</i>	68	32.6	564	71.5	0	44.5	37.9	22.2	13.4	4.1	-5.1
SEM	4	4.1	75	6.2	0	9.4	5.6	4.5	3.5	2.8	3.3

ranged from 0.9137 to 0.9997 and the slope of the regression lines ranged from 0.86 to 5.72. All regression lines were found to be statistically significant.

Inter-dose Fluctuations

Table III contains details of the starting (pre-dose) sodium valproate plasma levels, and the percentage change in sodium valproate plasma levels at hourly intervals for each chronically treated patient following the administration of a single dose of the drug. The changes in peak sodium valproate plasma levels ranged from 20.7 to 153.5%. In all cases valproate plasma levels returned close to the starting pre-dose value by the end of the 6-hour period.

The mean percentage change in sodium valproate plasma concentration in relation to time after a single dose is illustrated in figure 2. The changes in sodium valproate concentrations are most marked at 1 and 2 hours after the administration of the dose, thereafter falling rapidly to pre-dose values.

Discussion

The individual dose-plasma level relationships demonstrate that each patient exhibited a linear dose-plasma level response. The large differences in slopes of the regression lines suggest that there is a continuous variation in the metabolic and distribution characteristics of sodium valproate between patients.

The considerable inter-individual variations in the relationship between dose and plasma level for sodium valproate have been described earlier (Vajda et al., 1978; Klotz, 1977; Wulff et al., 1977). In previous studies patients concomitantly received other anticonvulsant therapy. It was suggested by Richens et al. (1976) that a reduction in the steady-state plasma levels of sodium valproate resulted from metabolic enzyme induction by other concomitantly administered anticonvulsants. In part, the large variation in the regression lines may be attributed to the influence of enzyme induction.

Dose-plasma level relationships for individual patients have been examined for phenytoin (Bochner et al., 1972) and carbamazepine (Hooper et al., 1974). In both cases, the relationship between dose and plasma level was found to be non-linear since a 2-fold increase in the dose in a patient resulted in a greater than 2-fold increase in the plasma level. This effect was attributed to saturation of the metabolic handling of the drugs. In contrast, sodium valproate did not exhibit this characteristic in the concentration range that was examined (*viz* 20 to 100 µg/ml), suggesting that a proportional increase in plasma level can be expected to follow a dosage increment within the boundaries of the proposed therapeutic range of 50 to 100 µg/ml.

Following the administration of a dose of sodium valproate to patients chronically treated with the drug, plasma levels increased by a mean 44.5% (SEM =

9.4). This was reached between 1 and 2 hours after the administration of a dose and was followed by a rapid decline in plasma level which returned to values close to pre-dose starting levels after 6 hours.

Recent work by Loisseau et al. (1975) showed that using post-dose samples for plasma sodium valproate measurements yielded a variable plasma level and poor correlation with therapeutic efficacy. This may be due to variations in absorption, the effects of food and individual variation in rates of stomach emptying. The use of post-dose peak levels is likely to result in greater and more unpredictable fluctuations in plasma levels than minimal (pre-dose) plasma sample measurements.

The large degree of fluctuation in plasma levels of sodium valproate between doses would indicate that the measurement of pre-dose plasma levels may be preferable to guide the clinical management of epileptic patients. In addition, giving the drug 4 times daily may avoid untoward effects resulting from excessively high peak plasma levels that would be achieved if larger doses were administered less frequently.

Summary

Individual dose-plasma level relationships were studied in 14 chronically treated epileptics, 10 of whom were concomitantly receiving other anticonvulsants besides valproate. Linear regression analysis showed each individual relationship to be linear with correlation co-efficients ranging from 0.9137 to 0.9997. A considerable inter-individual variation was found to exist in the slopes of the regression lines (range: 0.86 to 5.72). This may be the consequence of differences in absorption characteristics and metabolic handling of the drug. The results indicate that a proportional rise in plasma sodium valproate levels can be expected following dosage increments in an individual patient. Hourly plasma sodium valproate measurements for 6 hours between 2 successive doses, in the same group of patients, showed that the mean percentage change in post-dose peak plasma levels was 44.5%, and ranged from 20.7 to 153.5%. Plasma levels returned to values close to pre-dose starting levels 6 hours after the administration of a dose. The large degree of inter-dose fluctuation between doses indicates that it is preferable to use pre-dose plasma sodium valproate levels to guide the clinical management of epileptic patients.

Acknowledgements

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A Comparison of the Absorption of Phenobarbitone Given via the Oral and the Intramuscular Route

*J.K. Graham**

To prevent further seizures following an epileptic fit, a common practice used to be to give an intramuscular injection of 180mg of phenobarbitone.

As both diazepam (Hillestad et al., 1974) and phenytoin (Serrano et al., 1973) given intramuscularly as a single conventional dose, do not give plasma levels in the accepted anticonvulsant range it would seem reasonable to review phenobarbitone as an alternative drug.

The following study measured plasma levels reached in the first 4 hours or so after 180mg of phenobarbitone was given to 6 patients, and 120mg to 1 patient, to assess whether optimal plasma levels of phenobarbitone were reached in a reasonable time.

Materials and Methods

5 patients were loaded with phenobarbitone, using a single dose of 180mg in 4, and 120mg in 1 patient. Each of the 5 patients was loaded alternately by the intramuscular and oral routes, the order of the route of administration being randomised. Each patient was given the same dose on the 2 occasions, the interval between successive loadings varying from 4 to 7 days.

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Table 1. Particulars of patients and phenobarbitone dosage

Pat.	Age (years)	Sex	Epilepsy			Phenobarbitone, dose, route and interval
			type	duration	drug treatment (daily dose)	
A	34	M	Temporal lobe epilepsy	30yr	Phenytoin 460mg, carbamazepine 800mg, sulthiame 600mg	180mg IM, after 6 days, 180mg PO
B	40	F	Generalised epilepsy	10yr	Phenytoin 300mg	120mg IM, after 5 days, 120mg PO
C	41	M	Generalised epilepsy	1m	Phenytoin 300mg	180mg PO, after 4 days, 180mg IM
D	41	F	Generalised epilepsy	1m	Phenytoin 300mg	180mg PO, after 5 days, 180mg IM
E	56	M	Focal cortical epilepsy	4m	Phenytoin 700mg	180mg PO, after 7 days, 180mg IM
F	38	F	Acquired generalised epilepsy	37yr	Ethosuximide 750mg	180mg IM
G	33	F	Focal cortical epilepsy	16yr	Carbamazepine 600mg	180mg PO

1 further patient was given 180mg phenobarbitone orally and a second 180mg by intramuscular injection — both on a single occasion only. Details of the patients studied are given in table I.

The patients were asked to volunteer for the study and gave informed consent. Although some of the patients were already receiving other anticonvulsants (table I) this was accepted as being a likely situation in which patients would be loaded with phenobarbitone in clinical practice.

Samples of blood were taken at 0, 0.5, 1, 2, 3, 4 and 24 hours (approximately) after a single loading dose and assayed for plasma phenobarbitone level by gas liquid chromatography as described by Hooper et al. (1975).

Peak plasma levels reached in 4 hours were measured from the plots of plasma phenobarbitone levels against time following the single loading dose. The ratio of the amount of drug absorbed following oral administration compared to that after in-

tramuscular administration was obtained by the technique of cutting out and comparing the weights of the areas under the curve of the respective graphs.

Results

A typical graph of plasma phenobarbitone levels obtained following a single dose of 180mg of phenobarbitone given by the oral and the intramuscular routes is illustrated in figure 1.

Table II shows peak plasma phenobarbitone levels obtained following a single loading dose. Following oral administration, the mean plasma phenobarbitone level was 4.73mg L^{-1} whilst that following intramuscular administration was 3.51mg L^{-1} . The difference between these levels is not statistically significant.

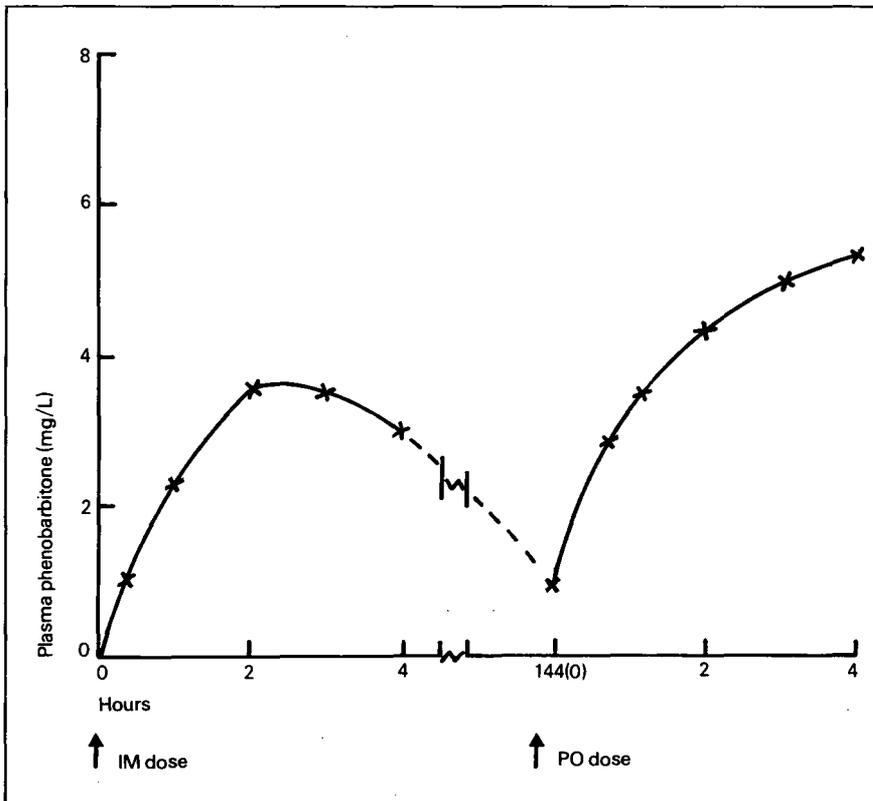


Fig. 1. Time course of plasma phenobarbitone levels after 180mg of the drug given by the intramuscular and oral routes, 144 hours apart.

Table II. Peak plasma values of phenobarbitone obtained with a single loading dose given intramuscularly and by mouth

Patient	Dose (mg/kg)	Plasma phenobarbitone (mgL ⁻¹)	
		PO dose	IM dose
A	2.2	4.4	3.7
B	1.76	3.15	3.85
C	2.53	4.45	4.7
D	2.09	4.9	0.9
E	2.37	4.9	3.7
F	2.86		4.2
G	2.77	6.55	

Table III. Comparison of weights of areas under the plasma level-time curves for the first 2 and 4 hours after single dose oral and intramuscular phenobarbitone (differences not significant)

Patient	Dose (mg/kg)	Time span (h)	Weight (mg)	
			PO	IM
A	2.2	0-2	213.5	195.0
		0-4	580.2	515.3
B	1.76	0-2	129	116.4
		0-4	281.4	234.1
C	2.53	0-2	227.2	214.8
		0-4	643.6	612.5
D	2.09	0-2	123.7	41.2
		0-4	447.9	41.2
E	2.37	0-2	35.3	151.1
		0-4	362.1	489.5

Table III shows a comparison of the weights of areas under the plasma level-time curves for oral and intramuscular single dose phenobarbitone administration. This gives an indication of the relative amount of drug absorbed via each route. There was no significant difference between the values for each route at either 2 or 4 hours.

During the study no patient had a further fit. Some patients, even at these peak plasma phenobarbitone levels, developed significant drowsiness which would cause some concern if the loading dose were to be increased.

Discussion

The doses of phenobarbitone given by the intramuscular route in this study were quite ineffective in achieving plasma levels generally recognised as being protective against epileptic seizures, unless of course the patient was already taking phenobarbitone. The accepted therapeutic range of phenobarbitone is 15 to 25mg L⁻¹ (Eadie and Tyrer, 1974).

The oral route of administration appeared to be at least as good as the intramuscular route in this study. However, if swallowing or gastric emptying were affected after a seizure, intramuscular administration might be necessary.

Summary

6 patients were given 180mg phenobarbitone, and 1 patient 120mg, and the plasma levels measured within the first 4 hours or so. These doses of phenobarbitone were quite ineffective in achieving, in a reasonable time, the levels generally recognised as being protective against seizures.

5 patients were loaded with phenobarbitone alternately via the oral and intramuscular routes to assess the relative absorption of phenobarbitone by each route. The oral route of administration appeared to be at least as good as the intramuscular, there being no significant difference between the two as judged by the peak levels of plasma phenobarbitone measured, or the amount of drug absorbed.

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Posterior Fossa Arachnoid Cysts: Two Case Reports

*G.H. Purdie and R.H.C. Rischbieth**

Arachnoid cysts or pouches, abnormal CSF or CSF-like fluid collections lined by arachnoid tissue, may occur at various sites in relation to the brain and spinal cord. Though rare, representing only 1% of Robinson's (1971) total brain space occupying lesions, they are protean in their manifestations. The site of predilection is the middle cranial fossa in relation to the sylvian fissure where they may produce a characteristic clinical syndrome. Males are affected more commonly than females and usual symptoms include headache, epilepsy and asymmetrical macrocrania. Mental development and neurological examination are frequently normal. Specific skull radiographic, angiographic and pneumoencephalographic findings are usually present.

Below the tentorium cysts are less common, Robinson (1971) reporting only 4 in the posterior fossa in a series of 25 arachnoid malformations. The common site is in relation to the large basal cisterns though they may arise in the cerebello-pontine angle simulating an acoustic neuroma. These cysts frequently obstruct the circulation of cerebrospinal fluid through the aqueduct, the 4th ventricle, or the surface subarachnoid pathways around the brain stem, leading to internal hydrocephalus. Presentation with sudden onset of headache and neck stiffness, suggesting subarachnoid haemorrhage or meningitis, may follow bleeding into the cyst or the subdural space.

The recent presentation of 2 cases (1 confirmed histologically) to the Queen Elizabeth Hospital provides a basis for discussing this interesting condition.

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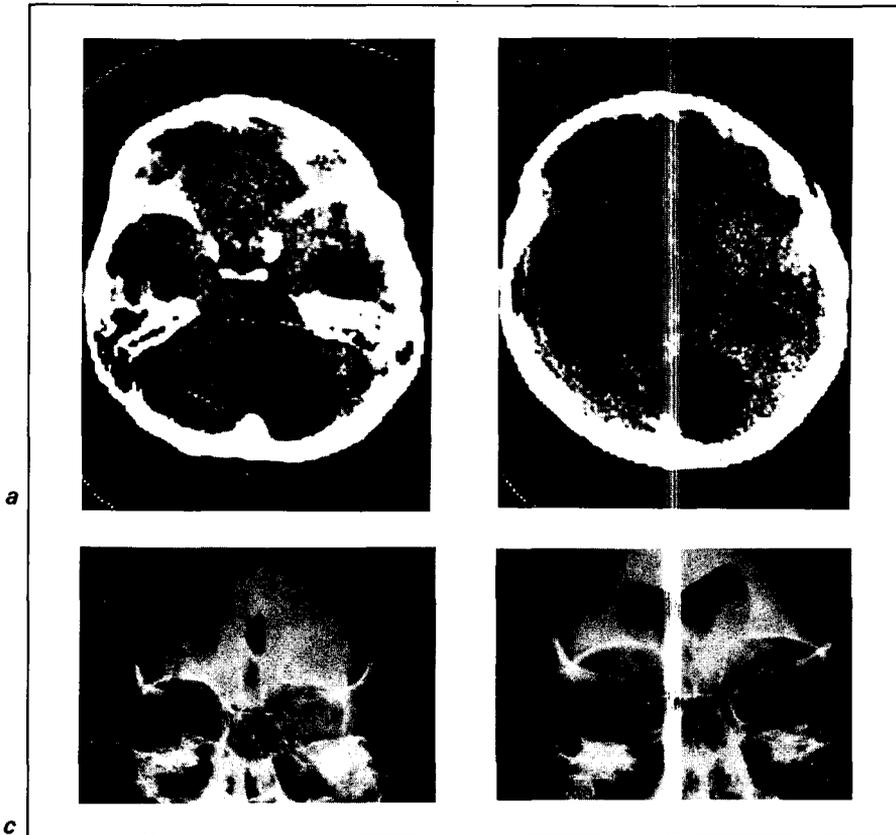


Fig. 1. a) Computerised axial tomography in a 13-year-old girl (Case 1) showing a posterior fossa cyst compressing the 4th ventricle and right temporal horn dilatation. b) Computerised axial tomography showing compression of the quadrigeminal cistern on the right. c) and d) PA views showing marked right temporal horn dilatation.

Case 1

Miss G.K., a 13-year-old school girl, was the first child of healthy Greek parents. Labour was markedly prolonged and difficult and at birth she was slow to breathe, lethargic and bruised. A congenital right squint and right torticollis were observed. At the age of 4 years she had her first generalised convulsion. Thereafter she continued to have frequent seizures which were often preceded by repetitive blinking of the right eye and clutching of the right side of the forehead with one or both hands. By 8 years of age she complained of pre-ictal right-sided headache and an ascending epigastric aura. In a recently witnessed seizure she was observed to put her right hand to her face, her eyes became glazed and she ceased talking. She then lurched forward and wandered about the room in an automatic fashion for one and a half minutes, unresponsive to spoken commands. Many anticonvulsants have been unsuccessful in controlling the seizures. In November, 1977 complex partial seizures were occurring daily and so she was admitted to hospital for stabilisation and further investigation.

General examination was normal. Neurological examination revealed a girl of low intelligence with a right convergent squint. There was a minimal left facial paresis. Power, tone, sensation and reflexes were normal. There was no gait abnormality but mild heel-toe ataxia and left upper limb dysmetria were present.

Skull radiographs and a left carotid angiogram were normal. Electroencephalography showed a nonspecific cerebral dysrhythmia but sphenoidal studies showed independent right sphenoidal and right mid-temporal spike and slow wave activity. A CT head scan showed marked right temporal horn dilatation, and a cystic posterior fossa lesion causing flattening of the 4th ventricle and compression of the quadrigeminal cistern on the right (fig. 1a and b). Air encephalography failed to show communication between the mildly dilated ventricular system and the cyst, but confirmed the CT findings (fig. 1c and d).

Though it was difficult to relate the epilepsy to the posterior fossa cystic lesion it was considered that the latter was acting as a space occupying lesion and should therefore be dealt with surgically. A posterior fossa craniotomy was performed, clear CSF being aspirated from a needle puncture before the dura was opened. A large cystic lesion was found in the region of the cisterna magna, the walls and the floor of which were composed of compressed cerebellar cortex. There was no clear representative of the cisterna magna. The cyst therefore possibly represented a sequestered cisterna magna with obliteration of the foramen of Magendie. The cyst was drained into the right side of the subarachnoid space. Histological examination confirmed the operative diagnosis of arachnoid cyst. It was lined by loose fibro-vascular tissue which was indistinguishable from the pia arachnoid covering the outer shell of the cerebellum (fig. 2).

Little change in frequency of seizures occurred in the first 3 months postoperatively. The seizures then lessened in duration and severity to occur once a fortnight.

Case 2

Mrs J.S., a 62-year-old housewife with mild arterial hypertension, presented to the Queen Elizabeth Hospital in November, 1977 following a sudden collapse after getting out of bed one morning. In her early teens she had suffered a head injury when riding pillion passenger on a motor bike but there was no loss of consciousness. In the previous 18 months, and particularly in the preceding 6 months, the family had noticed a marked personality change. She had become increasingly forgetful, weepy and irritable, and was prone to outbursts of anger and paranoid behaviour. Long standing marital conflicts had also become worse.



Fig. 2. Histological section from Case 1. The cyst lining is indistinguishable from the pia arachnoid covering the outer shell of the cerebellum.

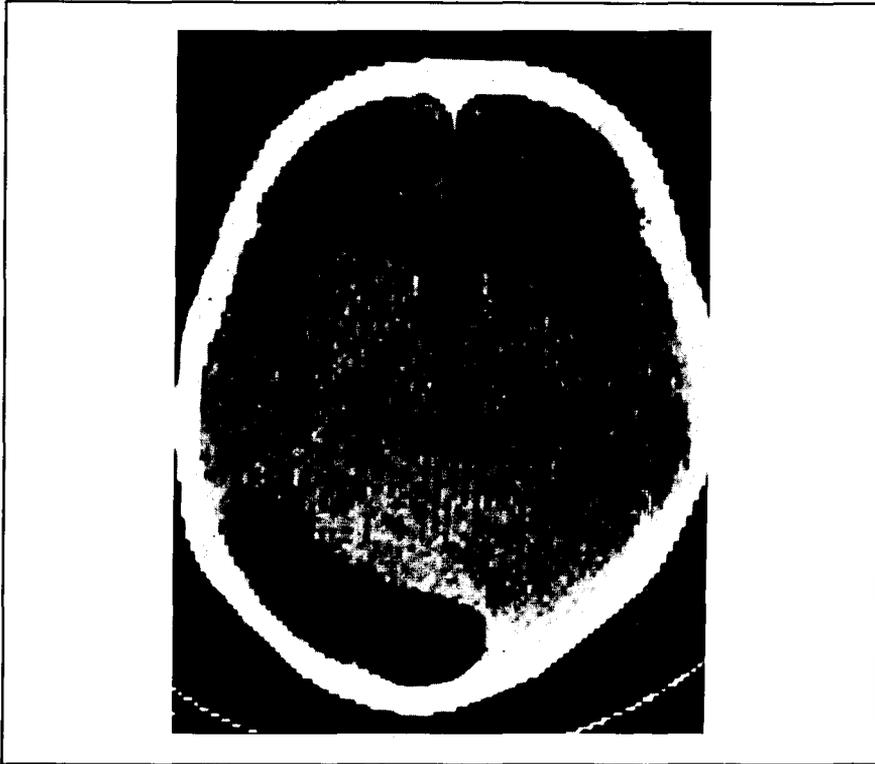


Fig. 3. Computerised axial tomography showing posterior fossa cystic lesion in 62-year-old woman (Case 2).

General examination was normal except for mild hypertension. Neurological examination showed moderate intellectual deterioration with profound short term memory loss and a tendency to confabulate. There was a mild expressive dysphasia and minor right-sided pyramidal weakness with accompanying hyper-reflexia and a right extensor plantar response.

Skull radiographs and a radionuclide brain scan were normal but a left anterior temporal delta wave electroencephalographic disturbance was present. A CT head scan showed a low density cystic lesion in the left posterior fossa consistent with an arachnoid cyst (fig. 3). There was also mild ventricular dilatation and widening of the cerebral sulci. CSF transport studies and investigation for reversible causes of dementia were negative. The patient was managed conservatively.

Discussion

In these 2 patients the finding of arachnoid cysts was quite unexpected, and it was difficult to see what relationship, if any, they had to the patients' symptoms. In Miss G.K., one postulate linking the two was that intermittent expansion of the cyst

caused compression of CSF pathways in the posterior fossa leading to sudden ventricular dilatation. Distension might be transmitted to the right temporal horn, perhaps precipitating a seizure. Though this theory has limitations it does give an explanation for the sudden pre-ictal right sided headache, a symptom which is uncommon in complex partial seizures. The temporal lobe atrophy associated with the marked cystic dilatation of the right temporal horn may be solely responsible for the epilepsy. Failure of the seizures to respond to medication in the future may mean that a right temporal lobectomy will be required. Aicardi (1975) suggested that marked temporal horn dilatation simply represents extreme dilatation of one part of the ventricle or alternatively a porencephalic cyst. Very rarely such lesions are paraventricular diverticula associated with hydrocephalus. It is tempting to link both the posterior fossa and the temporal lobe pathological changes to perinatal trauma in this case.

In Mrs J.S. it was concluded that the posterior fossa lesion was unrelated to her symptoms and signs. She was suffering from early presenile dementia possibly of the Alzheimer type. Asymptomatic cases of arachnoid cyst have been reported in late adult life.

The cause of the majority of arachnoid cysts is unknown. The term primary arachnoid cysts has been applied to this group. Those which can be attributed to infection, injury, inflammation, haemorrhage or associated with tumours have been called secondary arachnoid cysts.

Many theories have been proposed for the genesis of primary arachnoid cysts. It may be that they result from an error in development of the leptomeninges and the underlying nervous tissue. Robinson (1971) suggested that part of the brain lags in development. The resulting space becomes occupied with a compensatory focal enlargement or duplication of the subarachnoid space. In the infant, pulsations of the intracranial contents may then cause focal thinning and skull enlargement. This developmental theory would be consistent with the benign nature of many of these lesions.

Shuangshoti (1978) emphasised the role of CSF dynamics during fetal development and proposed that an aberration of flow during early differentiation of the arachnoid mater could result in the formation of a pouch within the arachnoid which may be closed off from the subarachnoid space and entrap fluid. The congenital arachnoid cyst is then formed intra-arachnoidally.

Dott and Gillingham (1958) favoured acquired local causes for CSF obstruction, but at operation observed CSF being discharged into the cavity of a cyst from basal cisterns synchronously with systole. They noted the close similarity between the patterns of distribution of cysts and that of major cerebral arteries, the fluid collections lying in the course of these vessels. Pulse waves following each other rapidly along the cerebral arteries propel the surrounding fluid in the blocked subarachnoid space. This may lead to local accumulation of fluid, and the formation of a subarachnoid pouch.

Williams and Guthkelch (1974), however, considered that pulsatile energy of arterial origin was far too inefficient to lead to progressive expansion of a pouch. The spinal subarachnoid space is much more sensitive to changes in venous pressure. If the mouth of the pouch is larger than the outlets of the 4th ventricle, then on coughing, sneezing, or straining, fluid would be propelled more easily into the cyst than the ventricles, leading to enlargement of the cyst. When the pressure falls again, fluid leaves the cyst more readily than the ventricle, and the ventricular system tends to expand. Progressive cystic enlargement then obstructs ventricular flow with resultant hydrocephalus.

Some of the confusion about the nature of primary arachnoid cysts has arisen because of inadequate histological descriptions in reported cases. The majority of cysts are lined by membranes which are slightly thicker than normal arachnoid but thinner than normal dura. Matson (1969) stated that it is not clear whether the cysts lie between layers of the arachnoid, between the arachnoid and the pia or between the arachnoid and the dura. There is no recognisable epithelium and no evidence of inflammation or tumour. The outer membrane is usually translucent and the inner part of the cyst may be walled off by fibrous strands. The fluid is generally clear, and the protein content varies from that of normal CSF to a modest elevation of 100 to 200mg/%. Some cysts with typical outer leptomeninges are lined with ciliated cubical or cylindrical epithelium. Shuangshoti (1978) would prefer to call these neuroepithelial or colloid cysts though many authors classify them with other arachnoid cysts. Wigglesworth and Husemeyer (1978) reported that separation of the squamous and lateral parts of the occipital bone (occipital osteodiasis) may be associated with haemorrhage into the posterior cranial fossa. This mechanism might be relevant to the two posterior cranial fossa arachnoid cysts reported here.

Summary

2 cases of posterior fossa arachnoid cyst are discussed. In the first, it is likely that perinatal factors were responsible for the temporal lobe pathology and the formation of the cyst. Progressive dilatation of the temporal horn may have then been caused by obstruction from the cyst. In the second case, minor head trauma was a possible mechanism for the cyst production, although it seemed irrelevant to the mode of clinical presentation.

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The Causalgia Syndrome Treated with Regional Intravenous Guanethidine

*J.T. Holland**

According to Sunderland (1968) the term 'causalgia' was first used by Weir Mitchell in 1872 to describe the severe burning pain that occasionally follows nerve injury. The proposed and tried treatments for relief of this often distressing condition have included chemical vasodilators, radiotherapy, temporary and permanent destructive attacks upon peripheral nerves and nerve roots and, more recently, acupuncture and peripheral and central stimulation techniques. However it is generally agreed that the best results are obtained by sympathectomy performed as early as possible after the syndrome commences. Sometimes temporary sympathectomy by local anaesthetic may completely relieve the syndrome although more often a permanent sympathectomy, especially of the preganglionic fibres over a fairly wide extent, is needed. Nevertheless, only between 50% (Sunderland, 1968) and 80% (Seddon, 1972) of patients are satisfactorily relieved.

Whilst the term causalgia is typically used to describe the pain syndrome seen following trauma of varying degree to a major peripheral nerve, it is recognised that it may follow trauma to a part without involvement of a nerve trunk, and in fact even physical trauma as such may not be necessary to give rise to a similar clinical picture. For this, Hannington-Kiff (1974a) used the general title 'sympathetic pain syndrome' (table I). Under the similar title of 'reflex sympathetic dystrophy,' Carlson, Simon and Wegner (1977) indicated that the syndrome may also be caused by osteoarthritis or a disc lesion at either the cervical or lumbar level, by a Pancoast or other tumour, by vasculitis, and bone or joint infection. Recently two children have been seen with

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Table I. Sympathetic pain syndromes (after Hannington-Kiff, 1974a)

Syndrome
Causalgia — after partial nerve injury
Post traumatic dystrophy without injury to a peripheral nerve trunk
Iso-segmental dystrophy
Hemiplegic dystrophy
Post sympathectomy pain
? Peripheral neuropathy

Table II. Nerve conduction studies (Case 1)

Nerve	Latency		Normal value (m/sec)	Velocity		Normal value (m/sec)
	Nov 77	April 78		Nov 77	April 78	
<i>Motor</i>						
R. deep peroneal n.	5.0	4.9	< 6.5	50	54	> 44
L. deep peroneal n.	4.1	—		55		
R. med. popliteal n.	5.5	4.2	< 6.4	53	58	> 34
L. med. popliteal n.	5.0	—		52		
R. median n.	—	4.2	< 4.5	—	49	> 57
R. ulnar n.	—	3.3	< 3.5	—	60	> 48

such a picture where trauma could not be documented. Both had involvement of one leg and one of these cases is described in more detail below. (The other child after one brief relapse recovered spontaneously after a period of four months.) The second case described below followed cervical trauma which involved the spinal cord and probably also the roots of the brachial plexus.

Hannington-Kiff (1974b) described the technique of regional sympathetic blockade using guanethidine. He further suggested that 'as certain types of pain notably are consistently alleviated by sympathetic blockade . . . experience suggests that guanethidine blocks are more likely to be successful in this respect, perhaps because the effect lasts longer.' In his textbook (Hannington-Kiff, 1974a) he further outlined the use of this technique in a number of sympathetic pain syndromes, including causalgia, although only single case examples were mentioned. McKay et. al. (1977) reported a case of post-traumatic causalgia of an upper limb treated by this method with benefit to the patient.

Table III. Nerve conduction studies (Case 1)

Nerve	Amplitude		Normal value (μ V)	Latency		Normal value (m/sec)	Velocity		Normal value (m/sec)
	Nov 77	April 78		Nov 77	April 78		Nov 77	April 78	
<i>Sensory</i>									
R. sural n.	6	9	> 8	4.0	4.1	< 4.1	30	29	
L. sural n.	45	24		2.5	3.0		48	40	
R. median n.	—	11	> 16	—	4.3	< 3.6	—	33	> 40
L. ulnar n.	—	11	> 8	—	3.4	< 3.1	—	38	> 40
<i>Nerve action potential</i>									
R. deep peroneal n.	8	5	> 5	6.9	6.9	< 6.9	41	40	—
L. deep peroneal n.	14	10		6.4	6.7		44	41	—

Method

The method used was described in detail by Hannington-Kiff (1974b). In essence it involves the infusion of 10 to 20mg of a solution of guanethidine sulphate in 20 to 25ml of saline with 500 to 1,000 units of heparin locally into a vein of the affected limb distal to a cuff to provide for ischaemia of the limb for periods varying from 5 to 30 minutes. In the case of the child the procedure was performed under light general anaesthesia. The assessment of the efficacy of the treatment can be monitored at the same time using skin temperature, following release of the cuff. Especially in the elderly, the patient should be kept flat and the blood pressure monitored until the effects of the guanethidine taken up by the local tissues and subsequently released into the circulation, have passed.

Case Reports

Case 1

S.R., aged 13 years, was admitted to the Royal Newcastle Hospital in November, 1977 with a four month history of pain in her right leg and foot but sparing the sole. The pain had commenced the evening following a sports afternoon at school but there was no memory of any injury. She had been seen and treated by psychiatrists and other doctors without benefit. There was no history of preceding or of family illness and she was doing very well at school.

Examination revealed an apparently healthy young lady who would not put her right foot to the ground. When lying on the bed she would hang the affected limb over the edge so that bed clothes would not touch it. The limb was swollen and blue below the knee with piloerection and sweating. Whilst she would allow the sole to be tested, and did try to cooperate with sensory testing of the rest of the limb as much as possible, the slightest touch up to the right knee gave rise to obvious severe pain of a burning nature which persisted for many minutes after removal of the stimulus.

Investigations, including full blood count and ESR, radiographs of chest, spine and leg, serum electrolytes, glucose, ASOT, anti-nuclear factor and rheumatoid factor all yielded normal results.

Examination under light general anaesthesia confirmed that the right leg was colder and moister than the left. Skin resistance measurements on the right were one third to one half those on the left. Nerve conduction studies performed on both legs (tables II and III) showed mild slowing of conduction in the right sural nerve and borderline abnormality of the right deep peroneal nerve.

An initial infusion of guanethidine failed to effect either a sympathectomy or relief of pain. However, a subsequent attempt the next day produced a good local sympathectomy and complete and dramatic relief of pain. Re-examination of the leg over the next few days showed slight motor weakness of all movements of the right lower limb and diminished sensation to light touch and pin prick (including the sole) up to the mid calf. The right knee and ankle jerks were perhaps marginally increased. Review six weeks later showed that the sympathectomy had largely resolved but that she was still completely free of pain and was walking normally. No motor or sensory abnormalities were found on examination.

In early April, 1978 the pain recommenced although not as severely as on the original occasion. Careful sensory testing once again showed diminished pin prick and light touch below the right knee, with relative sparing of the sole. Repeat nerve conduction studies at this time, including the right upper limb, again suggested a more generalised mild sensory neuropathy (tables II and III). A further infusion of guanethidine once more gave rise to complete relief of pain but on this occasion the sympathetic block was only partial. At this time it was learnt that our supplies of guanethidine had been in the hospital since

Table IV. Theories of the production of causalgia

Theory
Conduction of nociceptive impulses along sympathetic afferents
Ephaptic stimulation of somatic nociceptive afferents
Ischaemia
Modification of nociceptive afferent transmission by noradrenaline
Altered central control mechanisms

1970 and it was wondered if the drug was perhaps no longer effective. However, a fresh supply was obtained and the infusion repeated resulting in a complete local sympathectomy but without any relief of her pain.

Case 2

Mrs. K.P. aged 50 years, sustained a C 5-6 fracture dislocation of her neck in 1975 resulting in a mild upper motor neurone lesion of both legs (right more than left), together with some associated paraesthesiae and lower motor neurone weakness of the right arm, and minimal paraesthesiae of the left hand. The lower motor neurone weakness and sensory changes noted in the right upper limb were maximal in relation to the C 6-8 spinal cord segments or nerve roots.

Approximately six months after the injury, from which she made a good although not complete recovery, she began to experience continuous burning pain in the right upper limb involving all of the forearm and hand. The slightest touch to this region involved a marked exacerbation of the burning pain which persisted for some minutes after removal of the touch. Myelography was performed in July, 1976 and was normal.

In September, 1976 a right stellate ganglion block was performed with local anaesthetic resulting in a temporary sympathectomy associated with relief of pain only for the duration of the stellate ganglion blockade. However, because of the appearance of the ptosis resulting from the Horner's syndrome occasioned by the block, the patient did not wish to have a more permanent procedure performed. In December, 1977 regional block with guanethidine was attempted with partial relief of pain in the region of the forearm where the sympathetic block seemed most effective. Three subsequent infusions over the next four days resulted in complete sympathetic blockade in the forearm and hand together with complete relief of pain. However, both the sympathectomy and the relief of pain only lasted about 24 hours. Because of the very brief duration of the effect the patient declined any further infusions. However, in March, 1978 she again agreed to a further injection of her stellate ganglion; this was once again temporarily effective but for the same reason the patient again declined a more permanent surgical procedure.

Discussion

A number of questions arise from these cases. How does local sympathectomy relieve the pain of causalgia? Why was the procedure not equally effective on each occasion? If, having achieved sympathectomy, it relieved the pain once, why should it not do so subsequently? Can peripheral neuropathy itself give rise to the causalgia

syndrome? Answers to these questions must deal with the pathophysiology of the syndrome which still seems unclear. However, some pertinent facts are worth considering.

A review by Wall (1976) of current theories of the mechanism of causalgia (see table IV) suggested that

- 1) Conduction of nociceptive information along sympathetic nerve afferents
- 2) Ephaptic jumping of impulses from sympathetic efferents to somatic afferents, and
- 3) Ischaemia,

are all unlikely to be the cause of the syndrome (though Iggo [1976] did not discount ephaptic transmission as a likely mechanism of causalgia). However, there is now good evidence (Wall and Gutnick, 1974; Matthews, 1976; and Pepeu, 1976) that noradrenaline, perhaps as well as other chemicals such as bradykinin and prostaglandins (Handwerker, 1976; Guilbaud et al., 1976), may have profound effects on the modulation and threshold of nociceptive transmission at peripheral, spinal cord and higher levels. Whilst not necessarily an absolute prerequisite in the causalgia syndrome (Sunderland, 1968), most authors would accept local sympathetic overactivity as a characteristic phenomenon. Typically the causalgic limb is cold, clammy, and blue and it may show pilo-erection. Thus there is evidence for sympathetic overactivity. Sunderland (1968) examined the reasons for considering that disturbance of central mechanisms in the neuronal pool of the grey matter of the spinal cord underlies the genesis of causalgia, including the vasomotor disturbances. Unfortunately there is little evidence as to how such sympathetic overactivity arises. Indeed, recent extensive reviews on the subject of pain reveal but one very brief reference to the subject (Procacci et al., 1976).

That the pattern of stimuli arriving centrally in the posterior horn or higher may have an effect, at times permanent, on the physiological organisation of central structures is now documented (Nathan, 1977). In addition, impulses from damaged or regenerating afferent nerve fibres, themselves modified by factors such as temperature, vascular supply, sympathetic efferent impulses, chemical environment and previous stimuli, may yet further modify and influence central mechanisms of pain and sympathetic overactivity in related spinal cord segments (Wall, 1976), thus creating a vicious cycle. It might therefore be reasonable to expect that removing one or more of these focal factors (e.g. sympathectomy) may help break this cycle.

Guanethidine is known to be taken up by peripheral tissues, especially sympathetic efferent endings, where it displaces noradrenaline and prevents its reuptake. This effect may be quite prolonged (Hannington-Kiff, 1974). Hence it seems reasonable to suggest that the mechanism of action of guanethidine in relieving causalgia associated with sympathetic hyperactivity may be related to the drug's peripheral effect in reducing the local amount of noradrenaline released into the affected part. This might explain why in each case, at least originally, the relief of pain did not take

place until the local sympathectomy was effective. In Case 2 it was interesting to plot the coincidence of the increasing sympathetic block and the relief of pain.

It is more difficult to explain why a second infusion 5 months later, which gave rise to a satisfactory local sympathectomy, failed to be as effective as the first. At this stage one may postulate that this was due either to some other locally acting phenomenon at the peripheral level or was the result of some altered more central mechanism. It seemed possible that the failures to achieve a sympathectomy in Case 1 on some occasions and the need for repeated attempts in Case 2 (the resultant sympathectomy in whom was only of brief duration) may have been related to the fact that our stock of guanethidine was at least 8 years old. Successful sympathectomy was eventually achieved in each case and for the final infusion in Case 1 a new batch of guanethidine was used.

As far as is known the causalgia syndrome has not been reported as occurring as part of a peripheral neuropathy, although some neuropathies are well recognised as causing pain syndromes. That altered patterns of afferent stimuli may give rise to pain is not difficult to understand in the light of the mechanisms mentioned above. It therefore does not seem impossible to accept that on rare occasions the causalgia syndrome itself may be seen. Of course it is not possible to exclude completely some minor trauma that might have been overlooked, but at least no such trauma could be documented in Case 1.

Although it has not been possible to report long lasting relief with the technique of regional guanethidine infusion in these two cases, the procedure would still appear worth considering in all cases of causalgia. It should probably be done as early as possible after the syndrome is recognised. It is probably worthwhile repeating the infusion if the pain returns. It would certainly seem reasonable to suggest that guanethidine infusion be performed as a routine before considering more destructive procedures such as surgical sympathectomy. If the former is not successful in relieving pain in spite of a good local sympathectomy then surgical sympathectomy should not be performed.

Summary

Two cases of the causalgia syndrome have been presented, one probably related to a mild peripheral neuropathy and the second, more classically, following trauma. The technique of regional infusion of guanethidine has been shown to be efficacious in relieving the pain, if only temporarily, but as it is largely without risk it may be repeated if necessary. It should probably be performed as a routine before consideration of surgical sympathectomy in order to assess whether surgical intervention is likely to be effective. Mechanisms of the causalgia syndrome itself are considered and a rationale for the efficacy of the procedure is suggested.

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Detection of Experimental Carotid Ulceration by Radionucleotide Labelled Particles

*G.A. Donnan, W.J. McKay, D.P. Thomas and P.F. Bladin**

Over the last decade the focus of attention has shifted from carotid stenosis and haemodynamic change to the ulcerated carotid plaque which produces emboli as the aetiology of cerebral infarction. Detection of these plaques by conventional angiography remains difficult as many of these ulcers may be either too flat for detection or may be present in a plane not viewed by routine radiological procedures. The object of the present study was to set up an animal model of experimental carotid ulceration to determine types of radioactive material that may adhere to ulcer sites, thereby allowing detection of ulcers not readily visible on angiography. Pollak et al. (1976a) set up a similar model showing adherence of technetium labelled macroaggregated albumin (^{99m}Tc MAA) when given intra-arterially into carotid arteries of dogs. Other materials that have been used are indium III labelled platelets (Thakur et al., 1976), and tantalum (Dumont et al., 1972).

Materials and Methods

6 animals in all were used during the experiments: 4 mongrel dogs weighing 25 to 35kg and 2 sheep weighing 100 to 150kg. Dogs were anaesthetised with continuous intravenous sodium thiopentone (5% solution). Both carotid arteries were surgically exposed on all animals and arteriotomy was performed on right carotid artery. A section of intima was removed 5mm long over half of the circumference of

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Fig. 1. Right carotid angiogram of a dog (animal 1). The position of the experimental ulcer is clearly seen as an area of stenosis.

the vessel. Carotid angiography was performed on 2 animals by the indirect femoral puncture technique (Seldinger) in an attempt to demonstrate the site of ulceration. Following angiography, 10mCi of ^{99m}Tc macroaggregated albumin (^{99m}Tc MAA) was injected into the carotid arteries through a preshaped polyethylene (7 French) catheter which had been left *in situ*, followed by 5cc of normal saline. The animals were sacrificed 30m later. Right and left carotid arteries were removed and placed 10cm apart beneath a gamma camera (Toshiba G.C.A. 401 Jumbo model) and scanned for a total of 100,000 counts, using a high modulation collimator. Radioactive markers were used to check the positions of both test and control arteries.

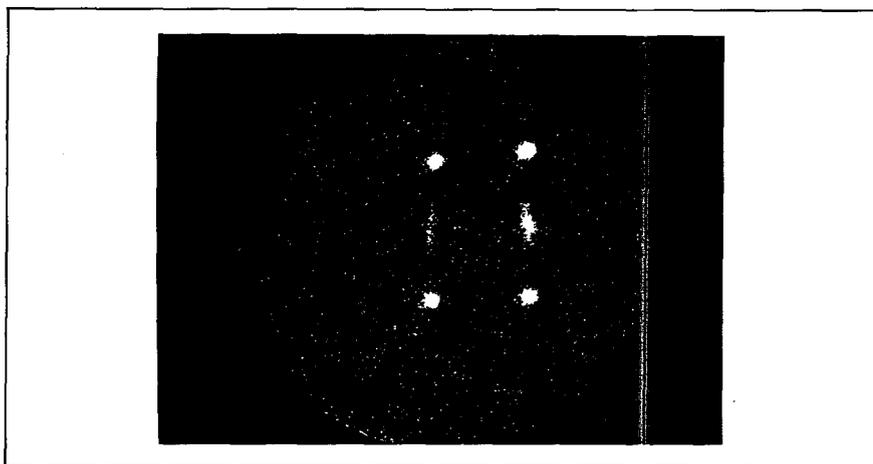


Fig. 2. *In vitro* detection of a carotid ulcer (animal 1). Increased uptake radionucleotide ^{99m}Tc MAA is clearly seen on the right with poor uptake on the control intima on the left. Radioactive markers are seen above and below the arteries to delineate their positions.

In the remaining 4 animals radionucleotide was given intravenously. A dose of 10mCi of ^{99m}Tc technetium labelled pyrophosphate (^{99m}Tc PYP) was given. 30 minutes later both control and test carotid artery were removed. At the time of removal of the arteries patency was ascertained by visualisation of adequate blood flow from the sectioned artery. Arterial specimens were placed 10cm apart beneath the gamma camera and scanned for a total of 100,000 counts. Radioactive markers were again used to check the positions of arteries.

Of the 2 animals in which angiography was performed, the position of experimental carotid ulceration was visible in only 1 (fig. 1). In the second animal angiography failed to reveal the ulcer site (figs. 3, 4). In both of the initial studies where the intra-arterial method of administration of ^{99m}Tc MAA was used, *in vitro* demonstration of ulcers was achieved (figs. 2, 5).

Intravenous administration of ^{99m}Tc PYP also demonstrated the position of carotid ulcers *in vitro* in all animals studied (fig. 6).

Discussion

The animal model set up clearly demonstrates that both ^{99m}Tc MAA and ^{99m}Tc PYP adhere to areas of experimental carotid ulceration. It has not been demonstrated previously that technetium labelled pyrophosphate may be used in this circumstance; previously the most common use of this substance has been in bone scanning and more recently in myocardial infarct imaging. Because of this latter application the

labelled pyrophosphate was considered for our studies. Obviously the intravenous route of administration of a radionucleotide would be preferable to the intra-arterial. In order for intravenous administration to be satisfactory, particle size of the material given must be such that passage through the microcirculation of the lung can be achieved, allowing entry into the carotid arterial system. For this, materials such as labelled red cells, platelets, pyrophosphate and tantalum would be satisfactory while macroaggregated albumin would not, its particle size being up to 50μ . Reduction in size of MAA particles from 50μ to 2μ in diameter by ultrasonification has been

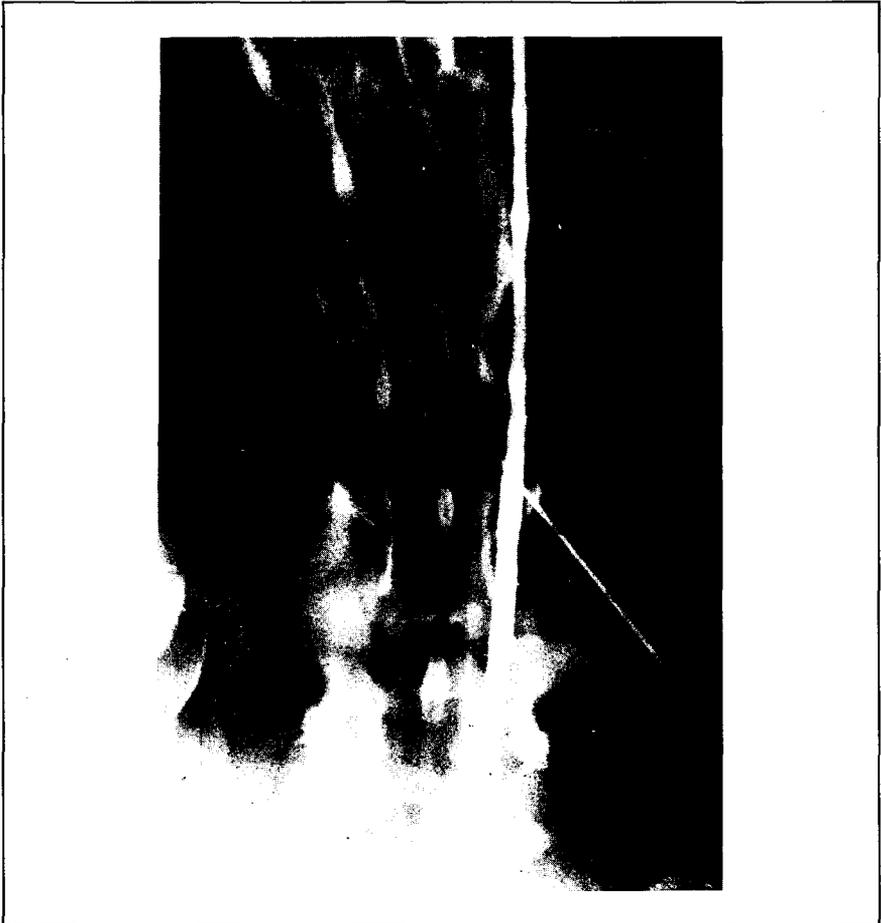


Fig. 3. Right carotid angiogram of animal 2 (AP view). The position of the experimentally produced ulcer cannot be seen clearly (stilette marker).

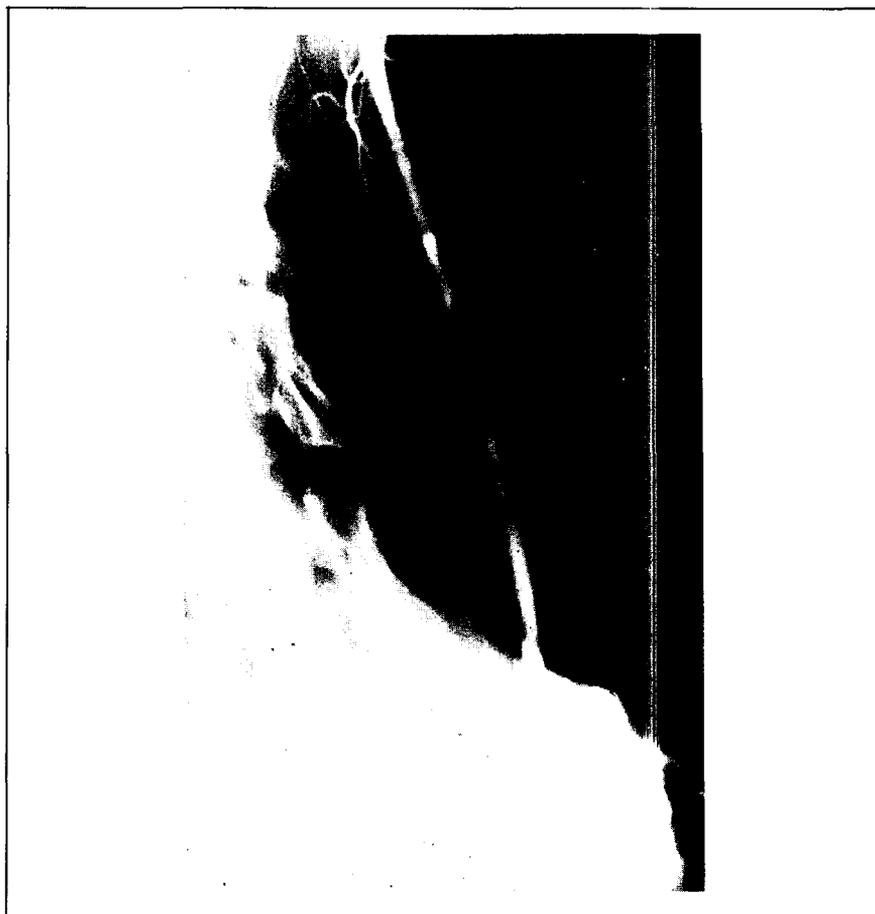


Fig. 4. Lateral view of right carotid angiogram (animal 2). Again the ulcer is not clearly seen (stillette marker).

achieved by Pollak et al. (1976b). These smaller particles would theoretically be suitable for intravenous administration.

Further research is required to determine the mode of adherence of radionucleotide to the ulcerated area. Previous workers have demonstrated uptake of ^{131}I -fibrinogen in pig aorta (Bell et al., 1974) and protein accumulation in the wall of pig aorta (Packum et al., 1967) but the mechanisms of uptake were unclear. Webber (1971) created *in vitro* clot and showed microscopically that MAA particles became entangled within fibrin strands of this clot.

Pyrophosphate is thought to require calcium ion to adhere to bone selectively and a similar mechanism is proposed for its adherence to damaged cardiac muscle

where calcium ions are also prevalent. This provides the rationale for the use of labelled pyrophosphate in myocardial infarct imaging. The mechanism of uptake of pyrophosphate in experimental carotid ulceration remains less clear and is an area requiring further research since excessive calcium ion concentration is thought not to be present in damaged arterial media.

Further extension of the present work would involve the demonstration *in vivo* of increased uptake of radionucleotide in the carotid artery on the side of experimental

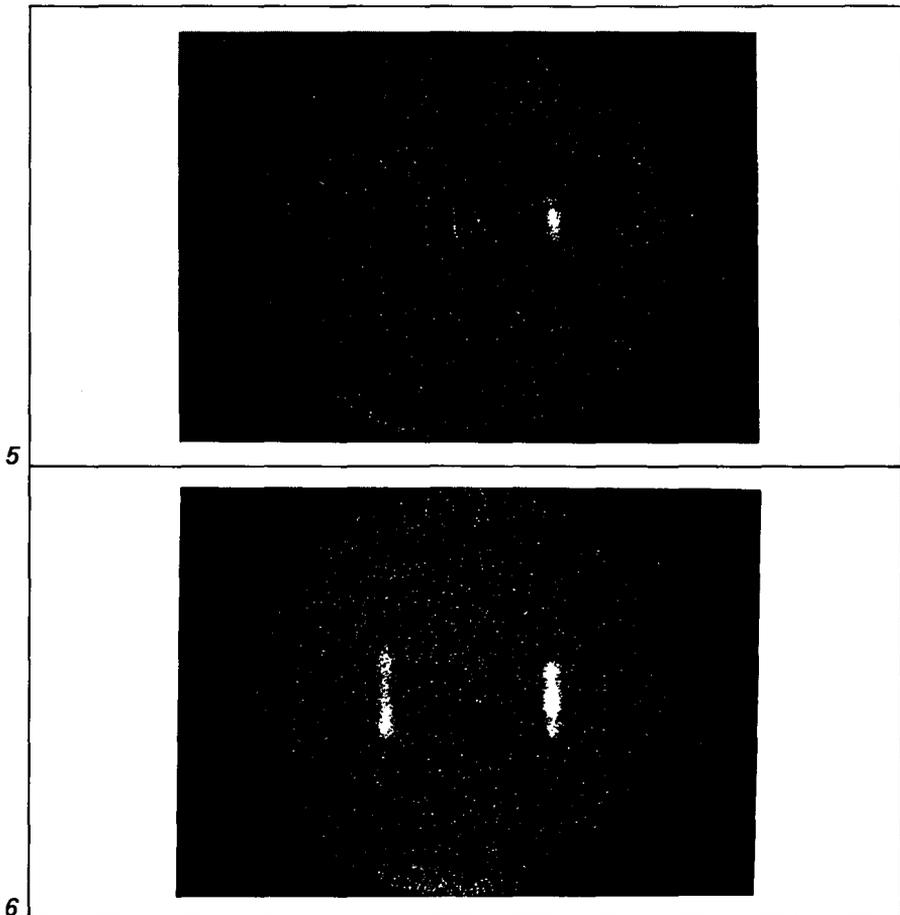


Fig. 5. Detection of carotid ulcer using ^{99m}Tc MAA given intra-arterially. Increased uptake is seen over the right ulcerated carotid. The control carotid on the left is barely visible.

Fig. 6. Intravenous administration of ^{99m}Tc PYP. There is increased uptake on the right side (ulcerated carotid artery) as compared with the control artery (left).

ulceration. Here the most satisfactory results may be obtained by a computer analysis and subtraction of background activity, thus simplifying the comparison between control and ulcerated carotid arteries. This approach would be particularly helpful in the case of technetium labelled pyrophosphate where uptake in underlying bone provides excessive background activity. Future research should also be directed towards the use of other radionucleotides attached to different particles, such as tetracycline which also has been used experimentally for myocardial infarct imaging. Extension to the human situation with the demonstration of atheromatous ulcers in carotid arteries would be the ultimate aim of this work. A preliminary report from Mettinger et al. (1978) using ^{123}I labelled fibrinogen given intravenously and computer analysis of differential counts over the right and left carotid arteries has been encouraging.

Summary

An animal model has been set up to study the adherence of various radionucleotide particles to experimental carotid ulcers. 6 animals were used in all, 4 dogs and 2 sheep. Carotid angiography was performed in 2 animals and in 1 of these the conventional mode of angiography failed to detect the carotid ulcer. Intra-arterial injection of technetium labelled macroaggregates in both of these cases showed the position of the lesion *in vitro*. In the remaining 4 cases, intravenous radionucleotide $^{99\text{m}}\text{Tc}$ pyrophosphate was used and in all cases *in vitro* the position of the experimental carotid ulceration was revealed.

Our studies show that both technetium labelled macroaggregates and technetium labelled pyrophosphate are suitable particles for use in this model. Further research is required to establish the mode of their adherence to the experimental area of ulceration. A further extension of this work would be to demonstrate the ulceration *in vivo*. Encouraging work in this regard has been done by Mettinger et al. (1978) in humans demonstrating, by subtraction methods, increased uptake over ulcerated carotid plaques as compared to controls.

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Acupuncture Analgesia for Chronic Low Back Pain

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The aim of this investigation was to assess the efficacy of acupuncture (AC) in the management of chronic pain. There are several ways of approaching this. For example, one could compare AC against a well established analgesic. We chose, partly because of the uncertain nature of AC, to compare the analgesic effect of traditional AC with that of placebo AC.

Patients and Methods

The trial design was of a double-blind, crossover type. Patients with chronic low back pain were included in the group to be studied if they satisfied the following criteria: they should have no compensation or litigation pending, have no overt psychiatric disease, be fluent in English, and have been referred by their attending doctor. 100 patients were accepted into the trial. It was explained that they were entering a trial of AC treatment, and informed written consent was obtained. 77 patients completed the crossover study and the data presented here are from this group.

The patients' mean age was 53.5 years, there were 40 females and 37 males, and the mean duration of their pain was 11.7 years.

The phases of the trial are summarised in table I. Initial assessment consisted of personal and illness history, a semi-structured psychiatric interview, and 6 psychometric tests (Mendelson et al., 1977). Physical examination centred on quantify-

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Table 1. Cross-over trial design (time intervals in weeks) for the comparison of traditional acupuncture (TAC) with placebo acupuncture (PAC) in patients with chronic low back pain. 100 patients were selected, 90 completed phase 1 and 77 phase II.

Patient selection			
Initial assessment			
Baseline measurements 2w			
Randomisation			
<i>Group 1</i>		<i>Group 2</i>	
Phase I TAC	4w	Phase I PAC	4w
Rest	4w	Rest	4w
Phase II PAC	4w	Phase II TAC	4w
Follow-up	4w	Follow-up	4w

ing spinal mobility. Pain was assessed by a visual analogue scale (0 = no pain to 100 = maximum pain), modified McGill pain questionnaire (Melzack, 1975), analgesic intake, spinal mobility and subjective rating of pain and disability. During the baseline period parameters which were going to be used most regularly to assess progress, the visual analogue scales of pain and anxiety state, were monitored. Patients were then randomised using a random number method before entering the first phase of treatment. 36 patients received traditional AC first, and 41 placebo AC first.

Traditional AC consisted of inserting a number of needles intramuscularly in the low back region and stimulating them manually. In placebo AC needles were inserted subcutaneously, a small amount of local anaesthetic was injected through them, and the needles were not stimulated. Treatment sessions lasting half an hour were given twice weekly over 4 weeks.

Before the second phase of treatment (table 1) a rest period of 4 weeks preceded the crossover of each patient group to the alternative treatment mode. The timing of treatment sessions was the same as in the first phase.

The pain level was noted twice weekly during the duration of the trial. Differences between the 2 groups were tested for significance using the 't' test.

Results

Preliminary results of the study are presented for the visual analogue scale of pain changes during the trial (table II).

Both traditional and placebo AC groups showed a significant drop in score in the first phase of treatment, the fall being 30% and 35% respectively from baseline values. These differences are not statistically significant. Following the crossover and

Table II. Mean pain scores (visual analogue scale) for 77 patients at 3 stages of the trial: baseline, rest period and follow-up. Patients had 6, 8 and 8 readings respectively at each of the 3 stages.

Trial stages (time in weeks)		Pain score	
		group 1, TAC ¹ first (n = 36)	group 2, PAC ² first (n = 41)
Baseline	2w	50.8 (SE 3.4)	52.3 (SE 3.8)
Phase I	4w		
Rest	4w	35.0 (SE 3.7)	38.5 (SE 4.2)
Phase II	4w		
Follow-up	4w	28.3 (SE 3.7)	28.9 (SE 4.1)

1 TAC — traditional acupuncture.
2 PAC — placebo acupuncture.

the second phase of treatment there was a further drop in values, this fall being 20% and 25% respectively for the 2 groups from rest to follow-up. For the whole duration of the trial the findings represent a cumulative total effect for both traditional and placebo AC of a 55% drop in pain rating from the starting baseline value.

The results are being further analysed to determine if a more temporary effect was evident during the actual treatment phase. Confirmation of the findings so far obtained will also be sought by an analysis of the other variables which were monitored.

Discussion

One problem which the study highlights is the difficulty of measuring such a real and common entity as pain. The methods available are indirect and imprecise. We have used a number of parameters which have been shown in previous studies to have some validity. Further, by comparing results obtained by the different assessment methods, some estimate of reliability may be obtained. Thus for pain we are at present correlating the results obtained using the visual analogue scale with those obtained from the McGill pain questionnaire, analgesic intake, spinal mobility, subjective assessment of pain and disability, and simultaneously monitored anxiety state readings.

It may be questioned whether it is possible to administer 'placebo AC'. This is complicated by the fact that even the method of traditional AC is not clearly defined, there being a number of schools or methods proposed (Lam, 1971). The traditional AC used in the present study was of a recognised classical type learned in mainland

China. The placebo AC needles were placed in non-traditional points, situated subcutaneously only and not stimulated. AC is apparently not effective if given in an area of reduced sensory input (Editorial, 1973).

The results show no difference in the effect of either treatment mode when compared a mean of 2 weeks after each treatment phase. The possibility of there being shorter term effects is being explored. It may be that the group chosen for study — one with chronic stable pain — is not one which responds to this form of treatment. We have previously shown (Mendelson et al., 1977), that this group varies significantly from an age-matched control group in a number of psychological variables. This may be one reason underlying the apparent lack of any specific effect of traditional AC in this group.

Summary

Preliminary findings are presented of a double-blind, crossover trial comparing the effects of traditional with placebo acupuncture in relieving chronic low back pain. 77 patients completed the study. Following initial assessment and baseline readings, patients had a 4-week course of active or placebo treatment given twice weekly. After a 4 week rest period patients received the alternate treatment, using the same time schedule. A 4 week follow-up period completed the trial. Using visual analogue scale readings as a measure of pain there was no cumulative difference in pain reduction achieved by traditional as compared with placebo acupuncture treatment. Both groups achieved a 55% overall reduction in pain level at the end of the trial, compared with initial baseline readings.

Acknowledgements

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Visuo-motor Skill and Visual Perception in Left and Right Handed Children of Superior Intelligence

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Many reports have appeared in the remote (Dejerine and Andre-Thomas, 1912; Pitres, 1884; Nielsen, 1946) and recent literature (Heilman et al., 1973; Poeck and Kerschensteiner, 1971) drawing attention to unusual patterns of disability occurring in left handed individuals with lateralised lesions in the central nervous system. The prognosis for recovery from cerebral lesions is better in left handed individuals than in right handed individuals (Zangwell, 1960). It has also been shown that even a positive family history of left handedness significantly improves the prognosis for right handed patients with left hemisphere lesions (Luria, 1966). The implication that may be drawn from these reports is that left handed individuals may utilise unusual pathways in the performance of some tasks involving higher intellectual functions. Implicit in this is the possibility that in normality some left handed individuals may possess either an advantage or a disadvantage in the performance of these tasks.

It was thought of some interest to determine whether the proximity of the leading hand area to the right parietal cortex in left handed subjects conferred an advantage with regard to the performance of tasks involving visuo-motor function.

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Methods and Procedures

2 tasks were given to 2 groups of children. The first, the Picture-completion Sub-test of the Wechsler Intelligence Scale for Children (WISC) was credited (Wechsler, 1949) as measuring 'visual organisation and ability to differentiate essential from non-essential visual percepts'. This task requires the child to look at a drawing with some essential part missing. The child has to state what is missing. The second task, the Block-design Sub-test of the WISC was credited by Wechsler as measuring 'visuo-motor coordination'. Here the child must reproduce a pattern represented on a card, using the appropriate number of blocks that have 2 white, 2 red, and 2 half red and half white sides.

The children comprised 44 full dextrals and 11 full sinistrals. Excluded from the right handed group were all children who had relatives or siblings who had any left sided preference. Laterality was decided by determining the hand used for throwing a ball at an object, the leg used for kicking a ball at an object, and the eye used for sighting an object through a pin hole aperture. 3 observations were made on each task in each subject.

Full dextrals were defined as those using the right arm, right leg, and right eye for all tasks. Full sinistrals were defined as those using the left hand, left leg, and left eye for all tasks. The mean age of the sinistrals was 9.64 years with a standard deviation of 1.03. The mean age for the dextrals was 10.84 years with a standard deviation of 0.72. The two groups were found to be dissimilar in age ($p < 0.01$) and to correct for this, age scale scores were used exclusively in the calculations. There were 27 males and 17 females in the right handed group and 4 males and 7 females in the left handed group.

Teachers were trained to administer the Picture-completion and the Block-design Sub-tests, and to determine the laterality of the subjects. The teachers rated the students on dominance and on the two WISC Sub-tests. All results were scored by a clinical psychologist.

Results

The results (table I) indicate that there was no difference within the groups on their performances in the Picture-completion and Block-design Sub-tests. A comparison of the performance of the right handed and left handed groups with regard to Picture-completion also failed to reveal any significant difference between the two groups. There was, however, a significant difference ($p < 0.01$) between the right handed and left handed groups with regard to the Block-design Sub-test; the left handers were significantly worse. Not only were they more inaccurate, they were also significantly slower.

Table 1. Differences between the performance of 44 right and 11 left handed children, using 2 tests of visuo-motor skill

Subject group	Task score	
	picture completion	block design
Dextrals	13.76	14.93 ¹
Sinistrals	13.73	11.27 ¹

1 $p = >0.01$

Discussion

As the members of the left handed group in the study were all of high intelligence, and all were fully right hemisphere dominant for eye, hand and leg function, it was assumed that none of the left handed group was left handed as a result of remote pathology, such as perinatal brain damage involving the left hemisphere. It was thought likely that members of the left handed group did represent left handedness occurring as the result of genetic factors (Jordan, 1914; Annett, 1964).

The impaired performance in the left handed group studied suggests that the simple juxtaposition of the leading hand area to the right parietal cortex does not confer, in this age group, any advantage; the opposite appears to apply.

This report is in accord with the findings of Miller (1971). However it is in conflict with the findings of Hardyck et al. (in press) who deny any difference between right handers and left handers. Each of these studies is in turn in conflict with the findings of Petersen and Lansky (1974) who showed visuo-spatial superiority in left handed groups. It is probable that age, sex differences (Stafford, 1961), and also cerebral lateralisation of language function do exert an influence on the results (Levy, 1969).

Any disadvantage exhibited by left handed children is however clearly not a permanent incapacity affecting all left handed individuals at maturity. Left handed individuals excel in some sporting activities and in other areas of creative activity involving great demands on visuo-spatial and visuo-motor skills.

Any impaired visuo-motor ability in left handed children is clearly not necessarily a fixed deficit, but one which may disappear with progress to cerebral maturity, or alternatively may be favourably influenced by training.

If the findings of this study, and those of Miller (1971) are correct, it would seem likely that left handed school children with intelligence equal to their right handed peers might be expected generally to perform less well in many of the school tasks requiring visuo-motor skill and that additional application and time may be required in order that a constitutional disadvantage be overcome.

Summary

It was thought possible that the proximity of the right parietal cortex to the leading hand area in left handed subjects may confer an advantage in tasks requiring visuo-motor function. However, the study showed the left handed group to be defective in the performance of the Wechsler Block-design Sub-test.

As some mature left handed individuals may excel in tasks requiring refined visuo-motor skill, it is suggested that any constitutional deficiency is not fixed, but may be expected to disappear with increased maturity, or as the result of training.

Acknowledgement

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Individual Free Fatty Acids and Migraine

*Michael Anthony**

The reduced plasma levels of serotonin during a migraine attack reflect a reduced content of platelet serotonin, since in the circulation the amine is concentrated almost exclusively in platelets.

There is evidence to suggest that the serotonin release reaction during migraine is mediated through a serotonin releasing factor, which appears in the blood during the attack (Anthony et al., 1969). This factor has a molecular weight of less than 50,000, thereby making it unlikely that it is a protein, an antigen-antibody complex or some other form of large molecule. On the other hand, free fatty acids (FFA), various amino acids, polypeptides, prostaglandins or monoamines, e.g. tryptamine, tyramine, catecholamines, qualify as candidates for platelet serotonin releasers in migraine (Anthony and Lance, 1975).

Certain FFAs, particularly stearic, palmitic, linoleic and behenic, are known to be quite potent in releasing platelet serotonin *in vitro* (Inouye et al., 1970). Several patients relate their migraine attacks to the ingestion of fatty meals and so far two studies have demonstrated a significant rise in total plasma FFAs during attacks of migraine (Hockaday et al., 1971; Anthony, 1976).

The purpose of this study is:

- 1) To identify which of the four most commonly occurring plasma FFAs (stearic, palmitic, oleic and linoleic) rises most during migraine, and which therefore might be responsible for the significant reduction in platelet serotonin observed during migraine

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Table I. Plasma levels of free fatty acids (FFAs) in normal subjects

FFA	Concentration		
	%	mg/L	nmol/ml
Total	—	290	1035.3
Palmitic	24.9	80.9	288.8
Stearic	14.9	43.2	154.2
Oleic	25.5	73.9	264.0
Linoleic	13.1	38.0	135.6
Palmitoleic	7.2	20.9	74.5
Arachidonic	2.4	6.9	24.8

- 2) To determine whether ingestion of linoleic acid (the most unsaturated of the above four FFAs) results in reduction in platelet serotonin content.

A list of the commonly occurring FFAs in the plasma of normal subjects, and their concentration, is given in table I.

Materials and Methods

10 patients with frequent and severe migraine headaches were admitted to hospital for study. All interval medication was stopped for one week and no ergot preparations or alkaloid analgesics were permitted for 3 days prior to admission.

Blood was collected 3 times daily, before and after the migraine attack, and at 4-hourly intervals during the headache. Patients were allowed the standard ward diet but were not permitted to have food or sweet fluids between meals. Blood was collected a few minutes before the three main meals, after the patient had rested for about 20 minutes. The purpose of the above procedures was to offset the possible effects of diet, posture and exercise on plasma FFAs.

10 non-migrainous subjects were asked to ingest 20g of linoleic acid (25ml of high-linoleic content sunflower seed oil) after an overnight fast. Blood was collected before, 2 and 4 hours after the ingestion of the oil, and the platelet serotonin content was estimated in each specimen.

Total plasma FFA levels were estimated by modification of Dole's extraction method (Trout et al., 1960). Individual FFAs were estimated by gas liquid chromatography (GLC), using ethelene glycol succinate (EGS) as the liquid phase into which were injected 2 μ l of the methylated plasma extract, using methyl-8 as derivatising agent. Oven temperature of the GLC instrument (Packard — model 417)

Table II. Mean total plasma free fatty acid levels in the 8 of 10 migraine patients who had increased levels (> 10%) during attacks

Observation period	Number of observations	FFAs (nmol/ml)
Pre-headache	34	340 ¹
Headache	60	485 ^{1,2}
Post-headache	34	322 ²

1 $p < 0.001$.

2 $p < 0.001$.

Table III. Increases in individual free fatty acids in 10 patients with migraine

FFA	Plasma level (nmol/ml)			Mean rise ¹ (%)
	Pre-headache	Headache	Post-headache	
Stearic	115.9	157.6	111.2	36
Palmitic	83.2	150.0	91.4	80.3
Oleic	143.0	278.8	156.3	95.0
Linoleic	41.3	91.8	72.6	137.5

1 Pre-headache cf. headache.

was 180°C, injection port 240°C and detectors 210°C. Platelet serotonin was estimated by a fluorometric technique (Crawford and Rudd, 1962).

Results

Total Plasma Free Fatty Acids

A rise in FFA level of more than 10% was found in 8 patients during the headache period. The highest individual rise, when pre-headache and headache values were compared, was 118%, the mean rise for the group being 49.3%. Mean values for pre-headache, headache and post-headache periods were 350, 485 and 322 nmol/ml respectively. Statistical comparison between headache, pre- and post-headache periods showed a highly significant difference ($p < 0.001$; table II).

Table IV. Fall in platelet serotonin in 8 of 10 patients with migraine

Observation period	Number of observations	Mean serotonin level (ng/10 ⁹ platelets)
Pre-headache	35	462 ¹
Headache	63	361 ^{1,2}
Post-headache	41	441 ²

1 $p < 0.001$.

2 $p < 0.001$.

Table V. Fall in platelet serotonin in 10 non-migrainous subjects after the ingestion of 20g linoleic acid

Sampling time (h)	Mean serotonin level (ng/10 ⁹ platelets)
Pre-ingestion (0)	279
Post-ingestion (2)	198
(4)	191

Individual Plasma Free Fatty Acids

All patients showed a rise in all FFAs during headaches except for one patient in whom there was no change in levels of stearic and palmitic acids. Pre-headache and headache values are shown in table III. The difference between the pre-headache, headache and post-headache periods was highly statistically significant.

Platelet Serotonin in Migrainous Patients

Of the 10 patients, 8 demonstrated a significant fall in platelet serotonin content during the headache period. The mean fall for the group, when pre-headache and headache values were compared, was 22%; the mean values for the pre-headache, headache and post-headache periods are shown in table IV. Statistical comparison between the three periods showed the lower values during the headache period to be highly significant.

Platelet Serotonin in Non-migrainous Subjects

Platelet serotonin content was reduced in all subjects after ingestion of linoleic acid. Maximal reduction was observed at 2 hours in 6 patients and at 4 hours in the remainder. The range of maximal reduction varied from 15.6% to 78.8%, mean value for the reduction being 43.2%. The difference between the pre-ingestion and post-ingestion values was highly significant ($p < 0.001$). The results are summarised in table V.

Discussion

The results of this investigation demonstrate that:

- 1) In the majority of patients a migraine attack is accompanied by a rise in total plasma FFAs and a fall in platelet serotonin content
- 2) In all patients the migrainous episode is associated with a significant rise of plasma linoleic acid, which in fact rose more than any of the other three plasma FFAs estimated
- 3) Ingestion of linoleic acid caused a significant release of platelet serotonin in all normal subjects investigated.

These results assume added significance when it is remembered that linoleic acid is the precursor of all prostaglandins in the body. Linoleic acid can be converted to arachidonic acid, from which prostaglandin E_2 (PGE_2) and $F_{2\alpha}$ ($PGF_{2\alpha}$) are derived, or to dihomo-linoleic acid, which gives rise to PGE_1 and $PGF_{1\alpha}$ (Weeks, 1969).

Of the naturally occurring prostaglandins, PGE_1 is the most powerful vasodilator. It depresses smooth muscle contraction in resistance vessels during intravenous infusion, thus causing headache in man (Carlson et al., 1968). Dilatation of the cranial circulation in the dog (Denton et al., 1972) and differential dilatation of the cranial circulation of the monkey, affecting the external more than the internal circulation, has also been demonstrated following intracarotid infusion of PGE_1 (Spira et al., 1976).

If raised levels of linoleic acid in plasma during migraine contribute to increased prostaglandin formation it is quite possible that they are also responsible for the release of platelet serotonin observed during the migrainous episode. This appears to be quite likely in view of the fact that this study demonstrates the ability of linoleic acid to release platelet serotonin in normal subjects.

Alternatively, the release reaction could be effected through the activity of prostaglandin endoperoxides which are intermediary compounds in the biosynthesis of prostaglandins, with a half-life of about 5 minutes (Samuelson, 1976). Serotonin is known to be vasotonic to the circulation (arteries and resistance arterioles) and reduction of its circulating levels would tend to reduce vascular tone which, coupled with

the vasodilating effects of the E prostaglandins, can lead to pathological vasodilatation in the carotid system, which manifests itself clinically as headache.

It is suggested that linoleic acid plays an important role in the biochemical process of the migraine attack, acting as a serotonin releasing factor as well as a source of PGE₁, the vasodilating action of which can aggravate the clinical symptoms of migraine.

Summary

Total plasma free fatty acids (FFAs), platelet serotonin content and plasma stearic, palmitic, oleic and linoleic acids were estimated in 10 migrainous patients before, during and after a migraine attack. Total and individual plasma FFA levels rose and platelet serotonin fell in most patients. Comparison of the pre-headache and headache mean values showed that of the FFAs linoleic acid rises most during headache. 10 non-migrainous controls had platelet serotonin content estimated before and after the ingestion of 20g linoleic acid. All showed a significant fall in platelet serotonin in the post-ingestion period.

It is known that linoleic acid releases platelet serotonin *in vitro*, and this study suggests that it has the same action *in vivo*. Further, it is the precursor of all prostaglandins in the body and its marked elevation during migraine may serve as a source of increased prostaglandin E₁ (PGE₁) synthesis. It is suggested that linoleic acid plays an important role in the biochemical process of the migraine attack, acting both as a serotonin releasing factor and a source of PGE₁, the vasodilating action of which can aggravate the clinical symptoms of migraine.

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Autonomic Dysfunction in the Landry-Guillain-Barre Syndrome

*R.R. Tuck and J.G. McLeod**

Hypertension, postural hypotension and cardiac arrhythmias are well documented disturbances in the Landry-Guillain-Barre syndrome (GBS). It has been suggested that, in some instances, involvement of the autonomic nervous system may account for these abnormalities and for otherwise unexplained fatalities in patients with this illness (Lichtenfeld, 1971).

A number of tests of autonomic function have recently been used to demonstrate autonomic neuropathy in patients with diabetes mellitus (Bennett et al., 1976; Low et al., 1975). These included tests of sweating and baroreflex sensitivity.

In this paper, the results of similar tests, performed on a group of patients with GBS, will be presented.

Methods

7 patients, 5 male, 2 female, with GBS, aged from 32 to 55 years, were studied. All had a rapid onset of weakness and sensory disturbance. In all but 1 case these symptoms were preceded by a brief 'flu-like' illness. Autonomic investigations were performed between 1 and 9 weeks after the onset of symptoms. The patients were taking no medications which might have affected autonomic function. 5 of the patients were unable to walk and 2 required urinary catheters. All had abnormalities

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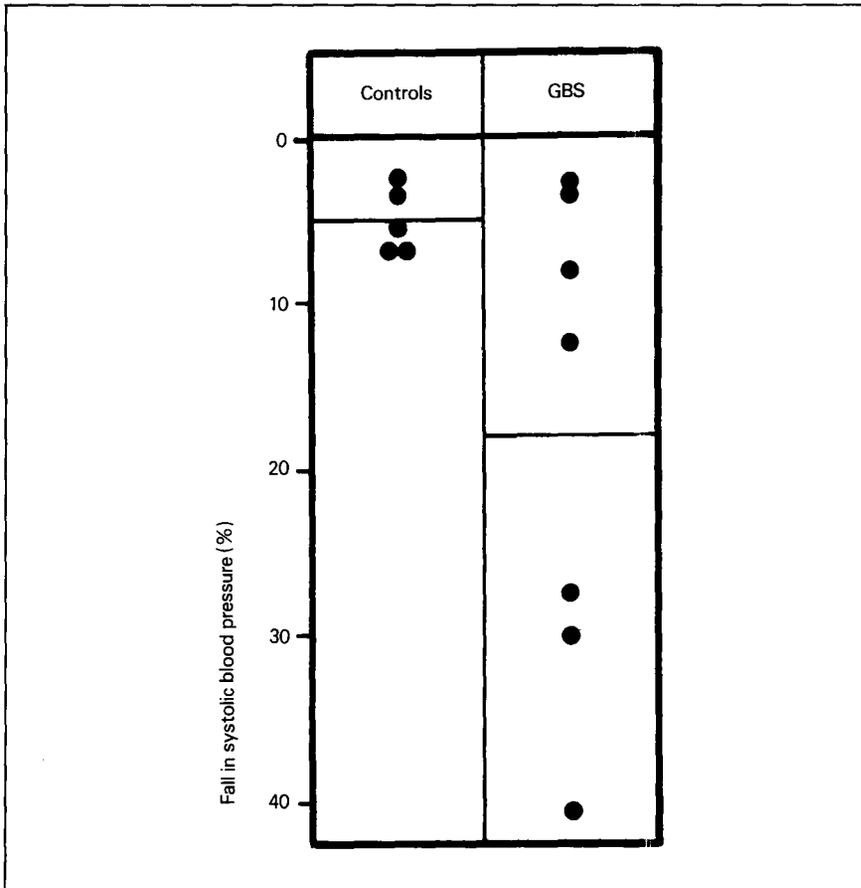


Fig. 1. The percentage fall in systolic blood pressure on tilting, in controls and patients with Landry-Guillain-Barre (GBS) syndrome. Horizontal bars represent the means of each group.

of peripheral nerve conduction and 5 had cerebrospinal fluid protein levels greater than 40mg/100ml.

The sweat test was performed by covering the patients with alizarine red (ICI), a powder which turns purple when wet. They were then warmed with a heating cradle placed over the chest and abdomen. Heating was continued until the oral temperature had risen 1° Celsius or until brisk sweating had occurred on the face.

Tests for postural hypotension and baroreflex sensitivity were performed on the 7 patients and 5 male age-matched healthy subjects. Blood pressure (BP) was recorded directly from a cannula inserted into the left brachial artery. This was connected to a Statham (P23AC) pressure transducer. The mean and pulse pressures

were recorded on a Grass (model 7B) chart recorder. Heart rate (HR) and heart period (HP), which is the R-R interval, were also recorded on the polygraph from lead II of the standard ECG. For estimation of postural hypotension, the subjects and patients were secured to a tilt table and then raised, either until they were vertical or until their systolic BP began to fall below 90mm Hg.

The sensitivity of the baroreflex was measured by comparing increases in HP with transient BP elevations induced with small intravenous injections of phenylephrine (up to 3.0ml of a 100 μ g/ml solution). As BP increases, so does the HP (i.e. the heart rate decreases). Each HP was plotted against the systolic pressure of the preceding pulse wave so that a series of points was obtained relating HP to BP. The baroreflex sensitivity is the slope of the linear regression of these points and the units

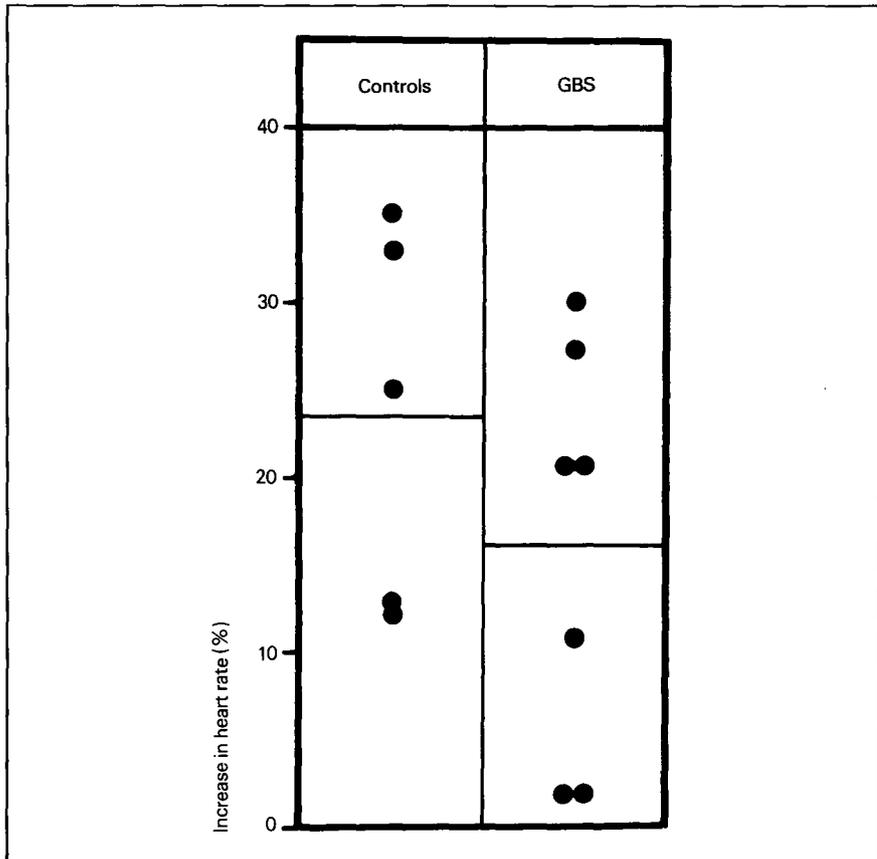


Fig. 2. The percentage increase in heart rate on being tilted in controls and patients. Horizontal bars represent the means of each group.

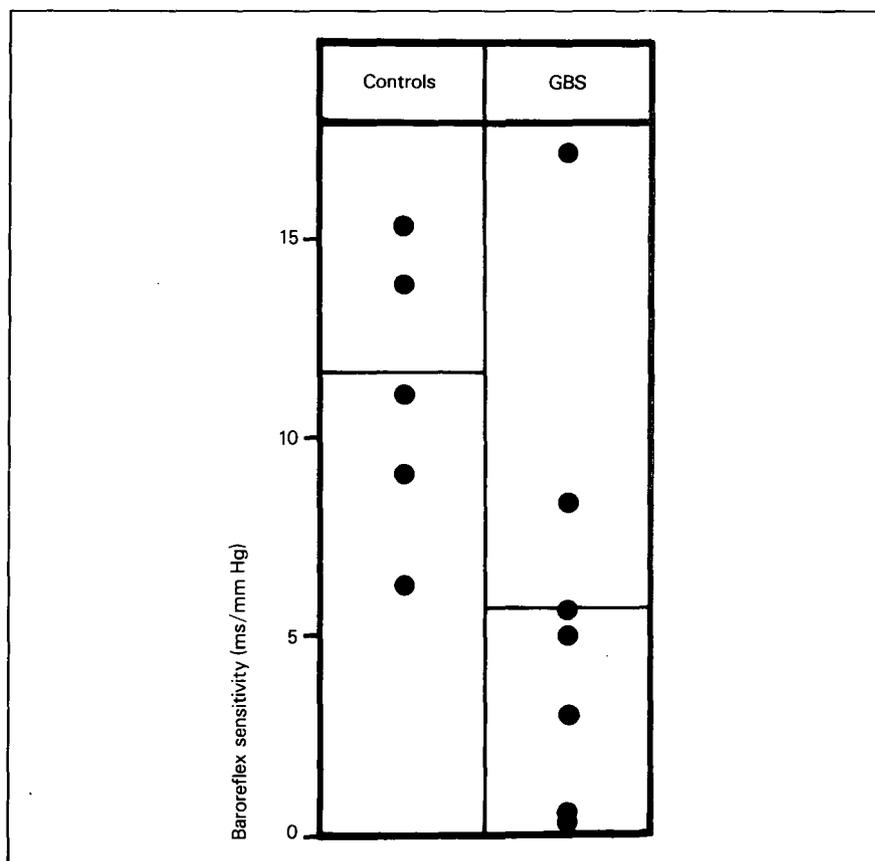


Fig. 3. The baroreflex sensitivities of the controls and patients. The horizontal bars represent the baroreflex sensitivities of the pooled control and patient data respectively.

are ms/mm Hg. HP is used in preference to HR because a more linear relationship is obtained (Smyth et al., 1969).

Results

1 patient could not tolerate the sweat test. Of the other 6, 5 had unequivocal involvement of sweating on the legs. 4 of these also had areas of anhidrosis on the trunk. The remaining patient (who was least affected clinically) had a small area of anhidrosis on the lateral aspect of the right foot and leg but otherwise sweated normally.

Postural hypotension was present in 4 of the 7 patients (fig. 1). In the control group the mean fall in systolic BP was 5.0 (SD 1.9) % compared with 17.9 (SD 13.7) % ($p < 0.05$) in the patients with GBS. The average increase in HR following tilting was 24 (SD 11) % in the controls and 16 (SD 12) % in the patients (fig. 2). These means are not significantly different. In 2 patients, however, the increase in HR was only 1.7% and 1.8% respectively.

The baroreflex in the 5 controls ranged from 6.3 to 15.4ms/mm Hg and in the patients from 0.16 to 17.2 (fig. 3). In 4 patients values were abnormally low, including the 2 who had little HR change with posture. Figure 4 shows the regression lines obtained by pooling the control and patient data respectively. The slope of the former is 11.8 compared with 5.7 for the latter. Thus the baroreflex sensitivity for the patients is approximately half that of the control group.

Discussion

Postural hypotension has been demonstrated in 4 of 7 patients in this study. This could be due to involvement of the sympathetic nerve supply to the splanchnic vascu-

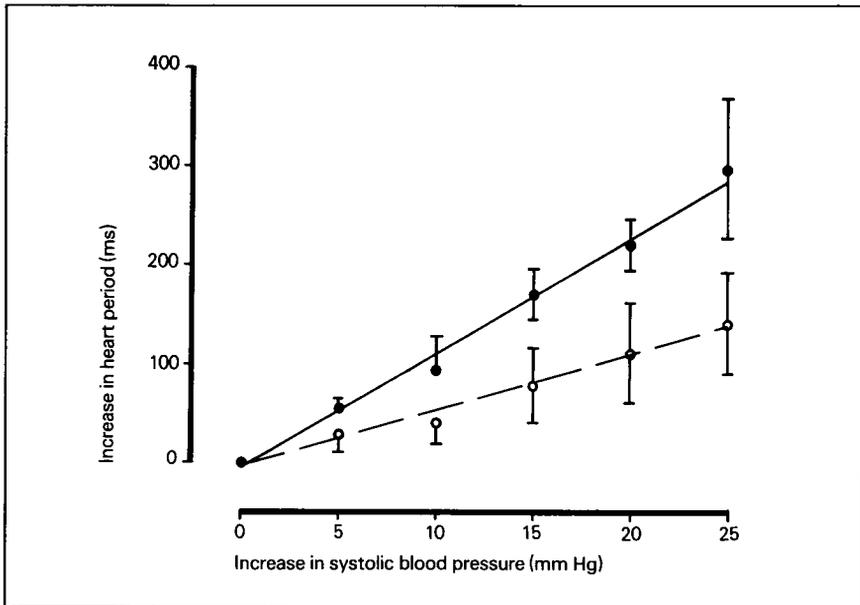


Fig. 4. Baroreflex sensitivities of the pooled control data (solid line) and patient data (broken line). The slopes are 11.8 ($r = 0.84$, $n = 29$) and 5.7 ($r = 0.50$, $n = 42$) respectively. They differ significantly ($p < 0.01$). Vertical bars represent \pm SE.

lar bed which is thought to play a major role in maintaining BP in the upright position (Rowell et al., 1972). However, it could be argued that motor paralysis of the lower limbs contributed to postural hypotension by allowing venous pooling to occur there. One of the 4 patients with postural hypotension had barely detectable lower limb weakness. He did, however, have an abnormal sweat test and reduced baroreflex sensitivity. 2 other patients, who had severe leg weakness, had no postural hypotension.

If one accepts that postural hypotension in some or all of these cases is due to autonomic involvement, the lesion(s) might be in the myelinated fibres of the sympathetic system (i.e. the preganglionic efferent fibres) or in afferents in the 9th and 10th cranial nerves from the arterial baroreceptors. There is evidence from the present study that the sympathetic efferents are involved in GBS. The abnormal sweat tests indicate that this is so. The patients with postural hypotension all had areas of anhidrosis on their abdominal and thoracic walls (as well as the limbs) while 2 of the 3 without a postural fall in BP had sweating abnormalities confined to the lower limbs. The co-existence of postural hypotension and anhidrosis on the trunk may reflect involvement of the sympathetic supply to the splanchnic vascular bed.

The sensitivity of the baroreceptor-heart rate reflex was abnormally low in 4 of the 7 patients with GBS. 2 of these had resting tachycardia (110 and 118 beats/min) and had baroreflex sensitivities close to zero. In normal individuals the bradycardia which follows transient BP elevations is mediated by the vagus nerves (Leon et al., 1970). Atropine blocks this response and produces a resting tachycardia. Thus it is possible that in these patients the vagus nerves might have been subjected to demyelination. However, lesions of the baroreceptor afferent fibres in the vagus and glossopharyngeal nerves could result in both postural hypotension and BP instability. 1 of the 2 patients with almost zero baroreflex sensitivity, who was normotensive prior to developing acute polyneuropathy, developed both postural hypotension and hypertensive episodes while in hospital, suggesting that both efferent and afferent pathways were affected.

Matsuyama and Haymaker (1967) demonstrated perivascular demyelination in the sympathetic chain and white rami of a patient dying with GBS. Recent work from our laboratory has shown that demyelination occurs in both the vagus and splanchnic nerves of animals affected with experimental allergic neuritis, a laboratory disease which is similar in many respects to GBS.

The above investigations provide evidence that the autonomic nervous system is involved in GBS. The results suggest that both the sympathetic and parasympathetic systems are affected.

Summary

Tests of autonomic function have been performed on 7 patients with the Landry-Guillain-Barre syndrome and 5 control subjects. These included a sweat test, and

measurement of both postural hypotension and baroreflex sensitivity. Sweating was definitely abnormal in 5 patients. Postural hypotension was present in 4 patients. The baroreflex sensitivity was significantly reduced ($p < 0.01$) in the patients when compared with the control group.

The results demonstrate that both the sympathetic and parasympathetic nervous systems may be affected in the Landry-Guillain-Barre syndrome.

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Electromyographic Study of Polysynaptic Responses from Muscles Not Supplied by the Stimulated Nerve: Preliminary Report

*J. Vernea**

Polysynaptic reflexes are usually but not always exteroceptive reflexes, most often of flexor type. Unlike monosynaptic reflexes, one of their important features is the phenomenon of plasticity which is caused by the presence in the reflex arc of internuncial neurones. Plasticity includes the following characteristics:

- 1) Variable latency (which is often reduced with increase of stimulus intensity), variable duration, shape and amplitude
- 2) Habituation on repeated stimulation (sometimes also sensitisation)
- 3) Summation of spatial and temporal type
- 4) Variation according to the state of alertness
- 5) Spatial diffusion: they can spread to other muscles, which are not always synergists or antagonists
- 6) Temporal 'diffusion', which is in fact an after-discharge.

The 'local sign' is considered to be a feature of these responses: the reflex discharge returns mainly, if not exclusively, to the same nerve or nerve root. These reflexes are also considered to show double reciprocal innervation: activation of flexors and inhibition of extensors of the ipsilateral side, and activation of extensors with inhibition of flexors of the opposite side.

Two components have been described in these reflexes:

- 1) An early component, with shorter latency, elicited by moderate intensity stimuli and mediated by group II afferent fibres

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Table 1. Polysynaptic responses elicited on stimulation of the median and ulnar nerves at the elbow and wrist in normal subjects and hemiplegic patients. The figures represent the latencies of the responses in msec. R stands for infrequent occurrence of the response and I for inconstancy of the response

Muscle ¹	Stimulation at elbow		Stimulation at wrist	
	median n.	ulnar n.	median n.	ulnar n.
B1	~ 30-40	R~ 40	R~ 35	I~ 35
FCR	R~ 45	R~ 45	R~ 45	R~ 45
EXT	R~ 50	R~ 50	R~ 55	R~ 55
TRI	no response	no response	no response	no response
APB	R~ 50	R~ 50	R~ 55	R~ 55

1	BI	biceps.
	FCR	flexor carpi radialis.
	EXT	forearm extensors.
	TRI	triceps.
	APB	abductor pollicis brevis.

- 2) A late component, with a longer latency, elicited by strong stimulation and mediated by group III afferent fibres.

Whereas there are numerous studies of polysynaptic reflexes in the lower limbs (Kugelberg et al., 1960; Hagbarth, 1960; Dimitrevic and Nathan, 1970; Shahani and Young, 1971; Bathien and Bourdarias, 1972) little has been published in relation to the upper limbs (Shahani et al., 1970; Cambier et al., 1974).

Subjects and Methods

The subjects examined included 15 persons with normal neurological examinations, 7 hemiparetic patients, 5 demented patients and 4 patients suffering from Parkinson's disease.

A Medelec electromyograph MS 6 system, with NT 6 stimulator and AS 6 averager was used. Most of the recordings were made with surface electrodes. On several occasions however, concentric needle electrodes were used, to assess the finer characteristics of the responses. The stimulation was delivered by surface electrodes, and consisted of a 1 msec duration square pulse below the pain threshold, and just above the motor threshold. The stimuli were applied at an interval of at least 20 seconds. The ulnar and median nerves were stimulated at the elbow and wrist, and the

activity was recorded from the following muscles; biceps (BI), triceps (TRI), forearm extensors (EXT), flexor carpi radialis (FCR) and abductor pollicis brevis (APB).

Results

Normal Subjects

On recording simultaneously from the muscles BI, FCR, EXT, TRI, APB during stimulation of the ulnar and median nerves at the elbow and wrist, one could obtain late responses only infrequently, with the exception of the biceps responses and a response in the extensors (table I).

On stimulation of the median nerve at the cubital fossa one could record a late response in the FCR in only 2 subjects. On stimulation of the median nerve at the wrist, one could record a late response of the FCR in 3 subjects, and stimulation of the ulnar nerve at wrist caused a late response in FCR in 4 subjects. The response in

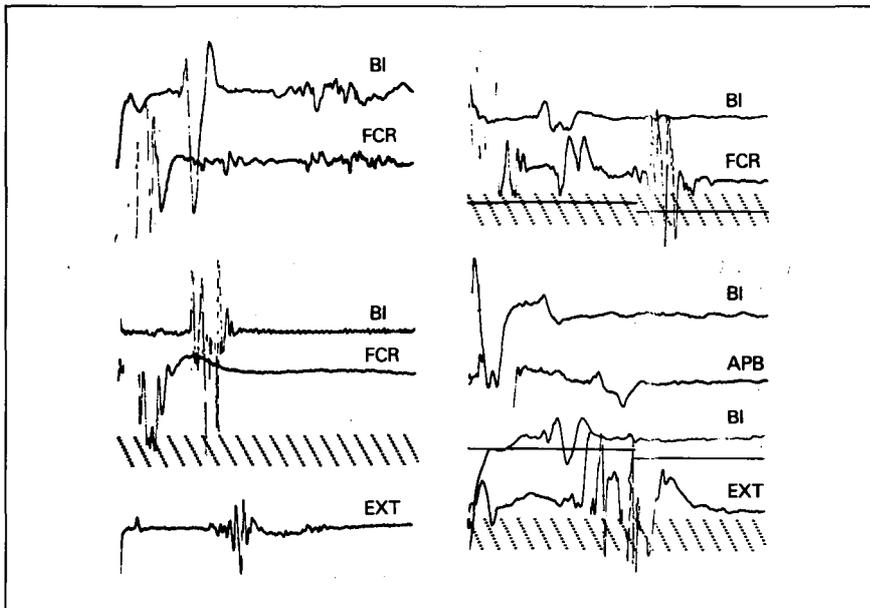


Fig. 1. Stimulation of the median nerve at the cubital fossa. The recordings on the right are from a normal subject, those on the left from a Parkinsonian patient (surface electrodes recordings).

The horizontal projection of a dotted line corresponds to 10msec and its vertical projection to 100 μ V. BI = biceps; FCR = flexor carpi radialis; EXT = forearm extensors; APB = abductor pollicis brevis.

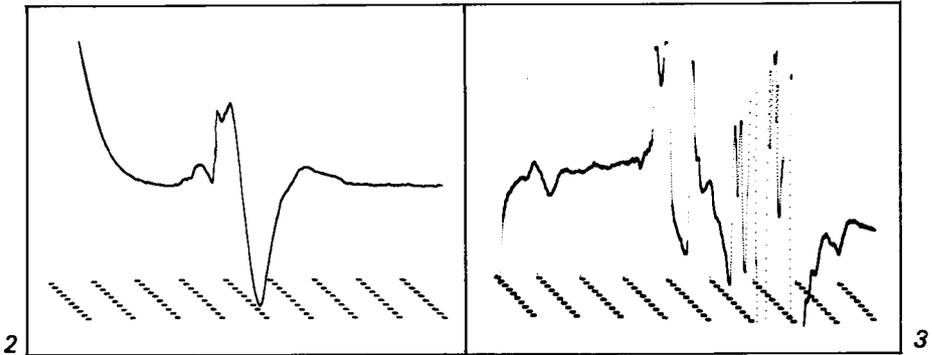


Fig. 2. Late response of the biceps muscle on stimulation of the median nerve at the cubital fossa in a normal subject (surface electrodes).

Fig. 3. Late response of the biceps muscle on stimulation of the median nerve at the cubital fossa in a normal subject (concentric needle electrode recording).

the forearm extensors was present in 11 subjects; its latency was approximately 45 to 55msec and its duration around 30msec (fig. 1). One could often record a late response from the biceps, especially on stimulation of the median nerve at the cubital fossa (9 subjects), and less frequently on stimulation of the ulnar nerve at the wrist (6 subjects). The stimulation of the median nerve at the wrist caused a late reaction in the biceps more rarely (2 subjects). The latency of the biceps response obtained from stimulation of the median nerve at the cubital fossa was between 25 and 45msec (usually around 25 to 35msec) and the latency from stimulation at the wrist was around 40msec. There was no visible contraction of the biceps corresponding to the recorded late response.

The duration of the response was about 30msec (between 10 and 50msec) and its shape tri- or tetra-phasic when recorded with surface electrodes (fig. 2). The recording with needle electrodes showed a pattern similar to the full interference pattern (fig. 3). The amplitude was between 20 and 80 μ V with an average of 200 μ V. This response usually habituated quickly (after 2 to 3 stimuli) even on stimulation, as infrequent as 0.2cps. However in 2 subjects it was facilitated by repeated stimulation at 0.5cps, 1cps and 2cps.

While in 4 subjects slight tension of the biceps or the Jendrassik manoeuvre seemed to facilitate the response, in others no such facilitation was seen. The marked variations in the occurrence, shape, amplitude and latency of the response could not be ascribed to any detectable factor such as position of the upper limb (e.g. pronation or flexion), state of arousal (e.g. sleepiness, apprehension, expectation or lack of expectation of the stimulus), previous stimulation, frequency or even intensity of stimulation. The biceps response could be averaged, but because of its variability the

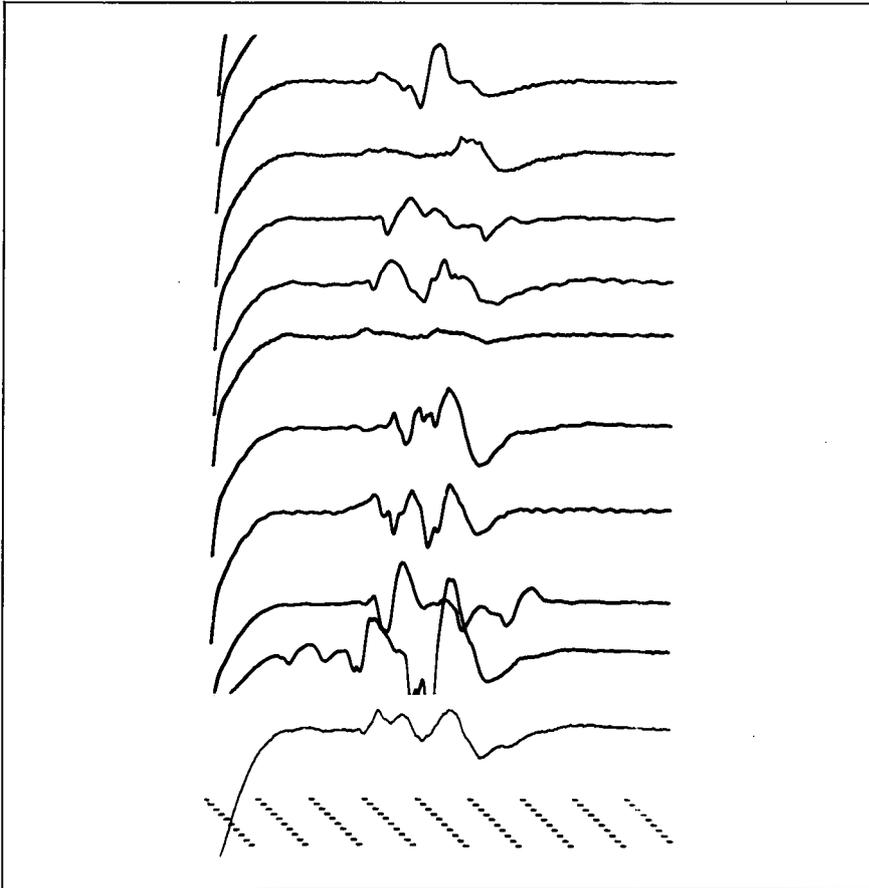


Fig. 4. The biceps response obtained on repeated stimulation of the median nerve at the cubital fossa. The bottom recording represents the result of averaging the curves of 16 stimulations at 25 second intervals.

resulting curves were of lower amplitude and longer latency than most of the individual recordings (fig. 4).

Hemiplegic Patients

In hemiplegic patients, the late responses occurred as infrequently as in normal subjects (table I), and had almost the same features (latency, amplitude, shape and duration). The biceps response however, was obtained more frequently than in normal subjects, being found in 6 patients out of 7.

It was possible to obtain recovery curves for the biceps response on paired stimulation (fig. 5). The recordings in which the first stimulus did not elicit any response were not included in the calculation, because in such cases the second stimulus caused a full response, a situation which would give false results. The excitability curves are different in normal subjects, compared with those in hemiplegics (fig. 6). There is an initial phase of up to 30 to 40msec duration between stimuli, in which the recovery is about 100%. At a 50msec interval between stimuli, there is suppression of the second response. So far the curves from the normal subjects and from the patients can be superimposed. In normal subjects the second response recovers slowly so that at a 400msec interval it reaches around 60% of the initial response. Afterwards, the recovery is from 30% to 60% between a 500msec interval and a 1000 msec interval.

In patients, the second response recovers faster, so that usually it reaches 90% at a 200msec interval and 100% or even over 100% at a 300msec interval, and remains around 100% up to a 1000msec interval.

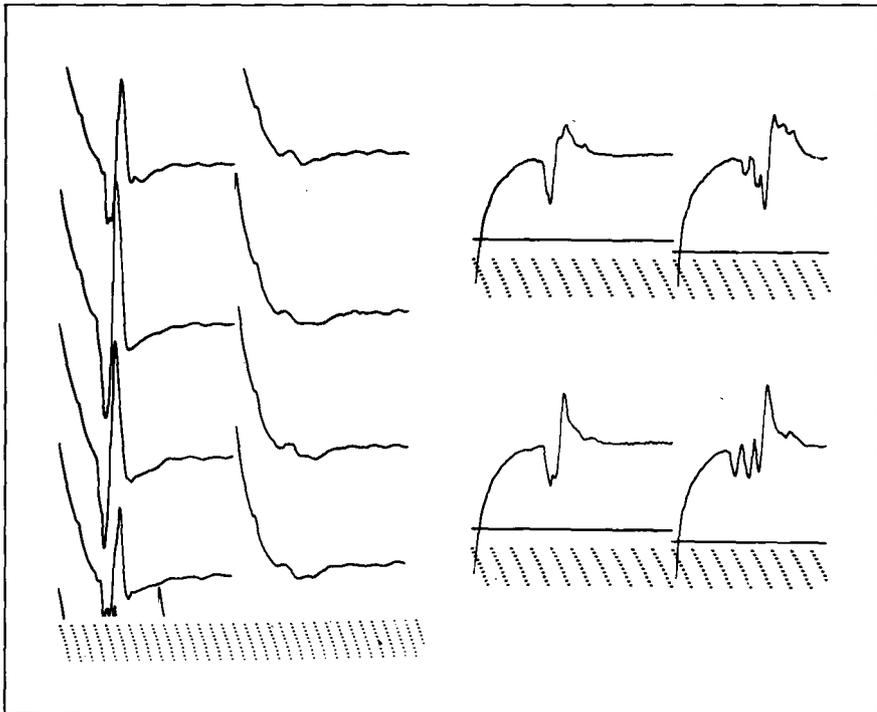


Fig. 5. Paired stimulation of the median nerve at the cubital fossa. Left, normal subject, stimuli at 150msec interval; right, hemiplegic patient, stimuli at 100msec interval.

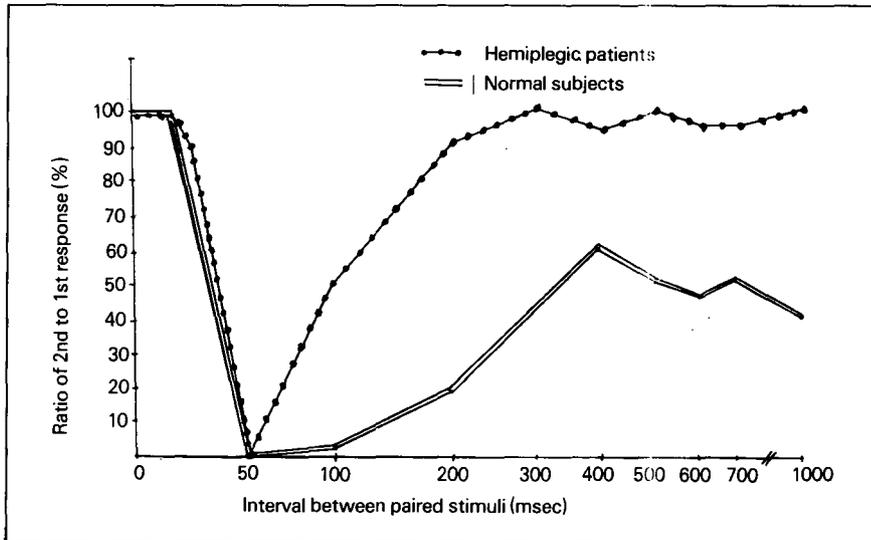


Fig. 6. Excitability curves of the biceps response showing the ratio of the second response to the first response following paired stimulation of the right median nerve at the cubital fossa.

Parkinsonian Patients

In patients suffering from Parkinson's disease the pattern of the late responses was similar to that recorded in demented subjects. As table II shows, one could elicit late responses in all the muscles examined, with the exception of the triceps. Recordings during stimulation of the median and ulnar nerves at the elbow and wrist show the configuration of the late responses in normal subjects and patients suffering from Parkinson's disease (figs. 1, 7 and 8).

Discussion

The responses recorded in our study are polysynaptic responses of short latency (between 25 and 60msec) and correspond to the early or first component described in exteroceptive reflexes (Shahani and Young, 1971). Though their latency is long enough for a long loop reflex, these responses are considered to be of spinal origin and mediated by afferent type II fibres (myelinated, of about 8μ diameter), as shown by animal experiments (Egger and Wall, 1971).

The early responses, involving larger diameter fibres, have a lower excitation threshold than the late responses, mediated by type III fibres of smaller diameter and higher threshold (Shahani and Young, 1971; Cambier et al., 1974). The fact that the

Table II. Polysynaptic responses elicited on stimulation of the median and ulnar nerves at the elbow and wrist, in Parkinsonian patients. The figures represent the latencies of the responses in msec. R stands for infrequent occurrence of the response

Muscle ¹	Stimulation at elbow		Stimulation at wrist	
	median n.	ulnar n.	median n.	ulnar n.
B1	~ 30-40	~ 30	~ 35	~ 35
FCR	~ 45	~ 45	~ 45	~ 45
EXT	~ 50	~ 50	~ 55	~ 55
TRI	R ~ 80	no response	no response	no response
APB	~ 50	~ 50	~ 55	~ 55

1 See table I.

stimulus intensity used was relatively low accounts for our recording of short latency responses only.

The conduction velocity of the afferent limb of the reflex arc could not be estimated by comparing the latencies on stimulation at the wrist and elbow, because of the variation of the latencies on successive stimulation at the same site. In fact, on stimulation of the skin over the biceps, extensors and triceps muscles, in the same conditions as those over the nerve, no late responses could be recorded from the respective muscles. It is noticeable that stimulation of the median nerve at the cubital fossa in normal subjects and in hemiplegic patients, elicited frequent responses from

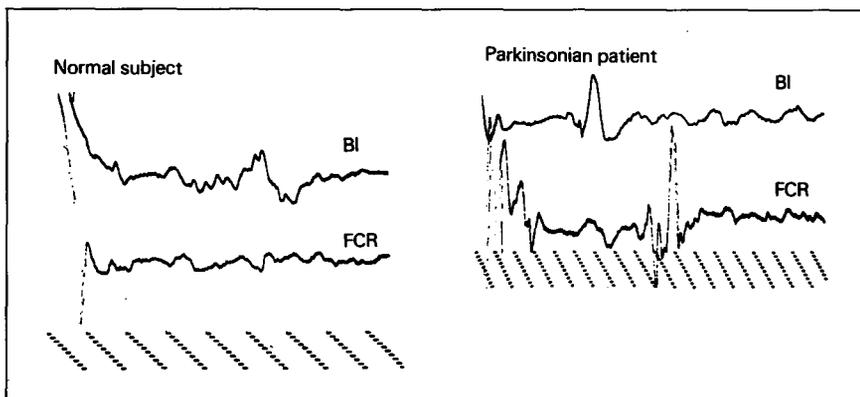


Fig. 7. Stimulation of the ulnar nerve at the elbow in a normal subject and a Parkinsonian patient.

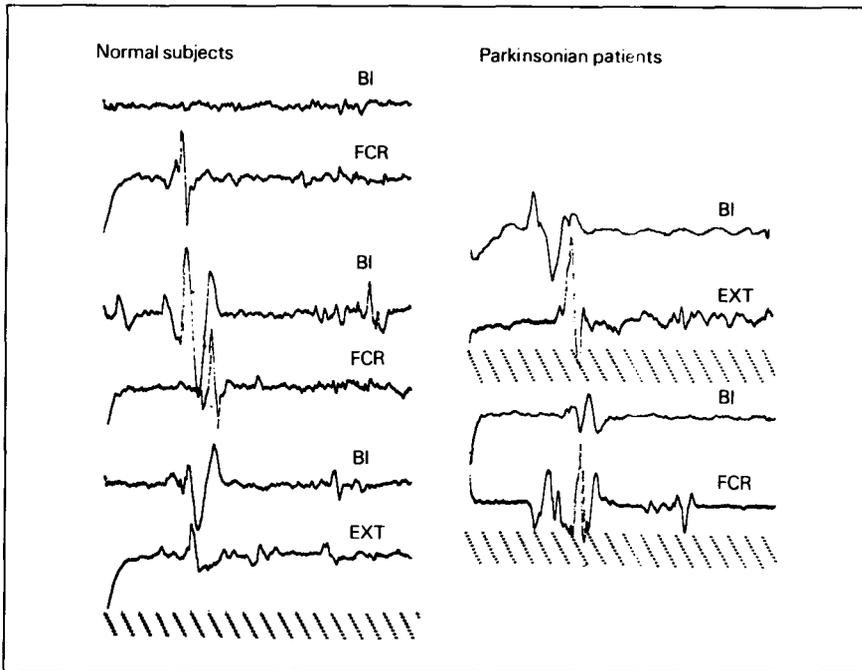


Fig. 8. Stimulation, at the wrist, of the median nerve (top) and the ulnar nerve (middle and lower) in normal subjects, and the median nerve (top) and the ulnar nerve (lower) in Parkinsonian patients.

the biceps muscle and forearm extensors, i.e. from muscles not supplied by the stimulated nerve. The presence of such responses shows that the rule of 'local sign' does not apply to these late responses.

Shahani and Young (1971) advocated stimulation of the skin rather than of nerves, which can contain fibres from large skin areas. However, this does not apply in our cases, since the median nerve never supplies the skin areas over the biceps or over the extensors of the forearm. The biceps response is elicited most easily by stimulation of the median nerve at the cubital fossa, though it can be obtained also by the stimulation of the ulnar nerve at the wrist, and occasionally by stimulation of the median nerve at the wrist or of the ulnar nerve at the elbow. The cause of its variability in amplitude, shape and latency is unclear.

If one examines the recordings with surface electrodes closely one realises that the curve of the response is made of several deflections, which are more or less constant. The variations of the amplitude of these deflections, corresponding to discharges of groups of motor units, and their occasional absence, can account for the observed variations of the response. For instance, if the first deflections are absent, the latency of the reflex is increased.

The late biceps response is probably the equivalent in the arm of the late response in the biceps femoris on stimulation of the sural nerve, described by Hugon (1967). The late biceps brachii response, though having the same morphological features and latency in normal subjects and patients with upper motor neurone syndromes, has a quite different excitability curve in these two situations. Indeed, the recovery after the depression at an approximate 50msec interval, is very fast in upper motor neurone syndromes. At the 150msec interval the recovery in normal subjects is never above 20% whereas in hemiplegic patients it is at least 80%. Consequently, in cases where the biceps response is obtainable, paired stimulation at this interval is of diagnostic significance, and the tedious plotting of recovery curves can be avoided.

This study shows that in Parkinson's disease there is a marked increase in the occurrence of polysynaptic responses (present in all muscles examined), a fact also observed by other authors (Delwaide et al., 1974). We observed the same phenomenon in demented patients. This is probably due to the fact that in demented patients there is, beside cortical atrophy, degeneration of the basal ganglia. This view is supported by other reflex similarities between demented and Parkinsonism patients, such as absent or delayed habituation and widened zone of provocation of the orbicularis oculi reflex (Vernea and Horvath, 1973).

Our findings show that it is possible to elicit a polysynaptic response in the biceps muscle by stimulation of the median nerve, especially at the cubital fossa, and that this response can be useful in the diagnosis of upper motor neurone syndromes. It is also documented that in Parkinsonism, as well as in dementia, where there is involvement of the basal ganglia, early polysynaptic responses can be consistently elicited. These responses were also present in muscles not supplied by the stimulated nerve, including antagonist muscles.

Summary

15 subjects with normal neurological examinations, 7 hemiplegic patients, 5 patients with dementia and 4 with Parkinsonism were examined. A 1msec duration pulse below the pain threshold was applied to the median and ulnar nerves at the elbow and wrist. The activities of the biceps, triceps, flexor carpi radialis, forearm extensors and abductor pollicis brevis were recorded with surface electrodes.

The most frequently observed response in normal subjects and hemiplegic patients occurred in the biceps, and had a latency of about 30msec. The other frequently elicited response in normal subjects and hemiplegic patients was in the forearm extensors.

Recovery curves were obtained for the biceps response. A significant difference between normal subjects and hemiplegic patients was found. In the patients suffering from Parkinsonism, as well as in demented patients, one could record early polysynaptic reflexes from other forearm muscles. This suggests the presence of basal ganglia damage in atrophic dementias.

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Memory Disorder in Vertebrobasilar Disease

*G.A. Donnan, K.W. Walsh and P.F. Bladin**

The amnesic syndrome described by Korsakow in 1889 in patients suffering from chronic alcoholism includes poor retention of new information and hence inability to learn new material. The most striking feature is not only the amnesic defect described but the relative preservation of intellectual function and short term memory, with relatively intact memory for past events. This syndrome, now known as the amnesic syndrome, Korsakow syndrome or axial amnesia has since been shown also to be due to other pathological processes such as cerebral trauma, tumours involving the third ventricle, herpes simplex encephalitis and cerebrovascular disease.

Amnesia secondary to cerebrovascular events as a global phenomenon is well recognised. Reports of a pervasive amnesia of the axial type following posterior cerebral artery occlusion have appeared sporadically in the literature since 1900, e.g. Bechterew (1900); Glees and Griffiths (1952); DeJong et al. (1969). Benson et al. (1973) termed this condition 'amnesic stroke'. We have extended this concept by studying 6 cases of vertebrobasilar insufficiency to determine if a pervasive amnesia exists in these people. The central core limbic or axial structures of the brain, damage to which is responsible for this syndrome, are supplied by the posterior cerebral arteries, which originate from the vertebro-basilar arterial system.

Materials and Methods

6 patients who exhibited signs and symptoms of vertebrobasilar insufficiency were studied. It was of paramount importance to establish clearly the diagnosis of

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this syndrome since the presence of a single symptom, such as vertigo, might merely be a manifestation of labyrinthine disorder. Patients were not included in the study unless other brain stem localising signs were present (e.g. diplopia, change in conscious state, blurring of vision, facial paraesthesias, hemianopia) in conjunction with vertigo and/or nausea and vomiting. The commonest accompanying symptom of vertigo was diplopia with or without change in conscious state (table I). Vestibular and cochlear function tests were performed to exclude further any labyrinthine disorder.

After establishing the diagnosis, patients were tested psychometrically. A minimum of two months later, to establish the relative permanency of the amnesic syndrome, if such existed, they were retested to see if any alteration in scores had occurred. The Wechsler Adult Intelligence Scale (WAIS) and Wechsler Memory Scale I (WMS I) were used on initial testing and WAIS (modified) and WMS II were used on retesting to reduce practice effect. Verbal intelligence quotient (VQ) was used as an indication of premorbid ability in each case, since this measure has been found to be relatively resistant to cerebral insult and reflects the clear mental state of the patient. Memory quotient (MQ) subtests were studied to establish the type of amnesic defect. The relative severity of vertebrobasilar insufficiency episodes, and the frequency and duration of attacks was tabulated with age of patient and degree of amnesic defect as indicated by VQ — MQ difference on initial and final testing. Severity of arterial insufficiency was graded as either Group A (complete prostration) or Group B (attack severe enough to warrant bed rest).

Illustrative Case Record

Mr A.S., a 72-year-old retired quarry owner, was well until 4 days prior to admission to hospital when he developed vertigo, followed by a syncopal episode. Similar episodes followed daily. On one occasion an episode was associated with left facial numbness, right lower limb paraesthesia and mild occipital headache. A further episode involved a period of dysphagia and dysarthria for an hour following the event. No tinnitus or deafness was noted. Alcohol intake consisted of only an occasional glass of wine. The patient had suffered from angina for 2 years but there was no history of skull trauma or previous significant neurological illness.

Examination revealed a fit, healthy looking man who was alert and well orientated. He was mildly hypertensive with a blood pressure of 175/100mm Hg and an irregular pulse due to multiple ectopic beats. There were no focal neurological signs except for bilateral grade I nystagmus. Cerebellar function was otherwise normal. Both Weber's and Rinne's tests were normal. No carotid or vertebral bruits could be heard and the remaining cardiovascular and general examination was normal. There were no stigmata of alcohol.

Neuropsychological assessment was performed on the day of admission. Using WAIS test the patient's verbal IQ (VQ) was 100. The WMS test showed his memory

Table I. Localising signs and symptoms of vertebrobasilar disease

Subject	M/F	Age (years)	Localising symptoms & signs
1	M	72	Vertigo, nystagmus, dysarthria, dysphagia, crossed sensory symptoms
2	F	50	Blackouts, vertigo, visual blurring
3	F	87	Diplopia, vertigo, visual blurring
4	M	69	Vertigo, blackouts
5	F	72	Diplopia, vertigo, blackouts
6	M	64	Diplopia, visual blurring, vertigo

Table II. Neuropsychological assessment results

Subject	Test					
	VQ ¹	MQ ²	(VQ-MQ) ^{1,2}	VQ ³	MQ ⁴	(VQ-MQ) ^{3,4}
1	100	72	28	95	77	18
2	101	89	12	100	86	14
3	110	79	31	110	76	34
4	119	98	21	—	—	—
5	120	99	21	—	—	—
6	100	90	10	102	97	5

1 VQ = Verbal I.Q., first test.
 2 MQ = Memory Quotient, first test.
 3 VQ = Verbal I.Q., second test.
 4 MQ = Memory Quotient, second test.

quotient as only 72. Since the Memory Scale was originally normed against the Wechsler Intelligence Scale this marked difference in scores is evidence of a memory defect.

His symptoms settled over a period of three days while in hospital and he was treated with aspirin and dipyridamole. Psychometric testing was repeated six months later. Over this time he had only had three further mild vertebrobasilar episodes. VQ was then estimated at 95 while MQ was 77. Thus, the VQ — MQ difference had

Table III. Neuropsychological assessment compared with the clinical state of the patients

Subject	Age (years)	Symptom			Test	
		duration	frequency	severity ¹	VQ-MQ ²	VQ-MQ ³
1	72	2 weeks	Daily	A	28	18
2	50	18 months	Weekly	A	12	14
3	87	18 months	Weekly	B	31	34
4	69	10 weeks	Daily	A	21	—
5	72	2 months	Weekly	A	21	—
6	64	9 months	Daily	B	10	5

1 A = prostration; B = confined to bed.

2 First test.

3 Second test.

decreased. The pattern of response on MQ testing indicated marked reduction in ability to retain new material while immediate and long term memory were relatively preserved. This was clearly shown by poor paired associate learning, prose recall and visual reproduction, whereas good scores were obtained with orientation, information and digit span. This was consistent with amnesia of an axial type.

Results

In all 6 cases studied the verbal intelligence quotient on initial testing was greater than or equal to the accepted average of 100 (table II). The memory quotient was markedly depressed in all 6 cases, the greatest VQ — MQ difference being 31 points in our third subject. In all cases the pattern of response on MQ testing was characteristic of an axial amnesia with poor retention of new material with relative preservation of long term and immediate memory. Repeat testing was not possible in Case 5 since the subject died. Case 4 refused retesting. The verbal quotient remained remarkably constant when compared to the initial testing as did the memory quotient except in Case 6 where the VQ — MQ difference had moved from 10 on initial testing to 5 on repeat testing.

Correlation of the clinical criteria of symptom severity, frequency and duration with age of patient and VQ — MQ differences (table III) was tested. No individual symptom parameter could be implicated as the major contributor to the amnesic state in this group of patients.

Discussion

The neuropathological basis of an axial memory defect of the type demonstrated in our cases has been the subject of investigation for some years. It is relatively clearly established that the central core limbic structures of the hippocampus, mamillary bodies and nuclei of the thalamus are primarily concerned in this syndrome. In 1889 Korsakow described his now well known syndrome and in 1891 Gudden postulated that lesions of the mamillary bodies were responsible for the amnesia of the Wernicke-Korsakow syndrome. Scoville and Milner (1957) clearly demonstrated that bilateral hippocampal lesions result in an axial memory defect. Victor et al. (1971) found 'the dorsal medial nuclei of thalamus . . . the parts most definitely related to memory abnormality'. Because of the central position of the structures involved in the amnesic syndrome Barbizet (1970) coined the term axial or mesial amnesia.

A major part of the vascular supply of these central core limbic structures comes from the posterior cerebral arteries. Damage to the axial or mesial structures seems to be the likely aetiology of Benson's syndrome of amnesic stroke, since he had demonstrated occlusion of the posterior cerebral arteries both angiographically and clinically. Benson et al. (1974) suggested that transient ischaemic episodes may result in some transient memory impairment. Our present findings (though tentative) suggest that the memory defect in some cases may be more lasting, though it may need neuropsychological testing to bring it out.

All our patients have demonstrated a clearcut axial amnesia with preservation of verbal IQ and the characteristic pattern within the WMS i.e. preservation of orientation, information and digit span in the presence of relatively poor prose recall, visual reproduction and, above all, poor new paired associate learning. No individual symptom parameter appeared to be more closely related than any other to the amnesic syndrome in our group although further studies may establish a trend.

Further areas of research might involve the degree to which measures of the effectiveness of learning and retention might serve as an index of vertebrobasilar disease.

Differentiation of the amnesic syndrome according to the site of emphasis of the lesion (hippocampal or thalamo-mamillary) by test features such as those reported by Lhermitte and Signoret (1972) may further delineate the nature of the amnesic syndrome of posterior cerebral arterial aetiology. Longitudinal studies of the memory processes in cases of vertebrobasilar insufficiency may help establish if there is improvement in the amnesic features when vertebrobasilar symptoms regress either spontaneously or with treatment.

While it would be premature to suggest that psychometric testing alone could clearly establish the diagnosis of vertebrobasilar insufficiency in a clinical situation where a variety of aetiologies may be considered, it may provide a useful adjunct in the diagnosis of vertebrobasilar disease.

Summary

Previous workers have clearly established that the central core limbic structures of the brain are primarily concerned in the production of amnesia of the axial or mesial type. The blood supply to these structures derives primarily from the posterior cerebral circulation. This was the rationale for Benson's work on 'amnesic stroke' in patients with posterior cerebral artery occlusion. We have extended this concept to show that a similar axial amnesia, as demonstrated by a classical response on Wechsler Memory Scale testing, exists in patients with vertebrobasilar insufficiency. Relative permanency of the amnesic syndrome was demonstrated by repeat testing at least two months after regression of the symptoms. The presence of such amnesia may be of assistance in the diagnosis of vertebrobasilar insufficiency.

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Delayed Radiation-induced Damage to the Brachial Plexus

*R.J. Burns**

The various effects of x-irradiation on the nervous system are well documented (Lampert and Davis, 1964). The complications that are seen clinically are delayed and are usually the result of coincidental irradiation of nervous tissue during the treatment of an adjacent tumour.

Peripheral nerves have the reputation of being more resistant to the effects of radiotherapy than the brain or spinal cord, although there is recent evidence that this is not always so (Bradley et al., 1977). Reports of peripheral nerve damage due to radiotherapy have been infrequent and yet the incidence of, for example, brachial plexus damage following irradiation for breast cancer has been as high as 73% in one series (Stoll and Andrews, 1966). The total dose, field size, field locations and dose rate are probably the most important factors in the ultimate development of the brachial plexus neuropathy.

It is the purpose of the present paper to describe 3 patients with delayed radiation-induced brachial plexus neuropathy, highlighting the clinical features and especially the long latent period between the radiation and the development of the neuropathy.

Case Reports

Case 1

R.U., a 60-year-old woman was first seen in July, 1977 with a 3 year history of painless weakness of her left hand. This had gradually increased so that eventually she could no longer do up buttons. A flex-

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or retinaculotomy had not been of benefit. She had subsequently developed numbness of the hand. In 1959 she had had a radical left mastectomy for cancer of the breast and this was followed by a course of radiotherapy. Treatment began on the 16th July and was completed on the 19th August, 1959 with 3 fields. The left parasternal strip was 4×12 cm and received deep x-ray therapy of 2610 rad and megavoltage x-ray therapy of 2250 rad — a total of 4860 rad in 34 days. An anterior-posterior field 18×8 cm to include the apical axillary and central axillary, lateral and sub-pectoral lymph nodes, received 5250 rad in 25 doses in 35 days. A posterior-anterior field to the axilla only, measuring 8×10 cm received 1890 rad in 10 doses in 35 days. The total mid-axillary dose was 5250 rad.

On examination she had signs of a left brachial plexus lesion. There was weakness involving the muscles innervated from myotomes C5 to T1. The deltoids and spinati were mildly weak, but the most severe degree of weakness was in the finger flexors and extensors and the small muscles of the hand, which were also wasted. Sensory examination revealed an area of impairment to all sensory modalities involving the hand and forearm. The deep tendon reflexes in the left upper limb were absent. The arm was swollen due to lymphoedema. There was evidence of the past mastectomy and radiotherapy.

Electromyography revealed evidence of widespread partial denervation of a varying degree in the left upper limb, with complete denervation in the hand muscles. The motor and sensory conduction studies were abnormal, and were consistent with a brachial plexus lesion.

A diagnosis of radiation-induced brachial plexus neuropathy was made. No treatment was given. In May, 1978 the weakness had possibly increased slightly, but the sensory signs were little changed.

Case 2

P.W., a 44-year-old woman presented in December, 1971 with a 4 year history of progressive weakness of the right hand. She had first experienced difficulty holding a pencil and eventually needed to write with her left hand. Subsequently she could not hold a knife to cut up her food and she was unable to sew or do up buttons. Two years after the onset of the motor symptoms she became aware of numbness in the hand. In 1959 she had had a radical right mastectomy for breast cancer followed by a course of radiotherapy. The anterior-posterior supraclavicular field which included the brachial plexus was 8×8 cm in size and she received 5500 rad in 25 treatments in 36 days. The posterior-anterior and anterior-posterior fields were 8×8 cm in dimension and received 5500 rad over a similar period.

Examination revealed slight weakness of the small muscles of the right hand as well as of the finger extensors and flexors. The right biceps, supinator and triceps jerks were depressed compared with the left and the right finger jerk was absent. Sensory examination revealed mild impairment of all sensory modalities in the right hand.

Electromyography showed evidence of partial denervation in the muscles of the hand and forearm and nerve conduction studies revealed slowing of motor conduction velocity in the ulnar and median nerves with an absent median sensory action potential from finger to wrist. The findings were consistent with a brachial plexus lesion. No other signs could be found apart from evidence of the previous radical mastectomy and radiation treatment.

A diagnosis of radiation-induced brachial plexus neuropathy was made. She was not given any treatment. When re-examined in October, 1975 there was clear evidence of progression with marked wasting and weakness of the small muscles of the hand and the forearm muscles. Electromyography revealed complete denervation in the hand. The deep tendon reflexes on the right side by this time were absent. The sensory signs had not spread although they were more dense than when she was seen originally. This time it was noted that the brachial plexus was tender to palpation. In May, 1978 there had been a slight further progression of the motor deficit but it had not spread beyond the muscles previously involved.

Case 3

E.S., a 69-year-old woman presented in July, 1976 with a 2 year history of numbness of the right hand, beginning in the thumb and index finger and extending to involve the whole hand. She had subse-

quently noted increasing weakness of the hand with difficulty performing fine movements. There was no pain. In 1959 she had had a radical right mastectomy for breast cancer followed by a course of radiotherapy from March 23rd until April 24th. In all she received 22 doses in 32 days, the supra-clavicular field being 8×8 cm in size and the total dose being 5250 rad. The axillary fields, both anterior-posterior and posterior-anterior, measured 8×8 cm, the central axillary dose being 4560 rad in 30 days.

Examination showed weakness and wasting of the small muscles of the hand. The finger flexors and extensors were also weak. There was less severe weakness of the deltoid, biceps and triceps muscles. Sensory examination showed a mild impairment of all sensory modalities in the hand and forearm. The biceps, supinator, triceps and finger jerks on the right side were absent. The brachial plexus was tender to palpation. No other signs could be found apart from the previous mastectomy and radiotherapy.

Electromyography and nerve conduction studies showed evidence consistent with a brachial plexus lesion. A diagnosis of radiation-induced brachial plexus neuropathy was made. No treatment was given. She was examined again in 1977 and 1978 when there was evidence of some increase in weakness of the small muscles of the right hand together with finger flexion and extension.

Discussion

Within the central nervous system, delayed complications of radiotherapy include panhypopituitarism, which has occurred as long as 11 years after irradiation for a nasopharyngeal carcinoma (Fuks et al., 1976), necrosis of brain tissue (Holdorf, 1974) and infarction of brain due to damage to the carotid or intracranial arteries (Conomy and Kellermeyer, 1975). The effects of radiotherapy upon the spinal cord have been well documented. The commonest syndrome is a progressive myelopathy (Burns et al., 1972), but occasional cases of infarction of the cord due to anterior spinal artery occlusion have been described (Reagan et al., 1968) and selective damage to the anterior horn cells causing a motor neurone syndrome has occurred rarely (Sadowsky et al., 1976). Experimentally, the effects of radiation on the peripheral nervous system are well summarised by Thomas and Cavanagh (1975). In 1942, sciatic nerves of rats were locally irradiated with 10,000 rad and no structural or functional disturbances over the next 2 months could be demonstrated. Subsequent experimental studies lent support to the notion that peripheral nerves were insensitive to radiation since doses far in excess of those used clinically did not produce any change in conduction function, although disturbances to membrane function of nerve were demonstrated with high doses.

If the principal effect of x-rays is upon the DNA of the cell chromosomes, then any subsequent expression of damage might depend on the degree of mitotic activity of that cell. In this respect the cells of the peripheral nervous system are clearly quite different to those of the gastrointestinal endothelium or bone marrow. In fact autoradiographic studies (Asbury, 1967) have shown no cells in the DNA synthesising phase in non-injured peripheral nerve, i.e. peripheral nerve is a static non-mitotic

tissue. In the event of injury, when cell division is stimulated, the effects of previous radiation damage will then be manifest, as was shown by Cavanagh (1968).

The clinical descriptions of the effects of radiotherapy on peripheral nerve tissue have been comparatively few. Radiation-induced cranial nerve palsies have been reported (Berger and Bataini, 1977), the commonest nerves affected being the tenth and twelfth. The exact frequency of this complication is not known but probably it is uncommon. The incidence of radiation-induced brachial plexus neuropathy has varied considerably in the few papers in which the frequency is mentioned. It invariably occurs as a result of coincidental treatment for breast cancer. Stoll and Andrews (1966) gave a figure of 73% in some of the patients and 15% in others, while Thomas and Colby (1972) suggested the incidence was 1%. In the series of 237 followed by Notter et al. (1970), 41 patients (17%) were involved, while Ricci et al. (1976) gave an incidence of 2.8%. No attempt has been made to estimate the incidence of this complication in South Australia.

There are a number of factors which are known to be of importance in the eventual development of the neuropathy. These include: level of peripheral nerve, species (in experimental animals), field size, total dose, dose rate, and especially, the time of observation. There are probably other factors such as the volume of the vascular bed. Recently Bradley et al. (1977) have shown in animals that the posterior roots are more vulnerable than the anterior ones, and also that there is variation in sensitivity of the neuraxis depending on the level. Perhaps age, race, climate, the state of the vascular system in general and nerve trauma may also be important. It is also possible that surgery, removal of muscle and occurrence of lymphoedema are of significance and these conditions have not been simulated in animal studies.

There is nothing unexpected about the clinical presentation. It is characterised by a progressive sensori-motor disturbance of the limb which is often painless. The medial cord of the plexus frequently seems to be involved so that symptoms commonly begin in the hand. The condition may not be recognised at first, because the neurological deficit is wrongly located to a peripheral nerve site e.g. the carpal tunnel as in two cases above, or the plexus lesion is thought to be due to malignant infiltration. Nerve conduction studies will help exclude a peripheral lesion; in the 3 cases reported here, electrical findings were consistent with a brachial plexus lesion. Pain was not a feature although it is not uncommon in the condition; with malignant infiltration pain is usual. Even so, as Thomas and Colby (1972) point out, differentiation between radiation-induced plexus neuropathy and malignant infiltration is not always easy and both can occur several years after initial treatment. However, if the symptoms have been present for more than four years, malignant infiltration is most unlikely. Surgical biopsy has been advocated as a means of differentiating the two conditions but it was not thought necessary in this group. The natural history of the disorder is one of progression over several years. So far, total brachial plexus involvement has not eventuated.

Nausea

3 patients on active drug experienced some nausea during the early stages of treatment, including the patient withdrawn because of severe nausea. More gradual increase in dosage allowed continuance of treatment in the other 2 patients.

Hallucinations

Hypnagogic hallucinations, nocturnal confusion and sleep disturbance occurred in 3 patients on active drug. The hallucinations were quite vivid, the patients reporting seeing dogs and other domestic animals, and vivid colours. 1 patient developed paranoid ideation, accusing his wife of infidelity and searching his house each day for intruders. He attempted to alter his will so that his wife and family would receive no money on his death. All these symptoms subsided with reduction in dosage of bromocriptine.

Dopaminergic Effects

2 patients developed oro-buccal dyskinesiae and another developed a dystonic reaction on active drug. 2 patients began to have alternating periods of freezing followed by dyskinesiae ('on-off' phenomenon) or good control alternating with sudden freezing ('akinesia paradoxa'). These symptoms responded to reduction of dosage or more frequent smaller individual doses. Although specific enquiry was made, atropine-like effects, nasal stuffiness and depression did not emerge as significant problems.

Laboratory Tests

Haematology and biochemistry profiles and ECG monitoring produced no evidence of adverse drug effects. 1 patient had previously shown glycosuria before bromocriptine treatment was started, and this symptom had been controlled by diet alone. After bromocriptine was given, he again began to show glycosuria on 40mg/day of the drug. Glucose tolerance tests with insulin levels revealed a mild delay in insulin release with a peak blood sugar level of 190mg % in response to a 50g glucose load. When bromocriptine was continued, glycosuria increased to 2% and the random glucose level was 300mg %. Bromocriptine was stopped and tolbutamide prescribed; the glucosuria is at present well controlled.

Discussion

This double-blind trial to test the efficacy of adding bromocriptine to levodopa therapy in patients with Parkinson's disease has not demonstrated any worthwhile

group, aged 41 to 71 years (mean 62.2 years). 4 were already stabilised on levodopa plus carbidopa at a dosage of 750 to 1250mg/daily (mean 1g/day), and 2 patients were taking levodopa 3g and 4g daily respectively. Mean maximum daily dosage of placebo during the trial was the equivalent of 36.7mg of bromocriptine (range 20 to 60mg). There were no significant differences between the two groups in terms of age, duration of disease or therapy before and during the trial.

Assessment of Response

The results of NUDS and physical examination assessments throughout the trial in the two groups are presented graphically in figure 1. The active drug group had a mean NUDS rating of 36 (range 26 to 45) in the pre-trial period and the placebo group had a rating of 37 (range 31 to 46). Mean PEDS ratings were 15 (range 9 to 27) and 16 (range 10 to 27) respectively. The pre-trial assessments in the two groups are not significantly different. During the treatment period, the active drug group achieved a maximum improvement in NUDS to 39.8 and the placebo drug group to 41.2. Analysis with Student's 't' test shows that the differences between the improvement in the two groups is not statistically different, and in fact the changes themselves are not significant in either group. The PEDS ratings improved to a score of 11.2 in the active drug group and to 11.5 in the placebo group. Again, the differences between the two groups, and the changes from pre-trial assessment, are not statistically significant.

At the completion of the trial, 5 of the 9 patients treated with active tablets were subjectively improved. 4 of the 6 patients on placebo tablets also considered that they had improved. Examination of individual NUDS and PEDS assessments in each of these patients suggested that improvement had indeed occurred in 4 patients on active treatment and 3 on placebo; in the other patients the objective assessment scales remained relatively unchanged. Both NUDS and PEDS showed similar alterations and neither was superior in separating active drug effects from placebo effects.

Adverse Effects

Postural Changes

4 patients complained of dizziness on standing at some stage of treatment with the active drug. In 2 of the 4 cases significant change in pulse and blood pressure occurred on assuming the erect posture: systolic blood pressure fell from 120 to less than 90mm Hg and tachycardia was noted. This symptom was controlled in all cases by dosage adjustment and by instructing the patient to assume the erect posture in stages.

Patients Completing Trial

15 patients completed the 9-months double-blind trial. 9 patients were found to have been taking the active drug. These comprised 8 males and 1 female, aged 61 to 74 years (mean 66 years). 8 had been stabilised on levodopa plus carbidopa at a dosage of 625 to 1500mg/day (mean 900mg/day) and 1 patient was taking enteric coated levodopa 2g/day. Mean maximum daily dosage of bromocriptine during the trial was 31.7mg (range 10 to 60mg). There were 5 males and 1 female in the placebo

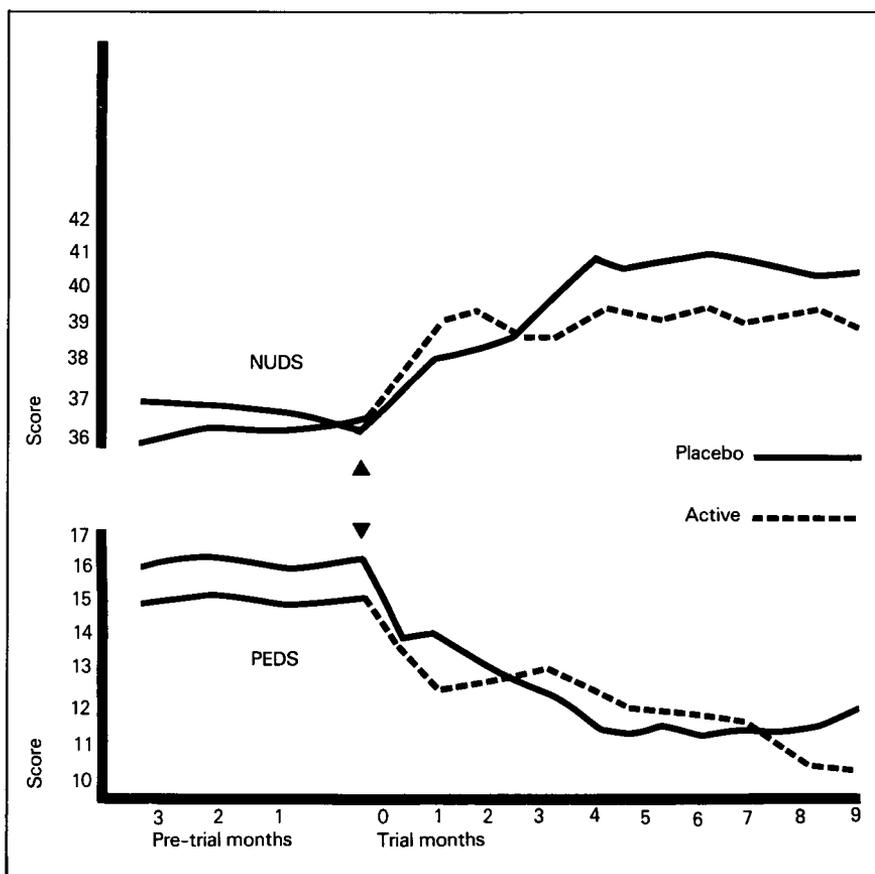


Fig. 1. Disability scores on NUDS¹ and PEDS² testing of 15 patients treated with either bromocriptine or placebo for 9 months.

- 1 Northwestern University Disability Scales (maximum of 50 represents normal function).
- 2 Physical Examination Disability Scales (maximum of 44 represents gross clinical abnormalities).

sions and were never issued with trial medications. 3 patients began trial medication but did not return for their first assessment at two weeks. When contacted, they stated that they did not want to take part in the trial because they felt the medication was not helping them. None had taken more than a dosage equivalent of 5mg/day and each was found to have been given placebo tablets. They were continued on conventional levodopa therapy.

Patients Withdrawn from Trial

22 patients either completed the trial or withdrew because of complications. 3 patients were withdrawn from the study after clinical deterioration necessitated further adjustment of levodopa dosage. The first was severely incapacitated by bradykinesia and freezing of gait, and when no improvement occurred with a dosage of 25mg/day the decision was taken to break the code. After it was found that he was on placebo, supplies of active drug were obtained and he was stabilised on a dose of 7.5mg/day with some improvement. The second patient developed dystonic reactions on 5mg/day of the trial preparation; the code showed that he was on placebo and his dystonia subsequently improved with reduction of levodopa dosage. The third patient was given trial medication to a dosage of 25mg/day without improvement. Because of severe disability the code was broken, revealing that he had been on placebo medication. He subsequently improved when his levodopa dosage was increased.

4 patients were withdrawn because adverse reactions were encountered while taking the active preparation. The first of these initially had improved mobility and reached a dosage of 15mg/day when she fell and fractured her hip. During her stay in hospital she developed severe pitting oedema of both lower limbs; investigations revealed a low serum sodium (123meq/L), together with low serum osmolality (250m OsM/L) and an inappropriately high urine osmolality (400m OsM/L). When water restriction produced no improvement, bromocriptine was withdrawn and frusemide 40mg/day administered. The oedema rapidly resolved, but subsequently returned during therapy with levodopa plus carbidopa alone and required continuous diuretic treatment. The patient has recently been restarted on bromocriptine without recurrence of oedema and with improvement in Parkinsonian features. The second patient reached a dose of 5mg daily and complained of dyspnoea, palpitations, 'giddiness' and general malaise. No cause for these symptoms was apparent on physical examination or laboratory tests but the patient refused to continue in the trial. This man has proved resistant or intolerant to all available medications. The third patient ceased medication at a dose of 5mg/day because of 'light-headedness'. This lady had a history of depression and has had similar non-specific symptoms with no obvious physical accompaniments to other medications. The fourth patient experienced severe nausea on a dose of 7.5mg/day after 2 weeks. The nausea resolved when bromocriptine was withdrawn.

Trial Period

Patients started the trial medication according to their allotted number, with bromocriptine 1.25mg (half a tablet) twice daily for the first 3 days, followed by 1 tablet twice daily (5mg daily) for the remainder of the first week. In the second week 1 tablet was taken 6 hourly. Thereafter dosage was increased as necessary, but in no circumstances more rapidly than 2.5mg/48h during the first 8 weeks. The medication was always to be taken with water and preferably after meals. For the optimal use of available trial materials, and patient convenience, the use of 10mg capsules was restricted to regimens of 40mg or more daily.

Patients were examined at intervals of 2 or 4 weeks throughout the trial. Assessment included general physical evaluation, measurement of lying and standing blood pressure and pulse rate, as well as the use of the Northwestern University Disability Scale [NUDS] (Canter et al., 1961). This scale assesses the degree of functional disability in 5 specific areas: walking, personal hygiene, dressing, eating and speaking. A maximum of 10 points in each area is possible, so that a score of 50 means normal function, and lessening scores mean increasing disability. The scales give a disability profile for each patient, and improvement in a particular area may be followed as well as changes in general performance.

Patients were also graded on a Physical Examination Disability Scale (PEDS) from 0 (no disability) to 4 (severe disability) for the following symptoms or signs: disturbance of gait, bradykinesia, tremor, dyskinesia, retropulsion, rigidity of each upper limb, speech, sialorrhoea, urgency of micturition and depression. Thus a PEDS score of 44 represents maximum disability.

Specific enquiry was made concerning the presence of the following side effects: nausea, vomiting, orofacial dyskinesiae, dystonic posturing, limb chorea, sleep disturbances, confusion, depression, drowsiness, hallucinations, dry mouth, constipation, blurred vision, nasal stuffiness, postural faintness or syncope, and urgency of micturition.

The following laboratory tests were performed at 4-week intervals throughout the trial: full blood count, partial thromboplastin time with kaolin (PTTK), direct Coombs' test, liver function tests, serum uric acid, blood glucose level, blood urea and creatinine. Electrocardiograms were performed regularly where a clinical suspicion of heart disease was present, and in all patients receiving 40mg or more of the trial preparations daily. Urine was analysed and weight was recorded at each visit.

Results

A total of 28 patients were assigned trial numbers and assessments started.

6 patients were unable to continue in the trial for reasons not attributable to the drug under study or its mode of administration. 3 patients attended only pre-trial ses-

The present study was designed to assess the usefulness of the drug in the treatment of Parkinson's disease in patients already established on optimal therapy with levodopa.

Methods

The trial involved a double-blind comparison of bromocriptine and placebo in two parallel groups. Medication consisted of buff tablets scored on one side, containing either bromocriptine 2.5mg or a placebo. Larger capsules, containing bromocriptine 10mg, or placebo, were supplied for the later phase of the trial. Sufficient supplies were available for 40 patients; numbers 1 to 20 were reserved for patients previously established on levodopa 250mg plus carbidopa 25mg ('Sinemet'). Numbers 21 to 40 were reserved for patients previously established on levodopa alone. Patients entering the trial were assigned numbers sequentially within the two groups. They were allocated to active or placebo treatment according to a table of random numbers. The nature and possible risks or benefits of participation in the study were fully explained to the patients and free consent obtained. All had idiopathic Parkinson's disease and attended the Neurology Clinic at the Prince of Wales Hospital for regular follow-up. All had been previously established on therapy with levodopa plus carbidopa, or levodopa alone, but had shown an inadequate or deteriorating clinical response.

1) An inadequate clinical response was defined as the persistence of signs or symptoms which were judged by the patient, relatives and physician as disabling after long term administration of the maximum tolerated dose of levodopa.

2) A deteriorating clinical response was defined as failure to maintain initial improvement at the maximum tolerated dose.

Apart from the signs and symptoms related to their Parkinson's disease, patients were in average physical condition for their age. Geriatric patients were not excluded for mild transient and reversible episodes of confusion, but were not admitted to the trial if there was evidence of gross cerebral damage or dementia. Patients receiving concomitant therapy which may have interfered with the absorption, distribution, metabolism, excretion or action of the drug, or from disorders which could hinder clinical assessment (such as renal, hepatic or severe cardiovascular disease), were excluded from the trial.

Pre-trial Period

Patients were assessed at approximately 12, 8 and 4 weeks prior to entry to the study. During this assessment period established therapy was not significantly altered, and the patients' condition remained relatively static.

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An Evaluation of Bromocriptine in the Treatment of Parkinson's Disease

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Over the last few years it has been established that bromocriptine (2-bromo- α -ergocriptine, CB 154, 'Parlodel'), a synthetic member of the polypeptide group of ergot alkaloids, inhibits prolactin release from the anterior pituitary and suppresses circulating levels of prolactin during puerperal lactation and in abnormal galactorrhoea. Thus in some respects it resembles levodopa; however, its duration of action is greater and the suppression produced can be sustained for many months on repeated dosage (2 to 4 times daily). The mechanism may involve both a direct action on the pituitary and a dopamine-like stimulation of prolactin inhibitory factor release in the hypothalamus.

More recently evidence has been produced that bromocriptine stimulates human growth hormone release in normal subjects but is capable of sustained suppression of this hormone in acromegalics. Although levodopa also produces these effects acutely, the suppression of elevated growth hormone levels in acromegaly is not sustained. Preliminary reports indicate that bromocriptine has a beneficial effect in Parkinson's disease (Calne et al., 1974). Theoretical considerations suggest that a centrally active dopamine agonist not requiring activation by dopa-decarboxylase could be advantageous. Initial studies employed doses of bromocriptine of 7.5 to 30mg/day, with a mean of 18.8mg/day (Claveria et al., 1975) but subsequently doses have been increased up to 75mg per day (Teychenne et al., 1975), then 300mg per day (Lees et al., 1975).

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Conclusion

Radiation-induced brachial plexus neuropathy with a latent period of greater than 7 years is uncommon. However, the true incidence is not known and at the present time the factors responsible for the development of the neuropathy and the pathogenic mechanisms are not fully understood. No treatment is of proven benefit. The condition is usually a painless progressive sensori-motor neuropathy with partial brachial plexus involvement. The deficit can evolve gradually over a period of 3 or 4 years, or more.

Summary

Three patients are described who developed a brachial plexus neuropathy following radiation treatment for cancer of the breast. The clinical features consisted of a painless, slowly progressive sensory motor disturbance, affecting especially the hand. The latent period between the radiation therapy and the onset of the neuropathy was exceptionally long, being 8, 15 and 15 years respectively. Two patients were initially incorrectly diagnosed as having a carpal tunnel syndrome. The possible mechanisms of the insidious neuropathy are discussed. At the present time no treatment is of proven benefit.

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Perhaps the most intriguing feature is the latent period between radiotherapy and the development of the neuropathy, being 15, 15 and 8 years in the above patients. Berger and Bataini (1977) in their series of 25 patients described one in whom a tenth nerve lesion developed 9 years after radiotherapy and a twelfth nerve lesion after 14 years. Two other patients had latent periods of 12 years before the development of twelfth nerve palsies. The interval between radiotherapy and the subsequent brachial plexus neuropathy has varied considerably in the cases that have been reported. The longest latent period in the series of Stoll and Andrews (1966) was less than 3 years, the majority occurring within 2 years and as early as 4 months. The symptom-free interval in the 14 patients reported by Thomas and Colby (1972) varied from 5 months to 20 years with a mean of 6 years. In the 41 cases of Notter et al. (1970) it was 5 to 46 months with an average of 20 months, while in another series of 8 cases (Mumenthaler, 1964) it varied from 15 months to 11 years. Just why the latent period can vary so greatly and in particular why it was so long in the present 3 cases is not clear. There is nothing to suggest that the method of administration of radiotherapy differed significantly from other centres. There is an impression that the neurological progression is more insidious when there is a long latent period.

In the few cases in whom pathological examination has been carried out, fibrosis within the brachial plexus, with loss of myelin, has been demonstrated in severe cases, while in mild cases the nerves have appeared normal although surrounding fibrosis has been present (Stoll and Andrews, 1966). Just why some patients develop a neuropathy and others do not, despite almost identical radiotherapeutic treatment, has not been explained. Further information might be gained if the brachial plexus of all patients who have received radiotherapy for cancer of the breast was examined carefully at autopsy, irrespective of whether there had been symptoms and signs of a brachial plexus lesion. It might be of interest also to perform serial nerve conduction studies in patients who have received radiotherapy to this area to assess the incidence of asymptomatic dysfunction of the nerves irradiated. It seems possible that the delayed effect on the Schwann cell is of particular relevance to the pathogenesis of the neuropathy, but other factors such as nerve entrapment, local fibrous tissue reaction, chronic oedema and ischaemia from endarteritis might also be relevant. The experimental studies of Cavanagh (1968) provided a new dimension in the understanding of delayed effects of radiation on nerve tissue when a functional disturbance following trauma was demonstrated, which increased with the radiation dose. It is possible that the brachial plexus in all people is subject to mild recurrent trauma over a period of years and that the effect of radiotherapy is to inhibit the normal reparative process. Exactly what happens to human peripheral nerve during the latent period is not known.

No treatment was given to the 3 patients described. Steroids, diuretics, triiodothyronine, a 'protein-free extract' and brachial plexus decompression all had their advocates but no convincing evidence has been presented that any treatment is of benefit.

Table V. Results of follow-up, ranging from 6 months to 8 years, of 20 patients with polyarteritis

Treatment	Number of patients	Acute remission	Exacerbation	Died (interval)
Steroids	16	13	5 (still on therapy) 1 (when steroids ceased)	2 (2 months in each case) 1 (from MVA)
No steroids	4	4	0	0

changes were seen on the cardiograph. At the time of discharge he was normotensive on a dose of propranolol 40mg three times a day, and the other abnormalities had resolved.

He showed repeated microscopic haematuria, and his creatinine clearance was significantly reduced at 82ml/minute. His serum creatinine (1.7mg%) and urea (130mg%) both increased initially and thus an intravenous pyelogram, renal arteriogram, and renal biopsy were performed. The intravenous pyelogram showed the right kidney to be enlarged with a simple cyst present at its lower pole as well as calyceal stones. The renal arteriogram showed some small aneurysms within the fine renal arteries. However the major abnormalities were seen in the coeliac arterial system where aneurysms were present within the hepatic, splenic, and pancreatic branches. Incomplete occlusion of several of the major splenic, and one of the major hepatic arteries provided an explanation for his high platelet count (1.5 million/mm³) and for the mildly elevated hepatic enzymes. Renal biopsy demonstrated hypertensive changes, as well as C3 deposition in the mesangium and some small vessels consistent with mild resolving glomerulonephritis. There was no specific arteritis seen. However the diagnosis of polyarteritis nodosa was thought to have been adequately proven.

This patient never showed any symptoms or signs of peripheral nerve involvement and had only the cerebral manifestations of PAN. He was discharged on 60mg prednisone/day and at this time still had a mild microscopic haematuria although his serum chemistry and platelet count were normal and his ESR was 45mm in one hour.

Prognosis

Results of follow-up are summarised in table V. Of the 20 patients, 16 received steroids initially, and 5 were also given cytotoxic drugs (chlorambucil in 1, azathioprine in 2, and cyclophosphamide in 2). Two patients died from PAN, both within 2 months of onset, and neither achieved any remission. Six other patients did enjoy initial remission, but had some form of relapse — usually whilst still taking steroids. All of this group however finally achieved prolonged remission, as did the 3 patients who did not have any significant initial response. Four patients were not treated with steroids and still recovered. Of these two were elderly and with predominantly systemic symptoms, one was 1.5 years of age and had mainly dermatological

Table IV. Results of 'diagnostic' investigations for suspected polyarteritis

Test	Number done	Number normal	Number 'diagnostic'	
Carotid arteriography	5	2	1	occlusion of multiple small vessels
Renal/coeliac arteriography	2	0	1	vascular occlusion and multiple aneurysms
<i>Biopsies</i>				
Skin	5	2	1	
Sural N.	2	0	2	highly suggestive of a vascular neuropathy
Muscle	7	4	3	
Renal	6	0	1	with 2 others highly suggestive because of focal glomerulonephritis
Rectal	7	5	2	
Subcutaneous nodule	1	0	1	

Case 2

An English-born 47-year-old man suffered an acute episode of skin vasculitis involving hands and feet in April, 1976. All immunological tests were normal, his ESR was 13mm in one hour, and the episode resolved with a 2 week course of steroids. The same symptoms recurred in August and October, and towards the end of 1976 he began suffering from intermittent severe generalised headaches. Neurological examination was normal, but an electroencephalogram showed a mild bilateral theta and delta excess; the CSF pressure was slightly elevated at 22.5cm of CSF and the protein was moderately elevated at 85mg%. He was recommenced on 50mg prednisone/day because of a provisional diagnosis of cerebral arteritis. This dose was gradually reduced to 10mg/day and the patient remained asymptomatic until October, 1977 when he suffered an acute episode of vertigo. His local practitioner found his blood pressure to be elevated and he was started on propranolol. Unfortunately he ceased taking his steroids at this time and 5 weeks later was admitted with an acute episode of vertigo associated with a left homonymous hemianopia.

On examination the hemianopia was complete but with macular sparing, the blood pressure was 150/95, and some non-specific abdominal tenderness was present. A computerised tomographic scan performed the next day showed right occipital infarction and an electroencephalogram showed a considerable increase in the bilateral slow activity compared with the previous tracing. Other investigations showed a neutrophilia (93% of 17,700 white cells) with an ESR of 70mm in the first hour. Immune tests (antinuclear antibody, rheumatoid factor, DNA binding, complement, serum electrophoresis and immunoelectrophoresis) were all normal and hepatitis B antigen was negative.

Over the following 3 weeks, the patient was maintained on 60mg prednisone per day, but showed evidence of other organ involvement.

His blood pressure became difficult to control, there was a persistent tachycardia of 90/minute (despite increased propranolol), mild cardiomegaly was present on chest x-ray, and non-specific ST

Table III. Results of 'general' investigations for polyarteritis

Test	Number done	Number abnormal	
Haemoglobin	20	5	mild anaemia usually
White cell count	20	9	leucocytosis
		6	absolute neutrophilia
		6	relative neutrophilia
		4	eosinophilia
ESR	20	15	> 20mm in 1h, none were < 10mm
Chest x-ray	20	5	cardiomegaly usually
Biochemical profile	20	12	globulin > 3.5g% 4 elevated hepatic enzymes 5 elevated cardiac enzymes 1 elevated urea or creatinine 8
Electrocardiograph	18	10	mainly nonspecific ST-T changes
Urine examination	18	8	haematuria
Glomerular filtration rate	7	6	
24h Protein collection	7	4	mildly elevated
Intravenous pyelogram	8	1	stones
Lumbar puncture	8	2	increased protein — one with xanthochromia
Electroencephalogram	10	6	mild, diffuse slow activity
Nerve conduction studies	5	5	generalised neuropathy 2 mononeuritis only 3
<i>Immunology</i>			
Antinuclear factor	15	4	
Rheumatoid factor	10	1	
DNA antibody binding	4	0	(normal < 20%)
Complement	9	5	slight increase
Serum electrophoresis	13	10	increased acute phase reactants
Cryoglobulins	4	1	
Extract of nuclear antigen	1	0	
Hepatitis B antigen	7	0	
Hepatitis B antibody	1	0	

asthma. Symptoms at presentation involved the nervous system in 15 patients, with peripheral neuropathy in 11, headache in 2, abnormal visual fields in 2, diplopia in 2 and epilepsy in 1. Systemic symptoms occurred in 6 patients, with rash and abdominal pains next in frequency.

Neurological examination was normal in only 5 patients. A mononeuritis multiplex was found in 8, a symmetrical polyneuropathy in 4, a 3rd nerve palsy in 2, optic atrophy in 1, and a homonymous hemianopia in 1. General physical examination was unrewarding, the commonest features being hypertension (diastolic greater than 100mm of Hg) in 6, a rash in 4, pyrexia in 3 and a tender abdomen in 2.

The results of the general investigations performed are summarised in table III, and those of the more specific diagnostic tests in table IV. Some patients were thought to have been adequately diagnosed without absolute biopsy proof — because of a highly suggestive clinical picture with 'non-specific' histological or immunofluorescence findings.

Two cases which illustrate peripheral and central nervous involvement are described.

Case 1

An Australian-born 70-year-old woman presented with progressive mononeuritis multiplex. In December, 1976 she suffered an episode of paraesthesia of the feet beginning in one foot and then involving the other a few days later. She also suffered from cramps in both calves and was treated initially for peripheral vascular disease. She was seen by a neurologist in August, 1977 when she was found to be mildly weak in the toe and foot extensors and the ankle evertors, there being vague areas of sensory loss over the dorsum of both feet. Nerve conduction studies showed slowing of the conduction velocity of the right peroneal and posterior tibial nerves. Needle electrode examination showed denervation of mild degree in the right lower limb and the right hand. Serum biochemistry, B12 level, blood count and chest x-ray were normal and her ESR was 25.

It was thought the problem was that of a generalised neuropathy, and as she had been gradually improving, she was treated empirically with vitamins.

The patient returned in early December, 1977 with a 2 week history of an acute, painful neuropathy of the left median nerve. The following day she developed a similar problem of the right ulnar nerve. She was admitted and treated with prednisone 50mg/day. On examination there were no abnormalities apart from the above median and ulnar palsies. Blood pressure was 180/95.

Diagnostic confirmation of polyarteritis nodosa was obtained by gastrocnemius muscle biopsy — and the sural nerve showed severe axonal loss consistent with an ischaemic aetiology. Other investigations performed showed a neutrophilia (70% of 16,000 white cells) and intermittent mild microscopic haematuria. Creatinine clearance was significantly reduced at 51mls/min. Normal tests included biochemical profile, chest x-ray, electrocardiograph, antinuclear antibody, DNA binding, extract of nuclear antigen, serum electrophoresis and immunoelectrophoresis, complement and hepatitis B antigen estimation. Her ESR never rose above 13mm in 1 hour.

Initially in hospital, whilst on steroids, her condition deteriorated and she developed a complete left peroneal nerve palsy, and an acute right sciatic palsy. Her severe painful paraesthesiae gradually decreased and when last examined in March, 1978 she had good return of proximal power of the right leg but only minimal return of function in the other muscle groups. She was able to walk with 2 leg calipers and was still on prednisone 40mg/day.

electron microscopy in 8 out of 27 patients. It was further shown that the titre of antigen fell in some patients during an exacerbation of the illness — consistent with the immune complex theory of aetiology. Immune mechanisms have also been implicated in the occurrence of PAN with angioimmunoblastic lymphadenopathy — a condition associated with intense immunological stimulation and immune complex formation.

Clinically, in PAN one sees both systemic features (such as fever, lassitude, weight loss, myalgia, arthralgia, and anaemia) common to other immune complex diseases, and also features directly caused by haemorrhage or thrombosis of a specific artery. These include gastrointestinal infarction or haemorrhage, hepatic, splenic or myocardial infarction, pericarditis, renal involvement, dermatological features, and many of the neurological complications.

20 patients with true PAN were reviewed to determine their mode of presentation, the frequency and type of neurological disturbances, the investigations most useful in obtaining a diagnosis, and finally the prognosis and its relationship to treatment.

Materials and Methods

All patients admitted to the Royal North Shore Hospital over the last 8 years with a diagnosis of PAN were reviewed — the initial group comprising 26 patients. 6 patients were excluded because there was either insufficient proof of the diagnosis, or because the condition was most likely Churg-Strauss arteritis (with pulmonary involvement).

A review was made of the clinical features of the 20 patients, their laboratory investigations, and their immediate and long term response to therapy. All patients not currently attending one of the hospital clinics were contacted, except for one patient who could not be traced. A long term follow up interval ranging from 6 months to 8 years was obtained. This period was 5 to 8 years in 8 patients, and 2 to 4 years in 7, with a mean of 3.3 years overall.

Results

The age at onset of symptoms varied from 1.5 to 74 years, with only 4 patients less than 30 years of age, and an even distribution throughout the remaining age groups. Males outnumbered females 1.5:1.

There was a past history of a neurological abnormality in 6 patients (these abnormalities being equally divided amongst peripheral neuropathy, unexplained headaches, hemiparesis, and visual disturbances attributable to optic atrophy or oculomotor nerve paralysis). Only 3 had any history of hypertension, and only 2 of

Table II. Differentiating factors in 3 forms of necrotising vasculitis

Type of vasculitis	Size of involved vessels	Histology and stage of lesions	Anatomical predilections
Polyarteritis nodosa	Muscular arteries, occasional arterioles	Necrotising inflammation, coexistence of acute and healing lesions. No extra-vascular granulomas or giant cells	Widespread, common at branching points of arteries. No pulmonary artery involvement.
Allergic granulomatosis (Churg-Strauss)	Muscular arteries, adjacent veins, occasional arterioles	Necrotising inflammation, coexistence of acute and healing lesions. Granulomas and giant cells present	Widespread, lung involvement frequent
Hypersensitivity vasculitis	Arterioles, venules and capillaries	Necrotising inflammation, all lesions at the same stage. No giant cells	Widespread, but common at skin serosal surfaces and glomeruli

Table I. Classification of the necrotising angiitides (Restifor, 1971)

Classification
Periarteritis nodosa
Hypersensitivity or allergic angiitis
Allergic granulomatous angiitis
1) Churg-Strauss type
2) Loeffler syndrome
3) Wegener's granulomatosis
Arteritis associated with collagen diseases (lupus, dermatomyositis, rheumatoid arthritis etc).
Giant cell arteritis
1) temporal arteritis
2) polymyalgia rheumatica
3) Takayashu arteritis

Pathologically, PAN is a necrotising vasculitis of predominantly medium sized arteries. There is initially fibrinoid necrosis of the vessel wall (particularly the medial and the internal elastic lamina) with intimal proliferation and polymorphonuclear infiltration of the vessel and surrounding structures. The inflammation is most prevalent at arterial bifurcations and may involve only part of the arterial circumference. Eventually fibrosis occurs where there has been necrosis and small aneurysms may form as a result of vessel weakness. Proliferation of the internal elastic lamina and fibrosis of thrombosed arteries is also seen in the chronic stage.

Aetiologically there appear to be several possibilities for what are indistinguishable pathological features. Severe systemic hypertension may cause diffuse vascular changes (Zeek, 1952) and similar changes may occur in the mesenteric vessels, particularly after repair of a coarctation. The association of PAN with antigenic stimulation was recognised at the beginning of this century, and its linking with viral upper respiratory tract infections, various specific bacterial infections, anti-sera, and drugs (such as sulphonamides) was summarised in Miller's paper in 1946. Citron (1970) described an angiopathy clinically and pathologically indistinguishable from PAN as a complication of drug abuse. Rumbaugh et al. (1971) suggested that methylamphetamine may be the active agent after experimentally producing cerebral arteritis in 5 monkeys given the substance intravenously. Finally Harris (1977) reported a case of mononeuritis multiplex after heroin addiction, the autopsy showing the typical features of PAN. Other authors have found hepatitis B antigen present in 30 to 40% of patients' sera, as well as a similar substance demonstrated in the vascular lesions of some patients — along with immunoglobulin and complement deposition. Zuckerkman (1976) examined sera from 55 patients with histologically proven PAN and found hepatitis B surface antigen present in 54.5%, with the surface antibody present in 28%. In this group, circulating immune complexes were found by

Neurological Features of Polyarteritis Nodosa

*G.L. Walker**

In 1866, Kussmaul and Maier described a systemic arteritis involving medium sized arteries which they termed 'periarteritis nodosa'. Some years later, in 1887, Eichorst writing on 'neuritis acuta progressiva' described an elderly woman who had fever and a painful neuropathy affecting several nerves. Autopsy showed the large nerve trunks to be diffusely bloody with punctate haemorrhages, and the vessels were congested with a lymphocytic infiltration of their walls. In the past 90 years there have been several reports of the neurological complications of the necrotising vasculitides — of which polyarteritis nodosa (PAN) is the prototype.

Necrotising vasculitis is a general term merely implying inflammation and fibrinoid necrosis of a vessel wall. Attempts at classification of these entities has been extensive over recent years, none being clinically more useful than that of Restifor (1971) [see table I]. The basic differences between the 3 types which are commonly confused (that is PAN, Churg-Strauss arteritis, and hypersensitivity vasculitis) are summarised in table II. In 1952 Zeek called attention to the fact that since the original description, the term 'periarteritis nodosa' had been used as a wastebasket for all vasculitides. Even in recent times, some reported series have included patients from particularly the allergic granulomatosis group — because of both the clinical and at times histological similarities between these diseases. Polyarteritis nodosa should therefore be regarded as a syndrome with incomplete boundaries.

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tion revealed no significant change in either group. Side effects encountered included nausea, dyskinesiae and hallucinations. It is concluded that bromocriptine does not offer any additional benefit in most patients with Parkinson's disease who are well stabilised on levodopa therapy, but may have a place in those patients who encounter side effects due to fluctuations in serum and tissue levels of levodopa.

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additional improvement with doses up to 60mg/day. More than half the patients in each treatment group (active drug and placebo) reported subjective feelings of increased wellbeing and mobility, but this could not be verified statistically with assessment scales of functional disability. Nausea and vomiting caused withdrawal of medication in 1 patient; the main factor limiting dosage increase was occurrence of dopaminergic side effects.

In considering the significance of these results, the following points should be noted. The patients were mostly elderly and had suffered from moderately severe Parkinson's disease for a number of years. They had attended a Neurology Clinic regularly and optimal therapy with levodopa and other anti-Parkinsonian drugs had been established before the introduction of bromocriptine. In many cases, a slight increase of levodopa dosage had evoked dyskinesiae and other dopaminergic side effects. These patients all presented difficult management problems and it appeared that no further improvement could be achieved by dopaminergic mechanisms. The failure of this trial to demonstrate a statistically significant improvement in function in these patients does not therefore imply that bromocriptine does not have a place in the management of Parkinson's disease. Because all patients were already taking optimal doses of levodopa, the incidence of dopaminergic side effects limited the dose of bromocriptine. Since completion of the trial we have been using active drug in an open trial on many of the patients who had been on placebo or who were still poorly controlled. So far it has not been possible to demonstrate a statistically significant improvement in control. However, by reducing the levodopa dosage to suboptimal levels and adding bromocriptine, we have been able to control akinesia paradoxa (1 case) and dyskinesiae (3 cases) without sacrificing mobility and general function. It seems that the place of bromocriptine in the management of Parkinson's disease may be in those cases with marked swings in control and those with side effects associated with fluctuating tissue levels of dopaminergic drug such as 'akinesia paradoxa' and 'on-off' phenomenon. We intend to continue to use levodopa for initial control and to use subtherapeutic doses in combination with bromocriptine in those patients in whom these problems of management are encountered.

Summary

22 patients entered a double-blind trial to test the efficacy of bromocriptine therapy in patients with Parkinson's disease already established on conventional levodopa therapy. 3 patients on placebo withdrew when no improvement occurred and control became complicated. 4 patients on active drug withdrew because of various symptoms, but in only 1 case were these (nausea and vomiting) thought to be a real drug effect. Of the 15 patients who completed the trial, 9 were on active drug and 6 were on placebo. Although more than half the patients in each group were subjectively improved, measurement scales of functional disability and physical examina-

features (responding to antihistamines), and in the last patient mononeuritis multiplex (due possibly to heroin) had already settled at the time of diagnosis.

Four of the patients who enjoyed a long term remission after steroid treatment were able to discontinue this drug after periods ranging from 6 to 12 months and remain asymptomatic during the present follow-up period.

Discussion

The present series demonstrates certain important features regarding PAN. Neurological manifestations are a common finding at the time of presentation. These manifestations were varied but mononeuritis multiplex or symmetrical polyneuropathy were the major findings and were present in 12 out of 20 (60%) patients. Frohnert and Sheps (1967) found a neuropathy in 50% of their patients, and thought that the 'symmetrical neuropathy' resulted from a more extensive mononeuritis multiplex and was therefore of the same pathogenesis — an arteritis of the vasa nervorum. At autopsy this pathological process has been shown to occur in up to 76% of patients with PAN, the incidence varying with the thoroughness with which the nerves were examined. There may be acute and chronic arterial lesions throughout the length of the nerves. Axonal degeneration follows, though this is found in only 44% of cases (Lovshin and Kernohan, 1948) and actual nerve infarction is now thought to be rare. The peripheral nerve lesions are more likely due to a more diffuse ischaemic process (Dyck et al., 1972).

Arteritic lesions in the central nervous system are less common and were found at autopsy in only 4% of 54 cases of proven PAN (Rose and Spencer, 1957). Arteritic lesions with infarction have been reported however, not only in the cerebral cortex but also in the medulla and spinal cord. The resulting symptoms most commonly include headache, meningism and seizures, though paraplegia, bulbar palsies, visual disturbances, and even personality change have been reported.

As suggested in previously reported series, little is to be gained from general haematological, biochemical and immunological studies apart from evidence of an inflammatory process (neutrophilia, increased sedimentation rate, increased globulins, and occasionally mildly increased complement levels). Investigation of renal function is necessary not only from the point of view of general assessment, but also to establish the diagnosis. Renal biopsy is abnormal in at least 60% of cases in most series — though this number includes 'non-diagnostic' features such as hypertensive changes and evidence of old glomerulonephritis. It was diagnostic in only one out of 6 patients in our series.

No one normal biopsy is exclusive of the disease. Biopsy of a tender subcutaneous nodule is best, but such a nodule can not often be found. Biopsy of a tender muscle or a skin lesion also has a high yield, and testicular involvement is common in autopsy studies — though such a biopsy during life is difficult to justify. Sural nerve biopsy usually does not show the arteritis directly, but may be highly suggestive if

severe axonal destruction is seen. Blind muscle biopsy — though useful in our series — was diagnostic in only 11 % (Reimold et al., 1976) and 20 % (Rose and Spencer, 1957) in another series. Rectal biopsy has the lowest yield, but is the simplest to perform.

Prognostic accuracy suffers from the lack of a strict definition of PAN; sample figures for 5-year survival in steroid treated patients are 48 % (Frohnert and Sheps 1967) and 70 % (Sairanen and Wasastjerna, 1972). Whenever treated and non-treated patients are compared, the non-treated survival is significantly less (for example 13 % in Frohnert's series). As in our group, most patients with PAN go into an acute remission and this is often maintained for several years. Although steroids are usually continued in maintenance dosage for many months or years, there are certain patients (8 out of the 20 in our series) who, either after a single course of steroids, or after no steroids at all, will go into remission and remain well without specific therapy. Therefore, provided there is no persistence or recurrence of disease, an attempt can be made to withdraw steroids gradually after a period of approximately 9 months of treatment.

Summary

A series of 20 cases of polyarteritis nodosa (PAN) is presented. Clinical features of 2 cases are described in more detail to illustrate the most common neurological complications. PAN is an uncommon disease but one which usually presents with some form of neurological disturbance, often a mononeuritis multiplex or a symmetrical polyneuropathy. Diagnosis requires a high degree of clinical suspicion as serological tests are at best non-specific, and absolute biopsy proof often requires examination of multiple sites. Early diagnosis is important, as treatment with corticosteroids usually induces symptomatic relief and provides a better chance of long term survival.

If an acute remission is obtained the patient not only should have a good quality of life but in a proportion of cases, where the remission is prolonged, steroid therapy may be ceased.

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Primary Empty Sella Syndrome and Benign Intracranial Hypertension

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The term 'empty sella' was introduced by Busch in 1951 to describe the appearance of the sella turcica at autopsy when the diaphragma sella is incomplete, or forms only a small peripheral rim. He found this latter situation in 21% of 788 patients with no known pituitary disease. In 40 cases (5.5%) the pituitary gland was flattened at the bottom of the sella together with intrasellar arachnoid membrane.

The term 'empty sella syndrome' originally referred to the findings at surgical exploration in a patient who had received irradiation for an intrasellar tumour, and subsequently developed visual symptoms (Colby and Kearns, 1962). Robertson (1967) first demonstrated intrasellar air on pneumoencephalography. Weiss and Raskind (1969) distinguished primary (idiopathic) and secondary forms (following surgical or radiotherapeutic procedures). Neelon et al. (1973) defined the primary empty sella as 'that which admits significant air at pneumoencephalography, in the absence of prior surgery or radiation therapy'.

Kaufman (1968), Berke et al. (1975), Foley and Posner (1975), Weisberg et al. (1975) and others have all drawn attention to the occurrence of patients with benign intracranial hypertension among cases of the primary empty sella syndrome.

Case Reports

Case 1

A 37-year-old female Sicilian immigrant presented to her family doctor with a 6 month history of headaches which were constant and generalised. There was no diurnal exacerbation and no nausea, visual,

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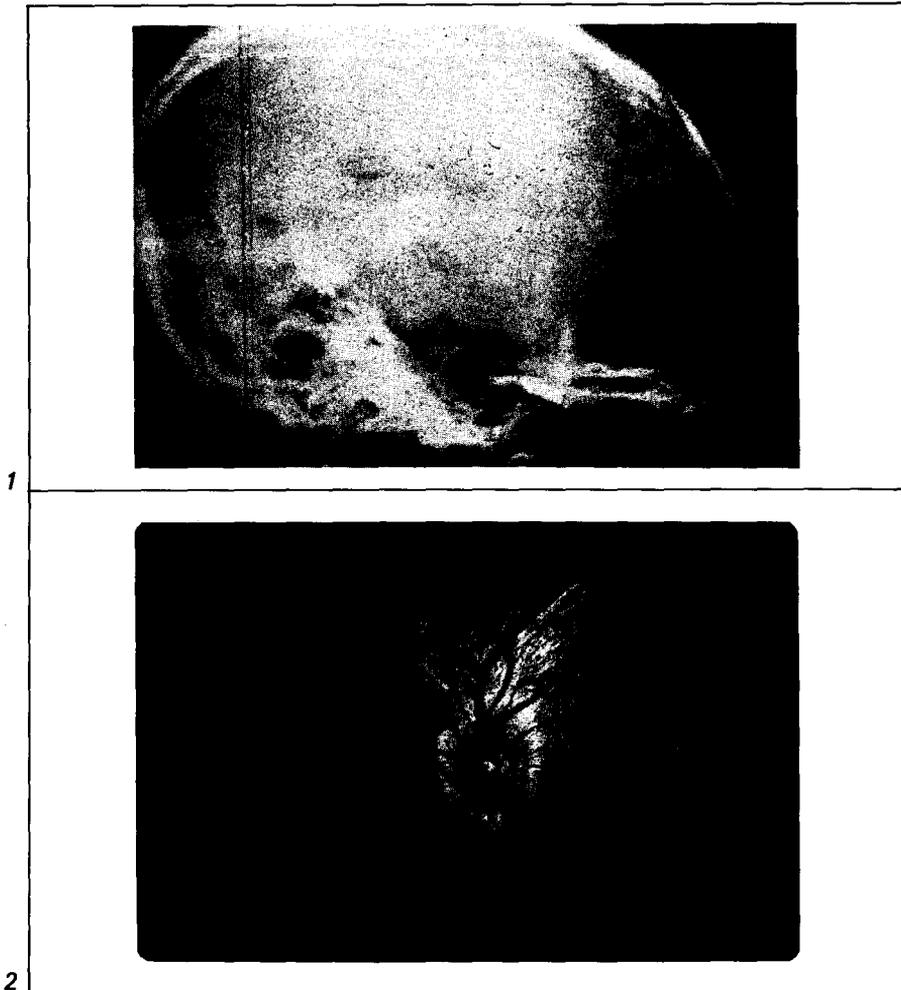


Fig. 1. Plain skull x-ray showing the 'ballooned' pituitary fossa with approximation of the anterior and posterior clinoid processes — the 'closed' configuration.

Fig. 2. The left fundus, Case 1, showing mild chronic papilloedema.

endocrine or additional neurological disturbance. A skull x-ray demonstrated a 'ballooned' pituitary fossa (fig. 1) and she was referred for neurological assessment.

Other than a finding of obesity, initial general, ophthalmological and neurological examinations were all normal. Pituitary function tests, including serum prolactin, gonadotrophins, growth hormone, thyroid stimulating hormone and insulin tolerance tests were also normal.

3 months later, at follow-up examination, her visual acuity was 6/5 on the right and 6/6 on the left with normal colour vision and normal visual fields. However there was mild left papilloedema (fig. 2) and

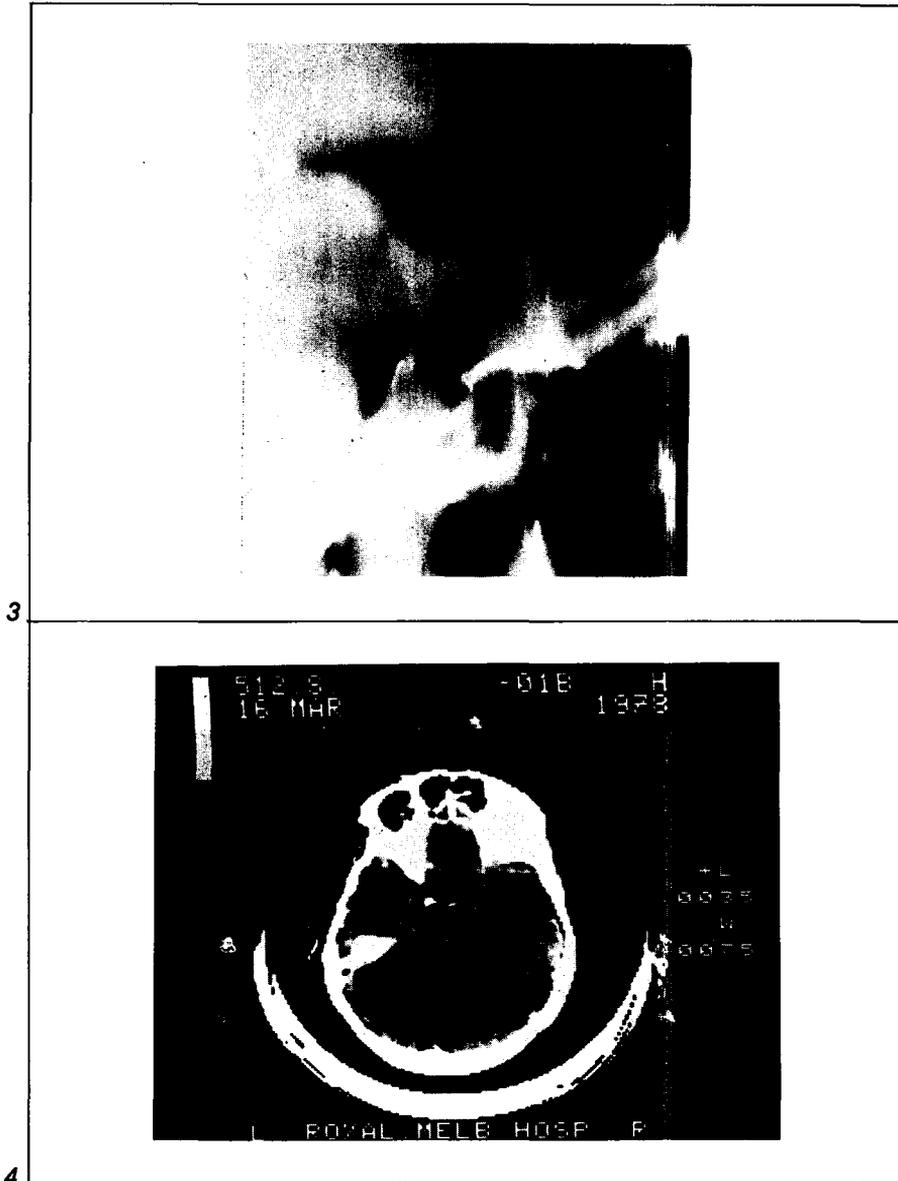


Fig. 3. Pneumoencephalogram, Case 1, demonstrating intrasellar air, and the absence of pituitary tumour.

Fig. 4. Computerised axial tomography, Case 2, showing an enlarged sella with internal density consistent with cerebrospinal fluid.

a left afferent pupillary defect. A CT brain scan and optic canal x-rays were considered to be normal, although retrospectively the CT scan showed probable intrasellar fluid.

6 months later the same findings were confirmed on examination. However the mild papilloedema was now bilateral. The patient was admitted to hospital and lumbar puncture and pneumoencephalography were performed. The opening pressure of the CSF was 290mm with normal biochemistry and cytology. Pneumoencephalography (fig. 3) demonstrated intrasellar air, confirming the diagnosis of the primary empty sella syndrome in association with benign intracranial hypertension.

Subsequently the patient has been managed with oral 50% glycerol solution and serial lumbar punctures, with resolution of her headaches and disc swelling.

Case 2

A 67-year-old obese Australian widow was referred for investigation, after a skull x-ray, prompted by 2 months of constant headache, revealed an enlarged pituitary fossa. On examination her visual acuity was 6/5 in both eyes with normal colour vision, fields and fundi. The remainder of the neurological and general examination was normal.

Review of her plain skull x-rays showed that the sella was globular in shape and deepened in the vertical direction. In the lateral films, calcification was noted to overlie the sella and tomograms showed it to be in the parasellar region. This was assumed to be due to calcification in the cavernous portion of the left internal carotid artery. A CT brain scan showed normal sized ventricles but an enlarged sella with a density consistent with cerebrospinal fluid (fig. 4). At lumbar puncture the pressure was mildly elevated at 230mm and analysis was normal. A pneumoencephalogram showed air to enter the sella, confirming the diagnosis of primary empty sella syndrome.

Pituitary function tests have been performed and the results suggested a diminished functional reserve. Target gland hormone levels (thyroid function, cortisols) and serum prolactin were normal, but insulin-induced hypoglycaemia resulted in subnormal elevations of serum cortisol and growth hormone. Baseline gonadotrophin levels were also lower than expected. Although these abnormalities revealed some anterior pituitary dysfunction, they were not thought to be clinically significant.

Discussion

Clinical Features

The empty sella syndrome usually occurs in women, of all age groups. As in our cases, headache is the outstanding presenting symptom, and the usual indication for the skull x-ray which reveals the abnormal sella turcica. Jordan et al. (1977) reviewed 12 of their own cases, as well as 247 cases in the literature and found that the other key features of the clinical profile were obesity, hypertension, benign intracranial hypertension and cerebrospinal fluid rhinorrhoea. It is of importance that all of these conditions may be associated with raised intracranial pressure. The CSF rhinorrhoea, which occurred in 9.7% of these cases, is due to an abnormal fistula between the herniated subarachnoid space and the sphenoid sinus.

Endocrine Studies

The finding of an enlarged or abnormal sella turcica may suggest the presence of an intrasellar, or parasellar tumour and endocrine studies are thus performed to

reveal functional pituitary adenomata. Endocrine abnormalities also occur in the primary empty sella syndrome, but are rare and are usually revealed on detailed laboratory investigation, rather than being clinically evident. Thus, they may reflect diminished pituitary reserve, rather than clinical malfunction. Figures in the literature are somewhat contradictory, and seem to depend on techniques and parameters used. Thus Brisman et al. (1972) reported that 58% of 19 of their patients with the empty sella syndrome had a decreased response of plasma growth hormone to insulin-induced hypoglycaemia, or low plasma luteinising hormone levels. No patients had clinically significant hormonal deficits.

More recently, Jordan et al. (1977) extensively studied endocrine function in 10 of 12 patients with the primary empty sella syndrome. They assayed plasma and cerebrospinal fluid adenohipophyseal hormone levels (adrenocorticotrophic hormone, growth hormone, prolactin, thyroid stimulating hormone, luteinising hormone and follicle stimulating hormone), target gland hormone levels (cortisol, urinary 17-hydroxycorticosteroids, thyroxine and T3-resin uptake) as well as tests of growth hormone and adrenocorticotrophic hormone reserve. 9 of these 10 patients had normal endocrine function. One had a prolactin-secreting tumour. Our second case demonstrated reduced pituitary functional reserve which was not clinically significant.

Careful pituitary function testing is of at least some differentiating value between empty sella syndrome and pituitary tumour. It would appear that diminished pituitary reserve can be demonstrated in a minority of cases of the empty sella syndrome. However the finding of abnormal endocrine function may influence the management of an otherwise typical case of empty sella syndrome toward the performance of major neuroradiological studies, particularly pneumoencephalography.

The finding of endocrine malfunction in some patients with the empty sella syndrome would seem to correlate well with the flattened gland visualised radiologically or at autopsy, due to the pressure of the herniated, pulsating subarachnoid space in the sella turcica.

Visual Function

Visual disturbances, although common in the secondary empty sella syndrome, are rare in the primary empty sella syndrome. Blurred vision and decreased acuity have been described (Berke et al., 1975) and visual field abnormalities have occasionally been documented. Papilloedema, due to associated benign intracranial hypertension, as in our first patient, is well recognised and was present in 8% of subjects in a review of 130 cases of empty sella syndrome collected from the literature (Foley and Posner, 1975).

The most frequent field abnormalities, demonstrated by perimetry, have been:

- 1) Peripheral field constriction (without raised pressure)
- 2) Varying degrees of bitemporal hemianopia or quadrantanopia

Perspective is provided by the rarity of these visual field abnormalities in large series of the empty sella syndrome. Thus Weisberg et al. (1976) had 25 patients with no field disturbances and Neelon et al. (1973) had 30 cases with normal fields and 1 patient with an unexplained field abnormality.

Optic atrophy with bitemporal hemianopia was documented in a case study by Xistris et al. (1977). They suggested two pathogenetic mechanisms in the formation of these visual defects:

- 1) Compression of optic nerves and chiasm by overlying structures such as the third ventricle due to flattening of the pituitary gland, and subsequent pituitary stalk traction.
- 2) Sagging of the optic nerves and chiasm into the enlarged and empty sella with subsequent vascular compromise.

Radiology of the Empty Sella

As in our 2 cases, the diagnosis of empty sella syndrome is usually suggested by the plain skull x-ray. Kaufman (1968) characterised the empty sella as a spectrum of remodelling and non-tumorous enlargement of the sella, although he also noted the empty sella could appear normal on plain x-ray. The sella is usually enlarged. 26 of 31 patients (84%) with empty sella syndrome had enlarged sellae (Neelon et al., 1973). The authors also emphasised the characteristic shape of the sella in the empty sella syndrome. 15 of their 26 patients had the classical appearance of 'symmetrical ballooning' of the sella with preservation of the anterior concavity of the dorsum sella and little thinning or fragmentation. The anterior and dorsal clinoid processes remained approximated, ie the 'closed configuration'. This closed or normal configuration was demonstrated in both of our cases (fig. 1) and is very useful in the differentiation of an abnormal sella due to the empty sella syndrome and that due to pituitary tumour. Although the configuration of 11 of Neelon's cases was indistinguishable from that produced by pituitary tumour, examination of the sellae of 100 patients with proven pituitary adenomata revealed none with the closed configuration.

The definitive diagnosis of empty sella can only be made by pneumoencephalography. With the patient in a brow-up or hanging head position air enters the confines of the sella deep to the diaphragma sella. Its presence is confirmed by tomography in coronal and sagittal planes (fig. 3).

Recent advances in computerised tomography indicate that it has a definite place in the diagnosis of empty sella. The difficulties of diagnosing lesions close to the skull base have been emphasised (Bajraktari et al., 1977). However Rozario et al. (1977) reported that all of 19 patients with an empty sella proven by pneumoencephalography were correctly diagnosed by CT scan with no false negatives. Using a group of 10 patients with pituitary tumours (on PEG) as a control group, 3 patients were incorrectly diagnosed on CT scan as having empty sella syndrome. All 3 had prolactin

secreting tumours which had necrotic centres at operation. These necrotic centres were thought to be responsible for the low attenuation values within the sella.

Bajraktari et al. (1977) pointed out the diagnostic problems caused by artefactually low intrasellar attenuation values due to:

- 1) Relatively thick 13mm standard brain slices scanned by CT
- 2) Computer overshoot errors immediately adjacent to the bony margins of the sella turcica

However the diagnostic potential of computer reconstruction of scan slices in the coronal plane was well demonstrated, as was the value of intrathecal injection of the water soluble contrast medium metrizamide which produced enhancement of the sellar contents (CSF).

Both our cases demonstrated the combination of the globular sella turcica ('symmetrical ballooning') together with CT scans demonstrating intrasellar attenuation values of CSF (fig. 4). In our 2 cases pneumoencephalography was performed to make a definitive diagnosis of empty sella syndrome, and to exclude pituitary tumour. Jordan et al. (1977) however, suggested that such patients with characteristic features of the empty sella syndrome (including 'closed' sella configuration, normal visual fields and pituitary function studies) could safely be followed up at regular intervals to avoid the potentially dangerous techniques of pneumoencephalography or arteriography. CT brain scan would appear to be a valuable, additional confirmatory tool in the diagnosis of empty sella syndrome, and particularly in the avoidance of unnecessary invasive neuroradiological studies.

Pathogenesis of the Empty Sella Syndrome and its Relation to Benign Intracranial Hypertension

The cluster of shared characteristics of the empty sella syndrome and benign intracranial hypertension is of great interest. Foley and Posner (1975) drew attention to this similarity in their review of the literature involving 130 cases of the empty sella syndrome and 138 cases of benign intracranial hypertension (table I). They found that female gender, presentation with headache and elevation of intracranial pressure were hallmarks of both groups. As well, a minority of patients with both disorders had visual field defects and endocrine abnormalities.

In addition to this similarity of the clinical features of the two syndromes, review of series of cases of benign intracranial hypertension reveals a significant percentage of the empty sella syndrome, and *vice versa*. Thus Weisberg et al. (1975) found 5 cases of an associated empty sella syndrome among their last 50 cases of benign intracranial hypertension (10%), whilst Neelon's series (1973) of empty sella syndrome revealed 13.1% with benign intracranial hypertension, and Berke's series (1975) of empty sella syndrome revealed 15.8% with benign intracranial hypertension.

Table 1. Comparison of findings in 130 cases of empty sella syndrome and 138 cases of pseudotumour cerebri from the literature

Patient details	Primary empty sella syndrome (130 cases)	Pseudotumour cerebri (138 cases)
Age (years)	16-63	6-56
Sex (female:male)	4:1	4:1
Headaches	79%	80%
Papilloedema	8%	100%
Visual field defects	16%	5%
Endocrine symptoms	25%	20%
Elevated CSF pressure	65% ¹	100%

¹ The 65% incidence of elevated intracranial pressure represents 26 of 43 patients in whom pressure was measured.

What then is the basis for this interconnection? The most plausible explanation is provided by consideration of the aetiology of the empty sella syndrome. Neelon et al. (1973) considered four possible mechanisms:

- 1) Rupture of an intra or parasella cyst
- 2) Infarction of the sellar contents
- 3) Pituitary hypertrophy and abiotrophy
- 4) Transmission of CSF pressure through a congenitally defective sellar diaphragm

They concluded, as did Kaufman (1968), that the fourth explanation was the most plausible on the basis of deficiency of the diaphragma sella and the pulsatile CSF pressure, both normal and elevated.

Foley and Posner (1975) hypothesised that as the empty sella syndrome is much rarer than the 39% of a random group of patients with diaphragmatic incompetence (Bergland et al., 1968), there must be a chronic elevation of intracranial pressure, in addition to a deficient diaphragmatic sella, to produce a prolapse of the subarachnoid cistern into the sella turcica. Raised intracranial pressure occurs in a variety of conditions including benign intracranial hypertension (pseudotumour cerebri), the Pickwickian syndrome (Kaufman, 1968) and congestive cardiac failure (Merritt et al., 1938). In the majority of cases, benign intracranial hypertension with or without the fullblown syndrome may be responsible for the raised pressure producing the herniation. Our first patient undoubtedly had pseudotumour cerebri and the second had mildly raised intracranial pressure, without apparent cause. It is possible that she may have suffered benign intracranial hypertension at some time.

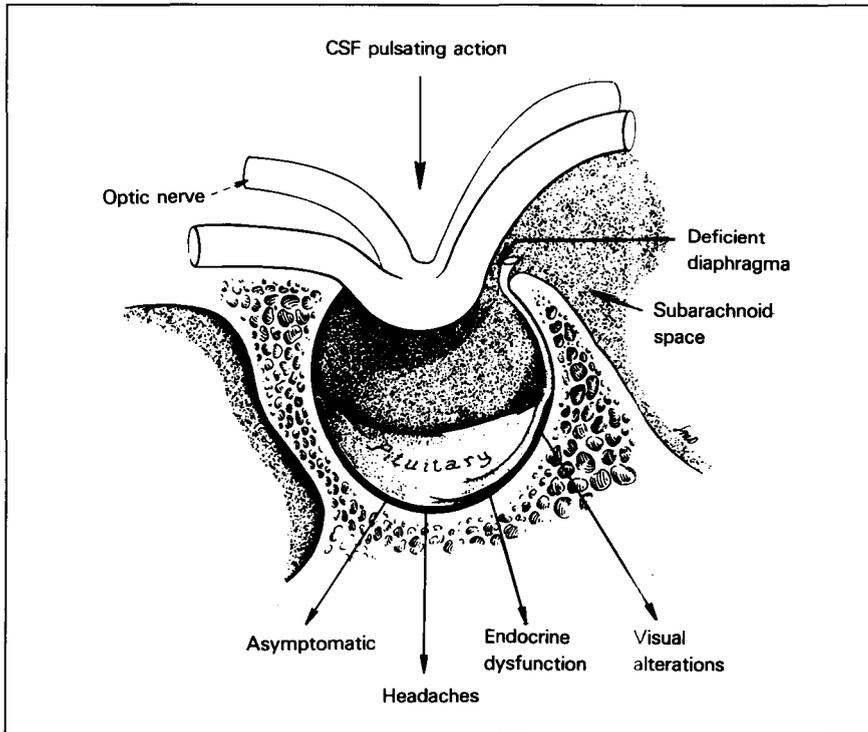


Fig. 5. A schematic diagram suggesting how the increased intracranial pressure of pseudotumour cerebri may produce the empty sella syndrome. The elevated pressure and pulsating action of the CSF can herniate both the subarachnoid space (stippled area) and the optic chiasm through an incompetent diaphragma sella compressing the pituitary gland. If the herniation of the optic chiasm and compression of the pituitary gland are sufficient, visual field defects, endocrine dysfunction, and even headache may result.

Thus, it seems most likely that both chronically elevated CSF pressure and a congenitally deficient diaphragmatic sella are required to produce the empty sella syndrome. The symptoms, visual and endocrine sequelae that may follow are explained on the basis of the prolapse of subarachnoid space, optic nerves and chiasm into the sella turcica (fig. 5).

Summary

Two patients presenting with headache and radiological features of an enlarged sella turcica were found to have the primary empty sella syndrome. Whilst under observation, 1 patient developed papilloedema and was shown to have benign intracranial hypertension. The second patient also had raised intracranial pressure. A relationship between the empty sella syndrome and benign intracranial hypertension

has previously been reported and it is suggested that in a patient with a congenitally incompetent diaphragma sella, chronically raised intracranial pressure causes herniation of the subarachnoid space into the sella turcica. Subsequently, sella turcica enlargement and remodelling occurs, sometimes with endocrine, visual and other sequelae. The clinical, radiological and CT scan features of the empty sella syndrome are discussed and the indications for major radiological studies are considered.

Acknowledgement

We would like to acknowledge the assistance of Dr Peter Ebeling and thank him for permission to report Case 1.

Table 1 and figure 5 are reproduced with kind permission of Dr J. Posner and the Editor of 'Neurology'.

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Occipital Neuralgia

*S.R. Hammond and G. Danta**

The clinical problem of occipital pain is no different from other painful states in demanding a careful history and examination for its correct analysis. When considering conditions that may present with occipital pain, occipital neuralgia is frequently neglected. Schulz (1977) states that fewer than 5% of his series of 92 cases had had the diagnosis considered prior to referral. The condition has received scant attention in the literature, and the majority of neurological texts either do not mention it or dismiss it in a few lines. A recent symposium (Diamond et al., 1974) on headache did not even mention the possible role of the occipital nerve in the production of head pain.

Patients Studied

We studied 23 cases of occipital neuralgia. The clinical features that were considered when making the diagnosis were:

- 1) Severe paroxysmal lancinating or continuous pain in the distribution of the relevant occipital nerve
- 2) The presence of a sharply circumscribed area of tenderness over the nerve trunk as it crosses the superior nuchal line (SNL) — the greater occipital nerve lies over this line midway between the mastoid process and the occipital protuberance and the lesser occipital nerve lies over it about 1.5 inches behind the ear

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Table I. Details of 23 patients with occipital neuralgia

Nerve involvement	Patients			Laterality		
	no.	male	female	right	left	bilateral
Greater occipital	19	7	12	11	5	3
Lesser occipital	2	0	2	1	1	0
Combined unilateral	2	1	1	1	1	0

3) Hypo-, para-, or dysaesthesiae in the appropriate distribution either during or following the clinical episode

4) The response of the acute episode or its aftermath to local forms of treatment, namely, infiltration of local anaesthetic near to the tender area of the nerve trunk, or occipital neurectomy.

These features clearly point to involvement of the occipital nerves themselves. All patients had, of course, to have at least the first feature to be considered for inclusion in the study.

Clinical Data

The age range was 21 to 63 years and the mean age was 42. Table I shows the incidence of individual and combined greater occipital nerve (GON) and lesser occipital nerve (LON) involvement, the sex incidence and the laterality.

Table II shows the incidence of the clinical features related to direct involvement of the occipital nerves. Of the 4 patients who did not have nerve trunk tenderness, 2 had tenderness over the upper cervical spine. All 4 were in clinical remission at the time of being seen. The 4 patients with dysaesthesiae and 1 with paraesthesiae were amongst the 10 with hypoesthesiae.

The incidence of associated migrainous features is shown in table III. Table IV shows the incidence of features located within the territory of the trigeminal nerve. None of the LON cases demonstrated these associations. The frontal extension to the pain was generally confined to the ophthalmic division although the maxillary division was also occasionally involved. 1 patient demonstrated unilateral sensory loss in the ophthalmic and maxillary divisions of the trigeminal nerve with a reduced corneal reflex. Extensive investigation which included a pneumoencephalogram and cerebral angiography failed to reveal any other cause.

Table V shows the aetiology considered to have initiated the attacks. The unfortunate subject of the attempted strangulation was unlucky enough to have received both a whiplash injury to the cervical spine and direct occipital trauma. Of the 2

Table II. Clinical features relating to the occipital nerves (21 greater and 4 lesser occipital nerve involvements) in 23 patients with occipital neuralgia

Feature	Nerve involvement	
	GON ¹	LON ²
Localised tenderness of nerve trunk over SNL ³	17	4
Clinical attack triggered by pressure over SNL	3	1
Sensory changes		
hypoesthesia	10	3
paraesthesia	2	0
dysaesthesia	4	1
<i>Total</i>	<i>11</i>	<i>3</i>
Types of pain		
neuralgic + continuous	10	2
neuralgic	9	3
continuous	10	1
<i>Total</i>	<i>23</i>	<i>4</i>

1 GON — greater occipital nerve.

2 LON — lesser occipital nerve.

3 SNL — superior nuchal line.

patients with rheumatoid arthritis, 1 had subluxation of C1 on C2 of more than 4mm extent, whilst the other had a radiologically normal cervical spine. The 3 patients in whom the only finding was of radiological cervical spondylosis below the level of C3 had no other discernible aetiology. There were 3 patients in whom neither the history, nor the clinical examination, nor cervical radiology gave any clues as to the aetiology. It does not seem likely however that they were examples of primary occipital neuralgia.

The subsequent precipitating or aggravating factors are listed in table VI. 7 cases with GON involvement could identify no definite triggering factors of their subsequent attacks. However as these generally occurred when the patients were engaged in some physical activity the attacks were likely to have been precipitated by changes in head and neck posture. One of the patients with combined unilateral occipital neuralgia noted that a change in the weather seemed to trigger an attack, as well as direct contact. He was unable to be more specific about this.

Table III. The migrainous features found in 23 patients with occipital neuralgia

Feature	Nerve involvement	
	GON	LON
Vascular headache		
occipital	0	1
occipitofrontal	4	2
frontal	3	0
frontomaxillary	1	0
generalised	1	0
<i>no. of patients</i>	9	3
Ocular aspects		
visual disturbance	4	1
pupillary dilation	1	1
photophobia	2	0
<i>no. of patients</i>	4	2
Vasomotor aspects		
lacrimation	2	0
facial flushing	1	0
nasal blockage	1	0
<i>no. of patients</i>	2	0
Gastrointestinal aspects		
nausea	6	1
nausea and vomiting	3	1
<i>no. of patients</i>	9	2
Miscellaneous		
hyperacusis	2	0
vertigo	2	0
<i>no. of patients</i>	4	0

Table IV. Eight patients with occipital neuralgia who also showed trigeminal nerve involvement

Feature	Number with GON involvement
Radiation of occipital pain to frontal region	7
Sensory disturbance	1

Table V. Factors considered to have initiated attacks in 23 patients with occipital neuralgia

Aetiological factor	Nerve involvement		
	GON	LON	combined unilateral
Trauma			
whiplash injury			
MVA	4	1	1
attempted strangulation	1	0	0
other injuries to cervical spine	3	0	1
direct trauma to occipital region			
MVA	2	0	0
other	2	1	0
<i>Total no. injuries</i>	<i>11</i>	<i>2</i>	<i>2</i>
Miscellaneous			
rheumatoid arthritis	2	0	0
cervical spondylosis	3	0	0
unknown	3	0	0
<i>Total</i>	<i>8</i>	<i>0</i>	<i>0</i>

Table VI. Subsequent trigger factors in occipital neuralgia

Trigger factor	Nerve involvement		
	GON	LON	combined unilateral
Head and neck movement	12	2	1
Contact with affected nerve over SNL	3	0	1
'Spontaneous'	7	0	0
Miscellaneous	0	0	1

Table VII shows the radiological changes found in the cervical spine. No significant spondylitic changes were found above the level of C3. No craniocervical abnormalities were demonstrated.

Table VIII shows the response to specific forms of therapy. Local anaesthetic injections were employed only when the condition was active clinically. The follow-up period of the occipital neurectomies is too short for unbridled optimism. The one

Table VII. Radiological changes in the cervical spine in 23 cases of occipital neuralgia

Radiological finding	Nerve involvement		
	GON	LON	combined unilateral
Spondylitic changes from C4 downwards	5	0	2
Subluxation of C1 on C2	1	0	1

recurrence was thought by the attending neurosurgeon to be due to stump neuroma formation.

Table IX shows the response to nonspecific forms of therapy. The cervical collar was only effective when being worn. Transcutaneous nerve stimulation provided good relief in both cases whilst it was in use but the after-effect was short lived, and up to 3 stimulations per day were required to provide adequate relief. Both prophylactic and acute forms of migraine therapy were used. The relief afforded when present affected only the migrainous component. The patient whose external carotid artery was ligated, was initially diagnosed as having migrainous neuralgia. Reviewing his history it became apparent that the attacks were preceded by a sudden neuralgic pain radiating from the suboccipital ridge to the frontal area.

The natural history of the condition is variable. Prior to referral, a number of patients had only 1 or 2 episodes of occipital neuralgia, usually following trauma, before the condition spontaneously remitted. Such patients were not treated but were invited to return should a further attack occur. However the majority of patients were experiencing serial attacks, sometimes spaced several weeks apart, and these constituted the group for whom specific therapy was necessary.

From the data given the following main points emerge about the clinical aspects of occipital neuralgia:

- 1) The GON is much more commonly involved than the LON
- 2) The most common findings in relation to the occipital nerves themselves are localised nerve trunk tenderness and hypoaesthesiae and that neuralgic and continuous pain have approximately the same incidence
- 3) Associated migrainous phenomena occur relatively frequently and of these vascular headache and gastrointestinal upset are the most commonly encountered
- 4) Involvement of the trigeminal nerve is not uncommon and is most often manifested by frontal extension of the occipital headache
- 5) Trauma and head and neck movement are the most common initial and subsequent aetiologies respectively

Table VIII. Response of occipital neuralgia to specific therapy. All patients had immediate complete relief of pain

Therapy	Nerve involvement ¹ (no. of patients)	Duration of effect (no. of patients)
Local anaesthetic	GON (11)	< 1 week (7) 4m (1) 6m (1) No relapse, 9 and 12m (2)
	LON (3)	< 2 days (2) No relapse, 1m (1)
Occipital neurectomy	GON (3)	No relapse, 2-8m (2) 4m (1)
	LON (1)	No relapse, 1m

1 GON — greater occipital nerve.
LON — lesser occipital nerve.

Table IX. Response of occipital neuralgia to nonspecific therapy

Therapy	Nerve involvement ¹ (no. of patients)	Effect (no. of patients)
Cervical collar	GON (4)	Complete relief (1) Moderate relief (2) Minimal relief (1)
	LON (1)	No relief (1)
Transcutaneous nerve stimulation	GON (2)	Good relief, shortlived (2)
Antimigraine drugs	GON (8)	Good relief (3) Moderate relief (1) No relief (4)
	LON (1)	No relief (1)
External carotid artery ligation	GON (1)	Moderate for 2m, then no relief (1)

1 GON — greater occipital nerve.
LON — lesser occipital nerve.

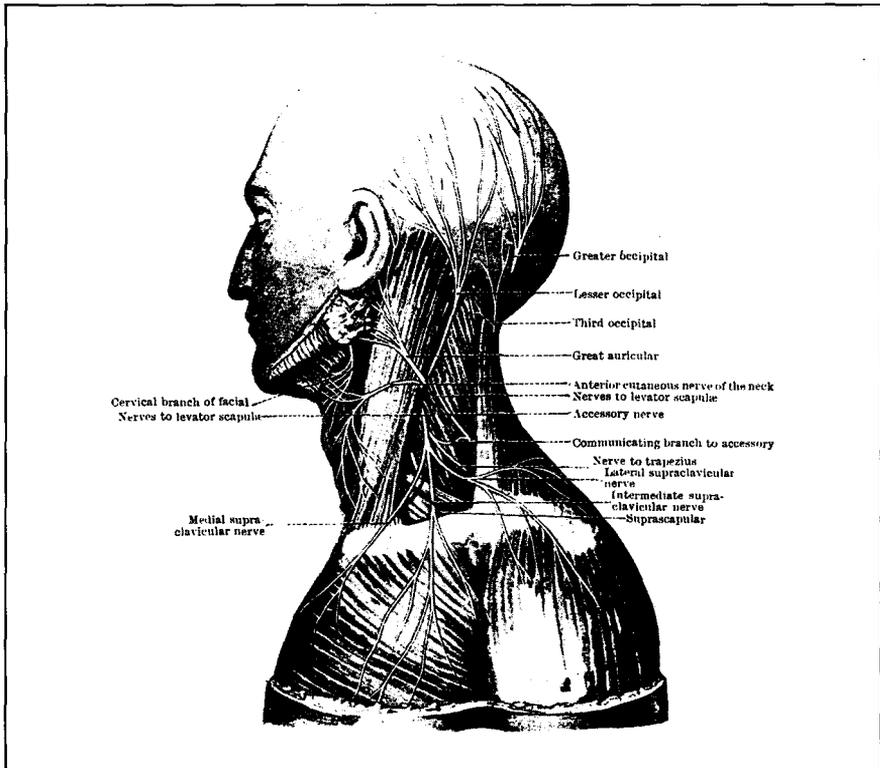


Fig. 1. The anatomy of the occipital nerves (from Cunningham's Textbook in Anatomy, reproduced with kind permission of the Editor, Oxford Medical Publications).

- 6) Local anaesthetic injections provide immediate relief but the benefit is poorly sustained in most cases
- 7) Occipital neurectomy is an effective form of definitive treatment
- 8) Nonspecific forms of treatment, at best, are of only temporary benefit.

Discussion

The clinical features of occipital neuralgia are pain and sensory change in the distribution of the relevant occipital nerve, a clear response to specific local forms of therapy, and localised nerve trunk tenderness. The last mentioned feature occupies a place of importance in the literature. Schulz (1977) insisted that palpation had to reveal distinct tenderness over the nerve trunk or to reproduce the patient's headache or to do both. Falconer and Harris (1968) state that 'typically the affected greater oc-

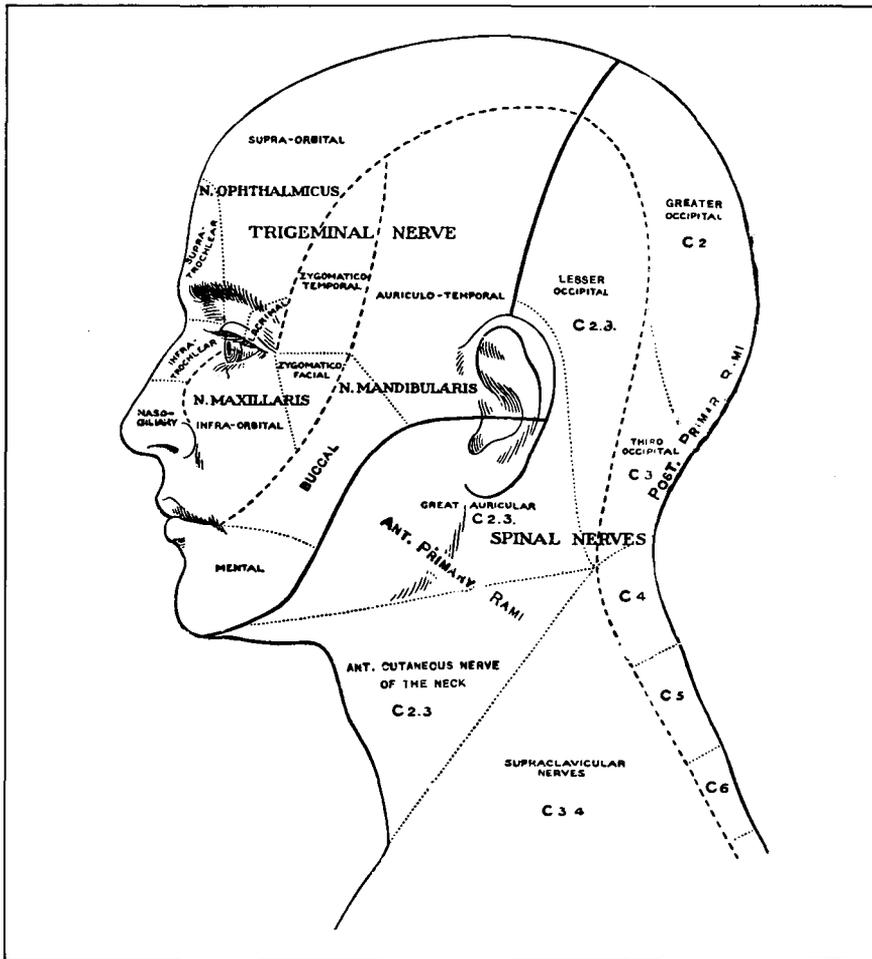


Fig. 2. The upper cervical dermatomes, and distributions of the occipital nerves (from Cunningham's Textbook in Anatomy, reproduced with kind permission of the Editor, Oxford Medical Publications).

cipital nerve is tender at the point where it crosses the superior curved nuchal line of the occipital bone'. However 6 of our cases did not show this feature but all were in clinical remission when first seen. None of them has returned with a further attack for this aspect to be reassessed. We found that reproduction of the headache by palpation of the tender nerve trunk was uncommon.

The existence of a primary form of occipital neuralgia, analogous to other cranial neuralgias, is controversial although Sigwald and Jamet (1968) maintain that it oc-

curs, albeit very rarely. An underlying cause is nearly always apparent. Predisposing causes cited in the literature include sustained contraction of the posterior cervical muscles (Schulz, 1977; Friedmann and Merritt, 1959), cervical arthritis (Hadden, 1940), minor subluxation and craniovertebral anomalies of the cervical spine (Dugan et al., 1962), trauma to the cervical spine as in whiplash injury (Seletz, 1958), neuritis secondary to local or systemic inflammatory disease (Sullivan, 1949), and persistent poor body posture or asymmetry (Hadden, 1940; Dugan et al., 1962).

The site of involvement of the occipital nerves remains conjectural. However, a consideration of the anatomy raises a number of possibilities. The GON is formed predominantly from the posterior primary ramus of C2. Theoretically there are 3 vulnerable points. Firstly, it emerges behind the lateral articular masses of the atlas and axis. Here it is not protected by the pedicles and facets that form the intervertebral foramina elsewhere in the vertebral column. The atlantoaxial joint is very mobile and thus the unprotected nerve is vulnerable between these bony surfaces. Secondly, the nerve perforates the atlantoaxial membrane. Stretching of this membrane occurs with even minor atlantoaxial subluxations and thus the nerve is potentially at risk at this point. Finally the nerve pierces the tendonous attachment of trapezius to the suboccipital base to become superficially placed. Here, at a point of relative fixation, it is liable to excessive stretching. Figure 1 shows the nerve at this last point and also illustrates the peripheral course of the LON.

The LON is derived from the posterior primary rami of C2 and C3. After coursing through the neck it pierces the deep fascia near the apex of the posterior triangle to

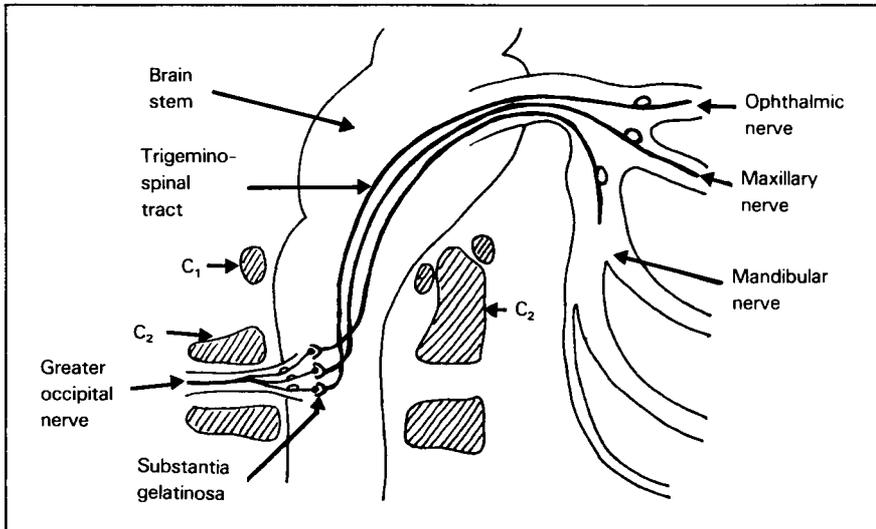


Fig. 3. Central connections of the trigeminal nerve and C2 nerve root.

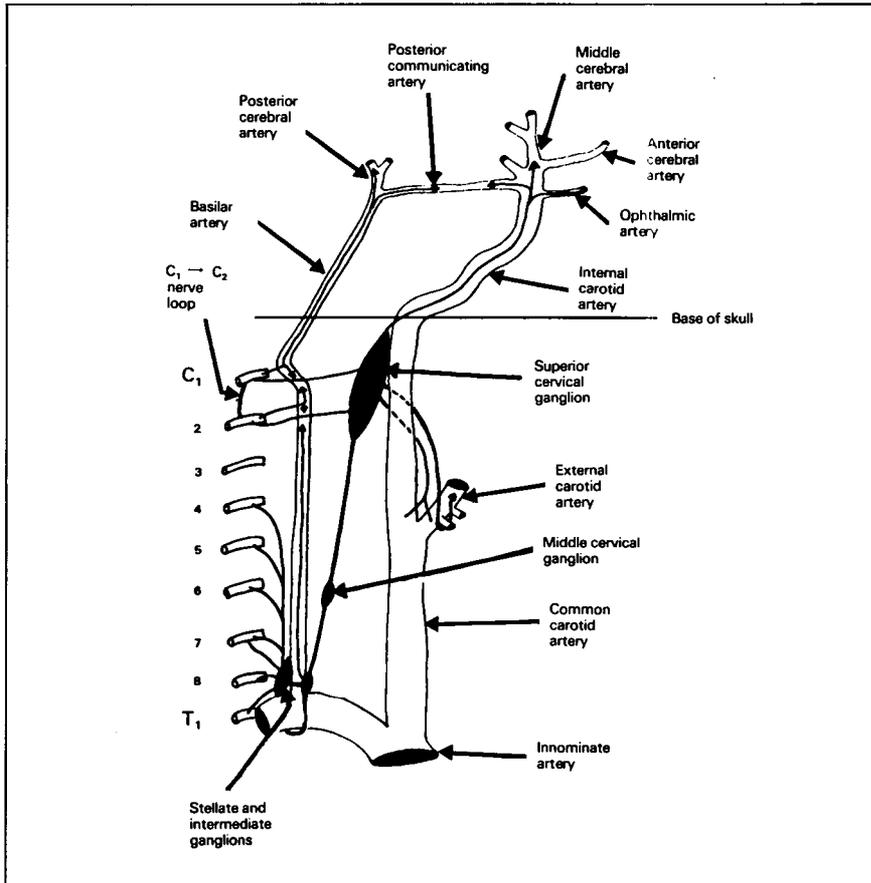


Fig. 4. The interconnections of the cervical autonomic nervous system.

become superficially placed, and here like the GON it is liable to excessive stretching. Figure 2 shows the standard view of the cutaneous distribution of the occipital nerves. The anatomy is in fact rather more complex. The occipital nerves, particularly the greater, interconnect with the trigeminal nerve and the autonomic nervous system, and both are of clinical importance.

Pain radiating to the facial areas is not uncommon in occipital neuralgia and was seen in 7 of our greater occipital neuralgias. Hunter and Mayfield (1949) quote the anatomical dissections of Zander (1897) which showed terminal filaments of the upper cervical nerves in all but the central portions of the face and confirmed them by careful examination of areas of anaesthesia following avulsion of the occipital nerve in the surgical management of occipital neuralgia. Figure 3 shows trigeminal fibres

descending in the trigeminospinal tract to the level of C2 with the ophthalmic fibres placed most distally. The trigeminospinal tract becomes continuous with the substantia gelatinosa of the upper cervical cord establishing a link between the C2 root and the trigeminal nerve, particularly with its ophthalmic division. Crue et al. (1968), Seletz (1958) and Skillern (1954) all attest to the neurophysiological link between these two structures. Thus the frontal radiation of pain may be explicable either peripherally or centrally.

Schulz (1977) comments on the frequent occurrence of migrainous features in occipital neuralgia and this is also our experience. Figure 4 illustrates the interconnections of the cervical autonomic nervous system. The C2 root has connections with the posterior cervical nervous system and hence with the vertebrobasilar plexus. It also has connections with the superior cervical ganglion and the vagus nerve which is not shown in this figure.

As Gayral and Nuewirth (1954) point out, it becomes understandable how a lesion of an apparently unrelated structure may cause autonomic reactions which may simulate entities such as basilar migraine, hemicrania, cluster headache, or even subarachnoid haemorrhage.

A number of treatment regimens are mentioned in the literature (Schulz 1977). Most advocate that local anaesthetic, sometimes combined with steroid, be injected into the nerve at its most tender point as a first line approach. This has been reported to produce lasting relief after a few injections. Failing this either occipital neurectomy or posterior rhizotomy of the upper three cervical roots has been recommended. The use of a cervical collar is extolled by some, and cervical manipulation by others. The latter is probably not to be recommended as it may facilitate further damage. Hunter and Mayfield (1949) demonstrated that manipulation of the atlantoaxial joint in a cadaver may traumatise the second cervical nerve.

Summary

The findings in 23 cases of occipital neuralgia are presented. The clinical features of the condition are pain and sensory change in the distribution of the relevant nerve, localised nerve trunk tenderness and a clear response to local forms of therapy. The clinical picture is often complicated by migrainous and trigeminal nerve features and the mechanisms by which these come about are discussed.

Occipital neuralgia is generally neglected in both the standard textbooks and the literature. The condition occurs sufficiently commonly to warrant more consideration in the differential diagnosis of head pain than it has received to date.

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Some Specific Neurological Complications of Acute Lymphocytic Leukaemia of Childhood

*D.B. Appleton, A.F. Isles and J.R. Tiernan**

Before the introduction of vigorous therapeutic regimens, children who developed acute lymphoblastic leukaemia died within months of the onset of symptoms. Cytotoxic therapy induced an initial remission in at least 90% of cases (Rhomes et al., 1971). Relapses were often due to meningeal proliferation while the bone marrow disease remained controlled (Hardisty and Norman, 1967). As a result, an effective prophylactic regimen utilising cranial irradiation (2,400 rads) and intrathecal methotrexate has been devised along with vigorous maintenance therapy with continuous mercaptopurine and intermittent intravenous cyclophosphamide, methotrexate, vincristine and oral prednisone and sometimes cytosine arabinoside, daunorubicin or L-asparaginase.

Neville (1972) reviewed the various neurological syndromes which may appear. These include:

- 1) Meningeal involvement
 - raised intracranial pressure
 - hypothalamic syndromes (hyperphagia)
 - localised cranial nerve paresis
 - hydrocephalus
- 2) Massive haemorrhage (secondary to thrombocytopenia)
- 3) Toxic effects of intrathecal drugs (? progressive degeneration secondary to folate depletion — Bleyer et al., 1973).

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Table 1. Details of 11 patients with acute lymphatic leukaemia

Patient and date of birth	Age at diagnosis	Irradiation		Methotrexate		Cytara- bine dose (mg/m ²)	CNS relapse	Neurological features	CT scan		
		dose (r)	date	dose (mg/m ²)	date				finding	date	
PS.	18.12.66	5y 10m	2400	23.7.74	522	28.2.73	618	+	Headache	Calcification, atrophy	13.9.77
MA.	23.5.72	3y	2400	25.6.75	291	23.6.75	—	+ (2)	Seizures, 6N paresis	Frontal calcification	29.6.77
DC.	1.3.73	2y 10m	2400	23.2.76	180	3.3.76	—	+	Ataxia	Calcification	21.11.77
FH.	12.4.70	3y 11m	2400	24.6.76	140	22.6.74	—	—	—	Calcification	7.11.77
RW.	30.1.70	3y 1m	2400	28.2.73	285	1.11.74	—	+	Bell's palsy, hemiplegia	Calcification	6.11.77
SM.	24.5.69	6y 6m	4400	22.6.76	175	24.6.76	180	+	Seizures, hemiparesis	Optic glioma	24.2.77
WW.	23.6.68	2y 10m	2400	3.5.73	260	5.4.73	564	+ (several)	Seizures	Normal	3.3.78
BC.	31.5.70	5y 10m	2400	4.5.76	149	6.5.76	—	+	Seizures	Calcification	19.4.78
KH.	9.5.71	2y 8m	2400	3.5.74	Dose uncertain Given elsewhere		—	—	—	Normal	11.4.78
BF.	15.4.62	12y 8m	2400	1.2.75	214	20.1.75	-	+	-	Atrophy	20.2.78
AA.	3.1.72	2y 6m	2400	26.8.74	220	27.8.74	160	+	Bilateral ptosis	?Normal	24.2.78

- 4) Multifocal infiltration
- 5) Toxic peripheral neuropathy
- 6) Opportunistic infection with fungi or viruses

Lumbar puncture with careful examination of the CSF may indicate the presence of meningeal disease. More worrying is the number of cases who appear to have parenchymal disease and features of progressive brain degeneration, without definite focal signs. Computerised axial tomography (CT scan) has been applied to determine more accurately which process is occurring.

Patients Studied

Details of the 11 patients studied are set out in table I, which also shows the presence of neurological abnormalities and the results of computerised tomography.

Of the 11 cases recorded in this paper only 2 had CT scans which could be reported as within normal limits. Another was suspiciously abnormal and a 4th had a coincidental optic nerve glioma and neurofibromatosis. 6 had periventricular and white matter calcification, and the remaining case showed cortical atrophy (figs. 1-4). In only 1 case could the calcification be seen on plain radiographs of the skull. There did not appear to be any trend to suggest that the dose of methotrexate was critical, nor the order of administration of irradiation or drug.

1 further patient, T.S. aged 10 years, was seen. He presented with seizures; progressive intellectual deterioration and cortical blindness some 2 months after cranial irradiation. He had received intrathecal methotrexate for the preceding 2 years. Treatment with folic acid produced slight improvement in neurological function until systemic relapse occurred 8 months later. Post mortem examination (Dr Ross Anderson) revealed mild meningeal infiltration, focal calcification in the mid-brain and basal ganglia with cystic degeneration and gliosis in the white matter.

Discussion

Flament-Durand et al., (1975) published the first report of intracranial calcification appearing in treated leukaemia patients. Earlier reports (Bresnan et al., 1972; Kay et al., 1972 and Norrell et al., 1974) had recorded an encephalopathy in which methotrexate was incriminated. Transient stiff neck, headache and fever might occur after intrathecal administration of the drug, with occasional more permanent motor or sensory symptoms (Baum et al., 1971). Saiki et al. (1972) suggested that preservatives in the methotrexate (methyl hydroxybenzoate and benzyl alcohol) were the cause but this hypothesis has not been supported by the observation that the process does not occur with other drugs containing the same preservative and does occur when methotrexate free of preservatives is used.

Rubinstein (1972) reviewed the early and delayed effects of radiation. He pointed out that calcification is very rare and the major lesion is a vasculopathy.

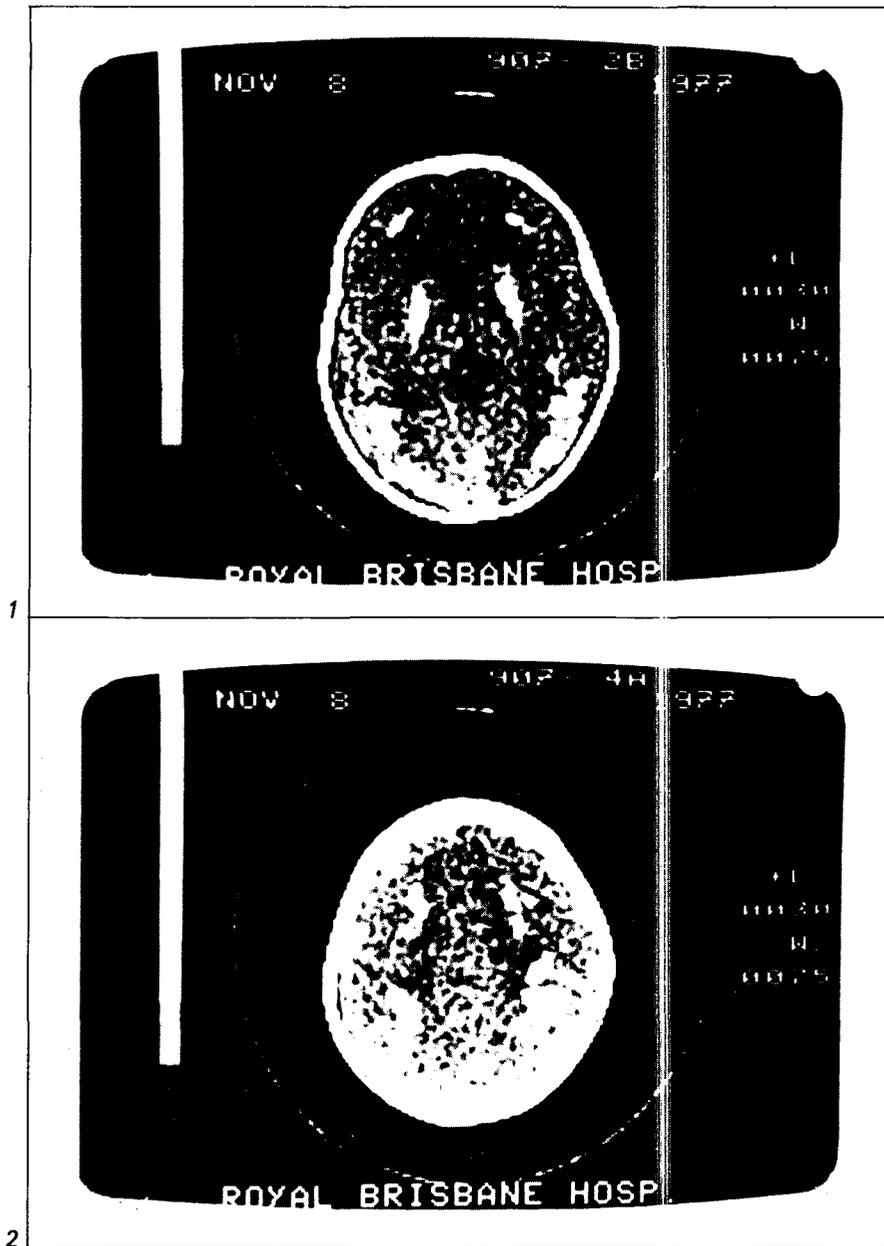


Fig. 1. Patient FH. CT scan without contrast. Extensive periventricular calcification.

Fig. 2. Patient FH. CT scan showing extensive white matter calcification.

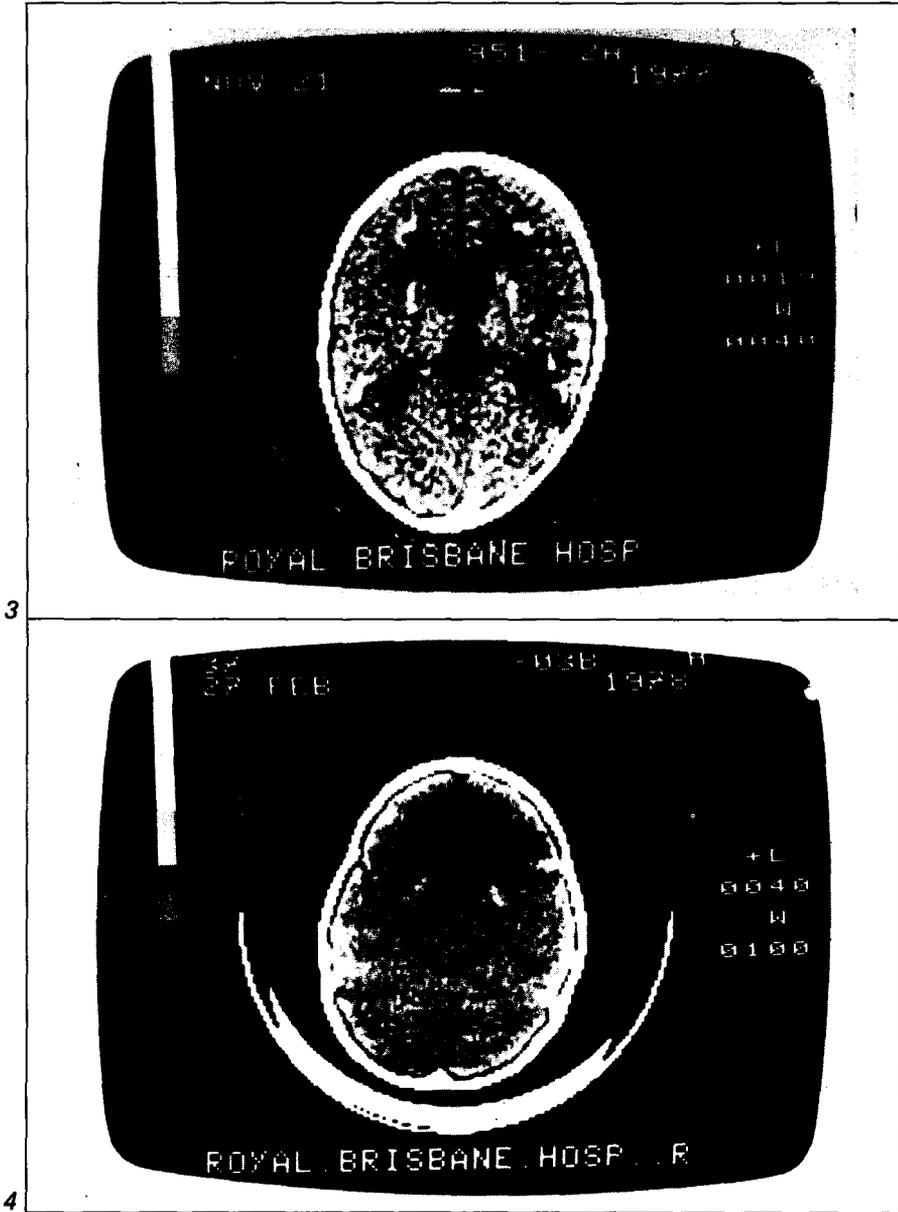


Fig. 3. Patient DC. CT scan showing basal ganglion and periventricular calcification which was not evident on plain skull films.

Fig. 4. Patient AA. CT scan showing early calcification in the basal ganglion.

Garwicz and Mortenson (1976) reported 2 cases of intracranial calcification mimicking the Sturge-Weber syndrome. One was a leukaemic treated with irradiation and methotrexate while the other was an epileptic with coeliac disease. They suggested that folic acid deficiency was the cause, precipitated by phenytoin therapy. 2 further cases in treated leukaemics were reported by Borns and Rancier (1974) and 3 by Mueller et al. (1976).

Price and Jamieson (1975) at St. Jude's Hospital reviewed the brains of 288 patients with acute lymphoblastic leukaemia and reported that 13 had a leukoencephalopathy. No correlation could be demonstrated with age at time of irradiation, bacterial infections, nutrition, or central nervous system relapse. Only those patients who had at least 2,000 rads followed by intrathecal or intravenous methotrexate developed leukoencephalopathy. It did not develop in those who had less than 2,000 rads of irradiation, regardless of the total dose of methotrexate. Interestingly, calcification was not reported in the histological material. The authors suggested that the irradiation induces vascular change which enables methotrexate to diffuse more readily into the brain substance. Rubinstein et al. (1975) suggested a similar pathogenesis.

McIntosh et al. (1977) reported a computerised tomography study of 48 patients of whom 10 exhibited brain calcification. They suggested that the risk was greater if both cytosine arabinoside and methotrexate were used.

The present study shows that the occurrence of significant brain damage can be determined with the aid of computerised tomography in patients undergoing treatment for leukaemia. The duration of that treatment and the total dose of methotrexate do not seem to be important factors since the 2 normal scans came from patients irradiated 4 and 5 years ago and the most prominent calcification was in the child given the lowest dose of methotrexate.

It is suggested that computerised tomography should be performed at intervals during treatment and that methotrexate should be discontinued at the first sign of any abnormality, though this may already be too late. Psychometric assessment at intervals may also be useful in finding early signs of intellectual dysfunction which may herald the onset of leukoencephalopathy. The small number of cases reported does not allow further elucidation of the evolution of the encephalopathy but it refutes the claim of Flament-Durand et al. (1975) that calcification is rare in the neural tissue of treated leukaemia patients.

Summary

Aggressive chemotherapy and prophylactic central nervous system irradiation have increased the survival time of children with acute lymphatic leukaemia. As a result of treatment complex neurological problems are appearing.

Computerised axial tomography allows more definite elucidation of these problems. 7 of 11 treated patients studied by this technique showed the presence of intracranial calcification and patchy cerebral atrophy, raising the questions of the quality of survival and the relationship of the findings to the cytotoxic drugs used.

Acknowledgements

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The Contribution of Evoked Potentials in the Functional Assessment of the Somatosensory Pathway

F.L. Mastaglia, J.L. Black, R. Edis† and D.W.K. Collins*

The recording of somatosensory evoked potentials (SEPs) allows an objective assessment of the functional status of the somatic sensory pathways and provides a means of studying the pathophysiology of conduction in these pathways. A number of studies of the cortical (Namerow, 1968; Baker et al., 1968; Mastaglia et al., 1977b) and subcortical (Mastaglia et al., 1976, 1977a and b; Small et al., 1977 and 1978) SEPs in patients with demyelinating disease have been reported but less attention has been given to these responses in patients with other types of neurological disorder (Halliday and Wakefield, 1963; Tsumoto et al., 1973; Nakanishi et al., 1974; Noel and Desmedt, 1975; Shibasaki et al., 1977).

We have studied the cortical and cervical responses (Matthews et al., 1974) in patients with a variety of neurological disorders to determine their value in assessing the functional integrity of the sensory pathways and to compare the effects of different types of pathological process on conduction in these pathways.

Patients and Methods

Details of the numbers of patients studied and of diagnostic categories are shown in table I. Normal ranges for temporal and amplitude parameters of the cervical res-

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Table 1. Categories of patient studied

Diagnosis	Number of patients
Multiple sclerosis	
clinically definite	36
early probable or latent	24
suspected	70
probable progressive	3
	133
Spinocerebellar degenerations	
Friedreich's ataxia	8
hereditary spastic paraparesis	7
cerebellar degenerations	10
mixed spinocerebellar syndromes	5
	30
Stereotactic thalamotomy	12
Progressive supranuclear palsy	6
Myoclonic epilepsy	4
Cerebrovascular lesions	7
Peripheral neuropathy	4
Cervical radiculopathy	3
Syringomyelia	2

ponse were established in 27 subjects, 21 of whom were normal volunteers and 6 of whom were patients in whom it was concluded after full investigation that there was no organic disease of the nervous system. Normal ranges for the cortical response were derived from 20 of these subjects.

The responses were recorded percutaneously using Grass EEG disc electrodes. In the case of the cervical response the optimal position for the active electrode was found to be over the spinous process of the second cervical vertebra (C2) with the inactive electrode at the vertex (fig. 1). In the case of the cortical response the active electrode was placed over the hand area of the sensory cortex (2.5cm behind and 7cm lateral to the vertex) opposite the side being stimulated, the reference electrode again being placed at the vertex. The stimulus used was a 100msec square wave electrical pulse applied to the median nerve at the wrist through padded silver-plated electrodes. Preliminary experiments in normal subjects showed that the maximum size and typical configuration of the responses was only achieved with stimuli more than twice threshold (fig. 2). For routine studies the cutaneous sensory threshold at the site of stimulation was first determined and a 3 times threshold stimulus was then used. The

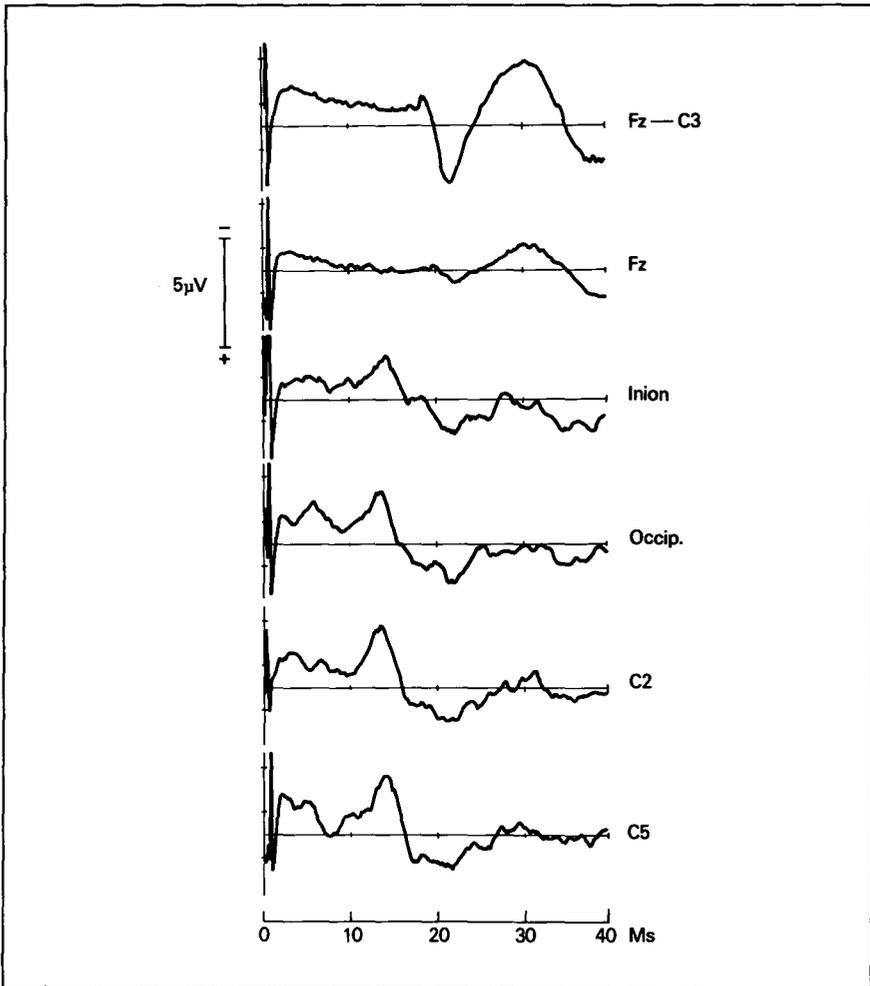


Fig. 1. Topographical distribution of the cervical SEP in a normal 36-year-old male. The response could be recorded most consistently with an active electrode in the upper or mid-cervical region (C2, C5) and diminished in size at higher level. The top tracing shows the early components of the contralateral cortical evoked response.

rate of stimulation used was 1 per second for the cortical response and 3 per second for the cervical response. After amplification signals were digitised and then averaged using a PDP 11/40 computer. Responses were displayed on a Tektronix 4010 graphics terminal from which time and voltage parameters were extracted using the cursor facility, and from which the responses were photographed for permanent record. The number of cycles averaged was 180 for the cortical response and 330 for

Table II. Normal values for somatosensory evoked responses (SER)

SER	Normal value (mean \pm 2SD)
Cervical (49 arms)	
latency	13.2 \pm 1.9msec
amplitude	2.7 \pm 0.8 μ V
Cortical (30 arms)	
N1 latency	18.7 \pm 2.3msec
P2 latency	39.6 \pm 8.3msec
N1-P2 amplitude	5.4 \pm 4.2 μ V
peak-to-peak amplitude	8.0 \pm 4.5 μ V

the cervical response. More recently a cross-correlation programme has been used to compare the responses obtained from stimulation of the two median nerves.

In the case of the cervical response (fig. 3) particular attention was given to the latency and amplitude of the major surface negative component (N14), while in the case of the cortical response the latencies of the first negative (N20) and the second positive (P40) components, and the N20-P40 and peak-to-peak amplitudes were noted (fig. 4). Normal values for these parameters are shown in table II.

Results

Multiple Sclerosis

The frequency of abnormal responses is shown in table III. It will be seen that the highest frequency was in patients with 'clinically definite' multiple sclerosis (MS), these being individuals with well-established disease usually of long duration (1 to 30 years), and the majority of whom had clinically manifest involvement of sensory pathways. On the other hand, although the frequency of abnormal responses was less among patients in the 'early probable or latent' and 'suspected' categories, such abnormalities were more often subclinical in these 2 groups. It will also be seen that the cervical responses were more often abnormal than the cortical responses in the 'clinically definite' and the 'early probable or latent' groups. However, in a small proportion of patients abnormalities of the cortical response were found when the cervical response was normal, and the overall yield of abnormal responses was therefore higher when the results of both types of study were taken into consideration.

In the case of the cervical response the most frequent abnormality found consisted of a reduction in amplitude with loss of the subcomponents of the response (fig. 5). In some cases, particularly those with longstanding disease in the 'clinically

definite' MS group, the responses from stimulation of both upper limbs were grossly reduced in size or completely absent, while in others there was a marked asymmetry between the 2 responses. In the other 2 groups the usual finding was of a unilateral or bilateral delay or asymmetry in the amplitude of the response which at times appeared to be desynchronised.

In the case of the cortical response, abnormalities more often took the form of varying degrees of unilateral or bilateral delay in the early components (N20 and P40), the most marked abnormalities again being found in certain patients with longstanding 'clinically definite' MS. In some patients with delayed responses the N20 component could not be identified. In others the only abnormality was a greater than usual degree of asymmetry in the size of the responses from the 2 sides.

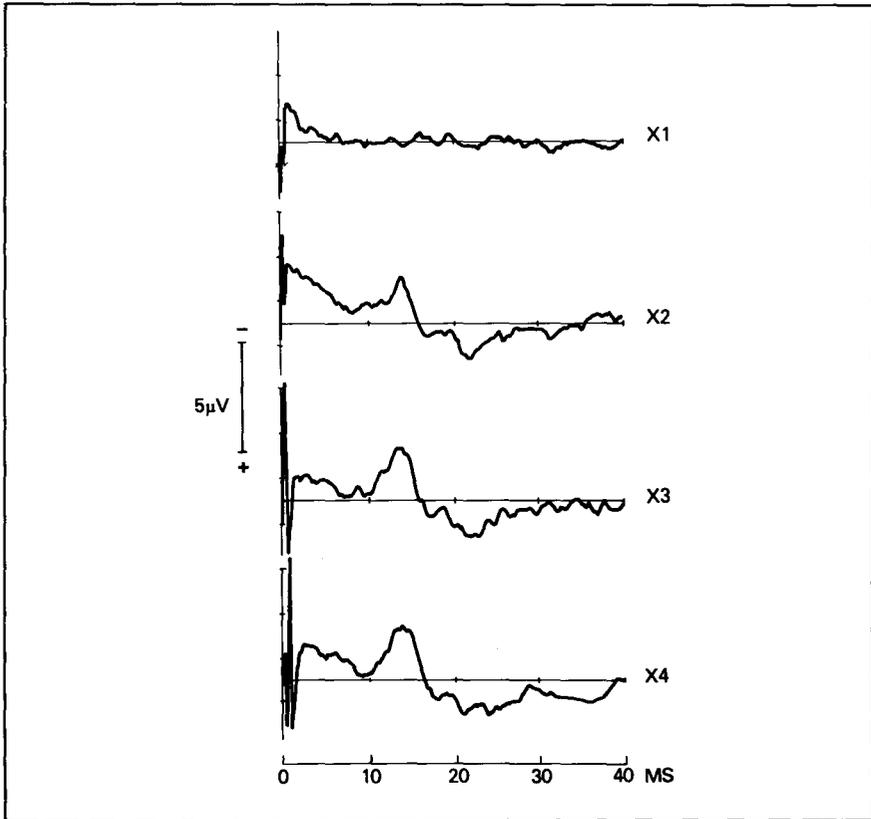


Fig. 2. Effects of increasing stimulus intensity on the cervical SEP in a normal subject. It is seen that the response is maximal in amplitude with stimuli 3 times the cutaneous sensory threshold or greater.

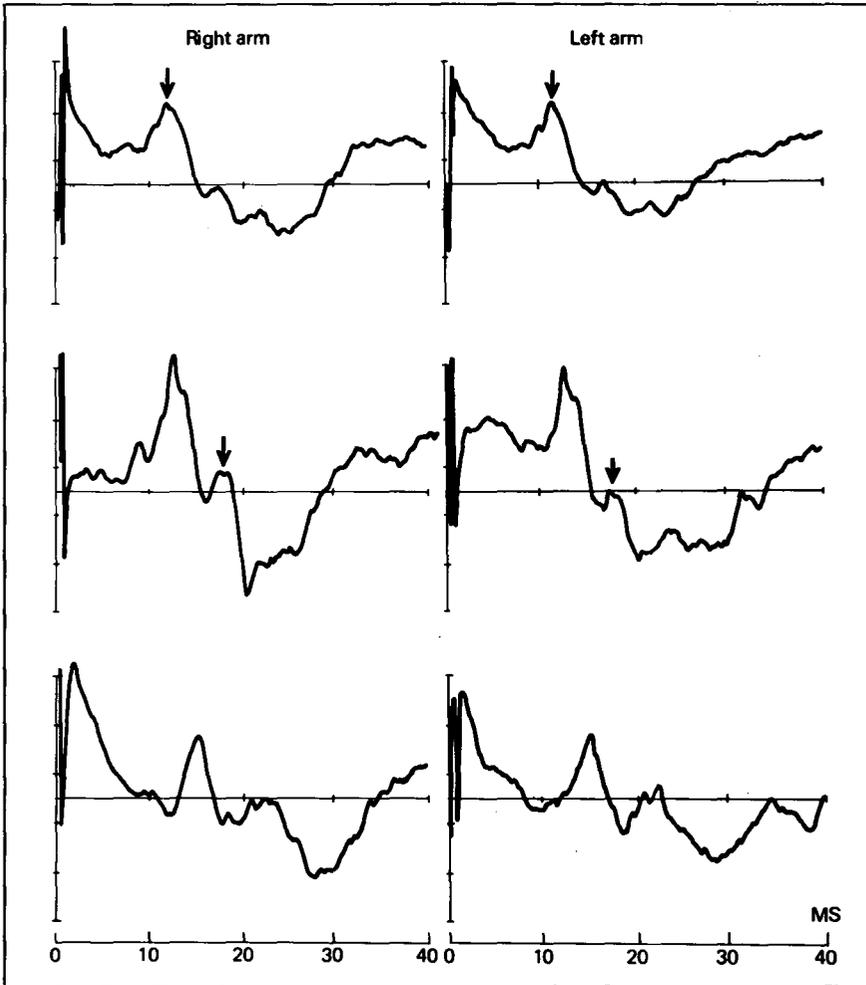


Fig. 3. Cervical SEPs in 3 normal subjects showing the symmetry of the response in each subject, and the variability in the size, latency and configuration of the major surface-negative component (arrow) in the 3 subjects. The later negative component (arrow) is also a consistent finding and corresponds to the early (N20) component of the cortical response.

Abnormalities of the cervical responses were usually found in patients with sensory symptoms or signs in the limbs. However, normal cervical and cortical responses were found in a patient with a cervical cord lesion which had resulted in selective impairment of pain and temperature sensation in one upper limb. Cortical responses of increased amplitude were found unilaterally in 5 patients with normal cer-

vical responses who had sensory symptoms but minimal or no clinical impairment of sensation (fig. 6).

Spinocerebellar Degenerations

The number of abnormalities found in various forms of spinocerebellar degeneration is seen in table IV. In Friedreich's ataxia the cervical responses were symmetrically reduced in amplitude or absent in all cases. In those patients in whom a response could still be identified no significant delay or desynchronisation was apparent. The cortical responses were within normal limits in 1 case but were markedly reduced in amplitude in 2 and significantly delayed in 4 other cases. In some cases the N20 component could not be identified. There was no apparent correlation between the degree of abnormality in the cervical or cortical responses and the severity of clinical sensory deficits.

In hereditary spastic paraparesis the cervical responses were within normal limits in all but 3 cases in whom unilateral or bilateral subclinical abnormalities were found. The cortical responses were present in all cases and were delayed and reduced in amplitude in 2 of the patients with abnormal cervical responses.

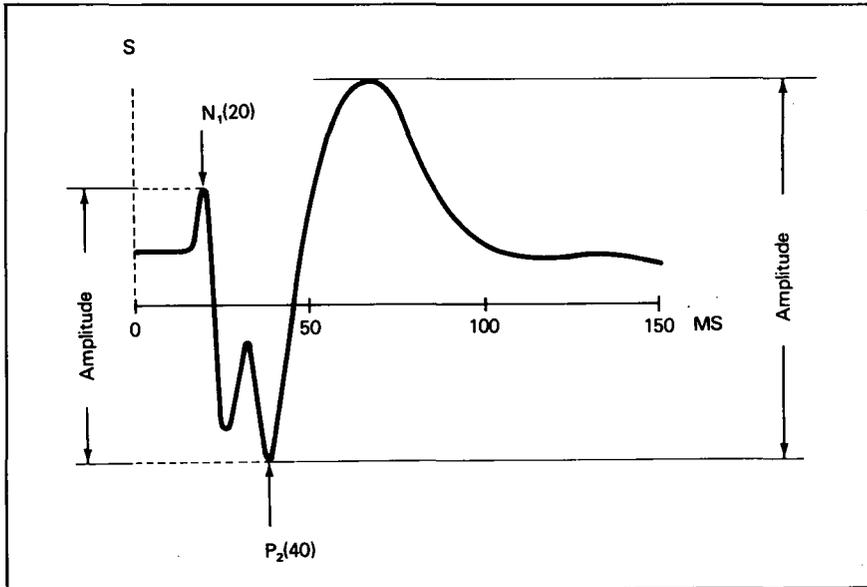


Fig. 4. Schematic representation of a normal cortical SEP recorded from an active electrode over the arm area of the sensory cortex during stimulation of the contralateral median nerve at the wrist. The latencies of the first negative (N1) and second positive (P2) components were measured and 2 measures of amplitude were made — the N1-P2 and the peak-to-peak amplitude.

Table III. Results of somatosensory evoked potential studies in 130 multiple sclerosis (MS) patients

MS classification ¹	Number abnormal/number tested (%)			Percentage with subclinical abnormality
	cervical	cortical	either/both	
Clinically definite	28/36 (78)	12/20 (60)	15/20 (75)	14
Early probable or latent	12/24 (50)	6/18 (33)	10/18 (56)	36
Suspected	9/70 (13)	5/52 (12)	10/52 (19)	54

1 Patients classified according to the criteria of McDonald and Halliday (1977).

Table IV. Numbers of patients with hereditary spinocerebellar degenerations in whom abnormalities of the cervical and cortical somatosensory evoked potentials (SEP) were found

Spinocerebellar degeneration (no. of patients)	Cervical SEP		Cortical SEP	
	abnormal	subclinical	abnormal	subclinical
Friedreich's ataxia (8)	8	—	7	—
Hereditary spastic paraparesis (7)	3	3	2/6	2
Primary cerebellar degeneration (10)	3	3	1/6	1
Other forms (5)	3	2	4	2

Table V. Conditions and numbers of patients in whom enhanced cortical somatosensory responses were found

Condition	Number of patients
Myoclonic epilepsy	4
Stereotactic thalamotomy	2
Brain-stem lesions	3
Multiple sclerosis	5
Spinocerebellar degenerations	2
Progressive supranuclear palsy	2
Syringomyelia	1

In the group of patients with pure cerebellar degeneration the cervical responses were normal in all but 3 cases in whom subclinical abnormalities were found. The response was reduced in amplitude bilaterally in 2 of these and unilaterally in the other. Cortical responses were recorded in only 6 patients in this group and were normal in all but 1 who also had an abnormal cervical response.

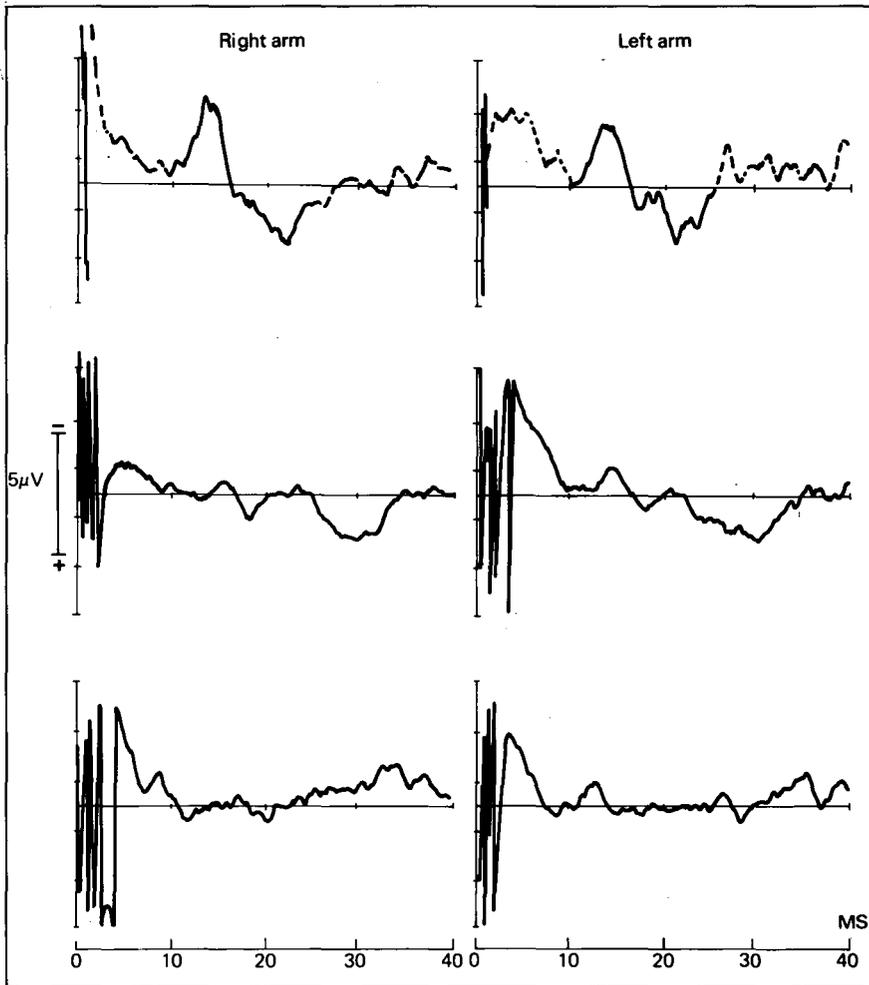


Fig. 5. Cervical SEPs in 3 patients with multiple sclerosis showing varying degrees of abnormality. In the top tracing the responses from stimulation of the 2 median nerves are asymmetrical in that the subcomponents of the major negative response have been lost on the left. The middle tracings show a reduction in amplitude of the responses on the 2 sides while the lower tracings show a bilateral loss of identifiable responses.

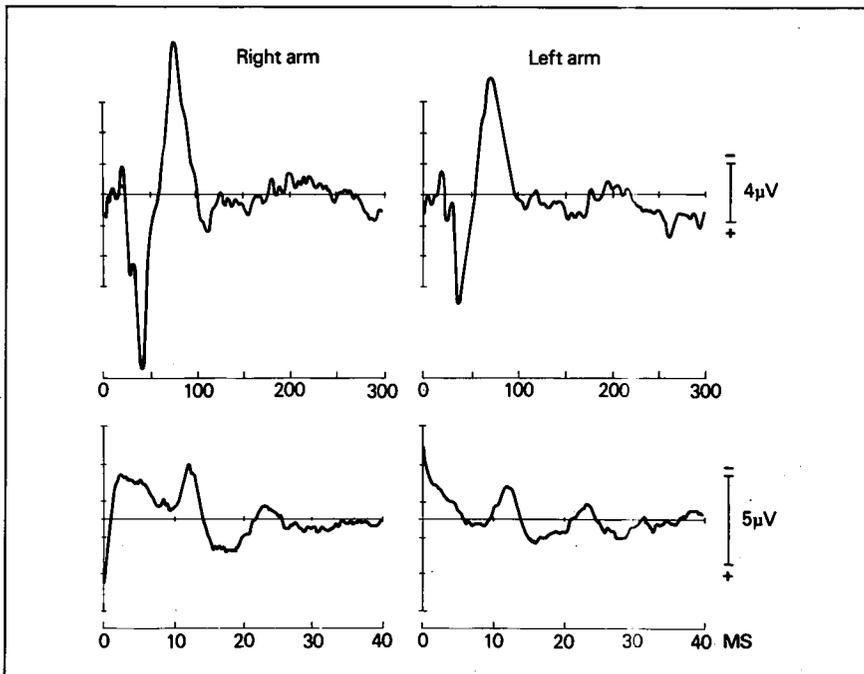


Fig. 6. Cortical (top) and cervical (lower) SEP tracings in a 58-year-old woman with multiple sclerosis showing enhancement of the cortical response to stimulation of the right median nerve. This patient had subjective sensory symptoms but no demonstrable sensory impairment.

In the patients with other forms of spinocerebellar degeneration not conforming to the above categories the cervical response was reduced in amplitude or absent, but not delayed, in 4 cases in each of whom the cortical responses were also delayed. In 1 patient with a normal cervical response the cortical response was of increased amplitude.

Brain-stem Syndromes

In a patient with the lateral medullary syndrome who had typical impairment of pain and temperature sensation on the right side of the body both the cervical and cortical responses were within normal limits. In another patient with a left-sided pontine infarction and severe impairment of all sensory modalities on the right side of the body both the cervical and cortical responses from right arm stimulation were grossly disorganised and barely identifiable (fig. 7). The cervical response from left arm stimulation was normal while the cortical response was of normal latency but just above the upper limit of normal in size (fig. 7). In a patient who was examined 3 years following a proximal posterior cerebral artery occlusion which had resulted in

mid-brain and thalamic infarction with severe left-sided cerebellar incoordination and dense left-sided hemisensory loss which had subsequently recovered leaving only an increased two-point discrimination threshold on the fingers of the left hand, both cervical responses were within normal limits while the cortical response from stimulation of the left arm was altered in configuration but within normal limits for latency and amplitude. In a patient convalescing after an episode of severe 'brain-stem encephalitis' the cervical responses were normal while the cortical response to left arm stimulation was of normal latency but of increased amplitude (fig. 8).

Stereotactic Thalamotomy

12 patients, 8 with Parkinson's disease and the others with various other types of involuntary movement, were studied 6 to 24 months after placement of radiofrequency lesions in the thalamus. In 7 a unilateral lesion had been placed in the ventral lateral (VL) nucleus, and in 5 bilateral lesions had been placed in the ventral lateral or lateral posterior nuclei or in the pulvinar. The cervical response was absent bilaterally in 3 of the 5 patients with bilateral lesions and in a patient with chronic MS with a

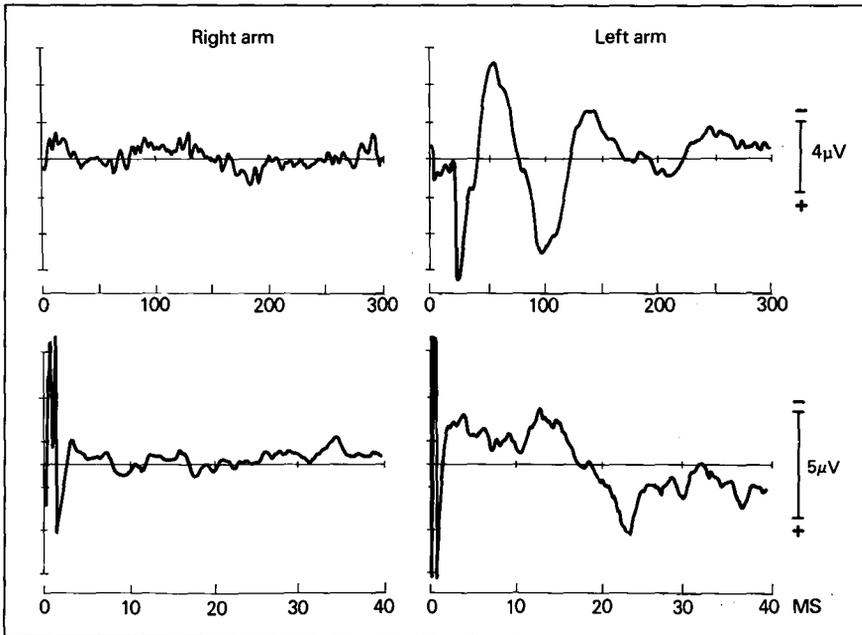


Fig. 7. Cortical (top) and cervical (lower) SEP tracings in a 51-year-old woman with a left-sided pontine infarction (see text) showing loss of both the cortical and cervical responses to stimulation of the right median nerve.

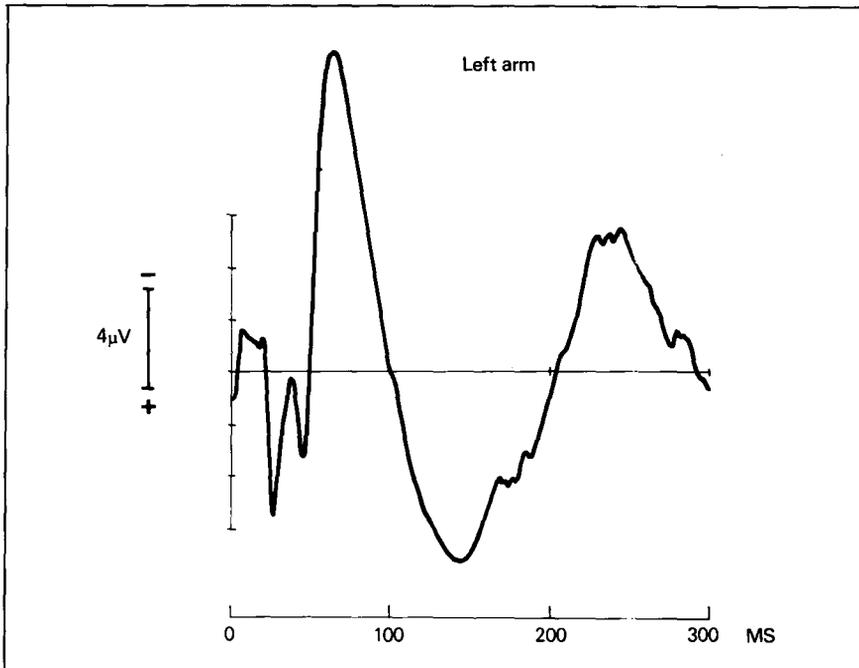


Fig. 8. Enhanced cortical SEP in a 32-year-old man who was recovering from a brain-stem encephalitic illness and who had no demonstrable sensory impairment.

unilateral VL lesion. Responses of reduced amplitude and/or increased latency were found unilaterally in 3 cases, in 2 on stimulation of the contralateral and in the 3rd on stimulation of the ipsilateral upper limb.

The cortical responses were abnormal unilaterally or bilaterally in 6 of the 8 patients with Parkinson's disease. In 2 patients with VL lesions the only abnormality was an increased peak-to-peak amplitude of the response (fig. 9), in 1 ipsilateral to the lesion and in the other contralateral to the lesion. In the other 4 cases the abnormality consisted of a delay in the P2 component which was ipsilateral to the side of the VL lesion in 2, contralateral in 1 and bilateral in a patient with bilateral VL lesions. In 3 other patients with MS or congenital encephalopathies the responses were grossly abnormal bilaterally.

Cerebral Hemisphere Lesions

In 2 patients with hemiplegia and hemisensory loss due to middle cerebral artery occlusion who were studied several weeks after the stroke the cervical responses were normal while the early components of the cortical responses over the damaged

hemisphere were delayed. In 1 of these patients the cortical responses over the 2 hemispheres were of approximately the same amplitude while in the other the response over the damaged hemisphere was considerably smaller. In a 16-year-old boy with a congenital left hemiplegia resulting from extensive destruction of the right cerebral hemisphere presumed to be due to occlusion of the internal carotid artery, stimulation of the right upper limb evoked a normal response over the left cerebral hemisphere with no discernible ipsilateral response, while stimulation of the paralysed left upper limb evoked no recognisable contralateral response but a clear-cut ipsilateral response (fig. 10). In a patient with an infiltrating right cerebral hemisphere glioma who had a left hemiparesis and whose only sensory abnormality was an increase in the two-point discrimination threshold on the left index finger, the cervical response from left arm stimulation was significantly reduced in amplitude while the right cortical response was abolished.

Spinal Cord Lesions

The cervical responses were reduced in amplitude or absent in 3 patients with cervical spondylosis and radiculomyelopathy. In a patient with syringomyelia and

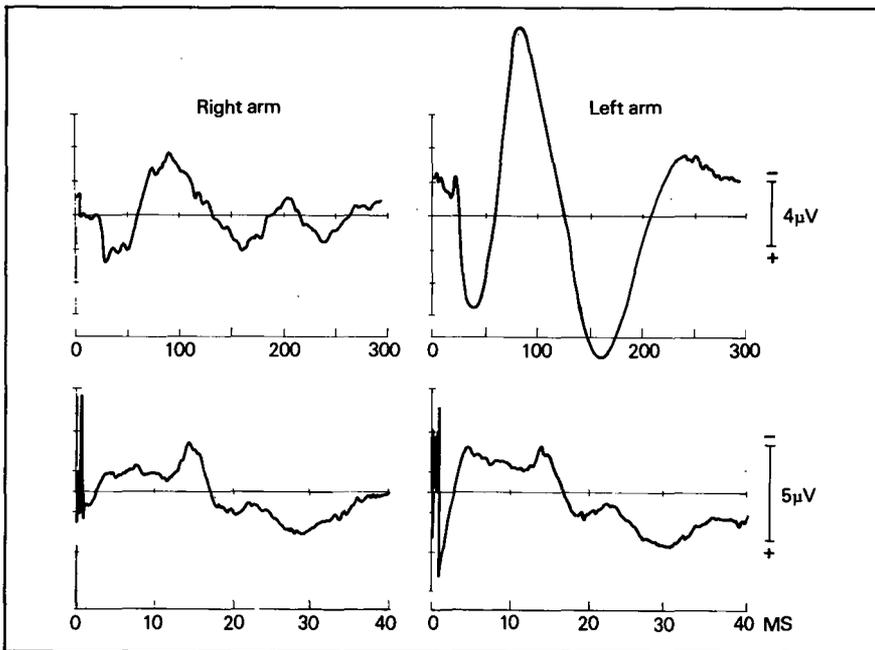


Fig. 9. Cortical (top) and cervical (lower) SEP tracings in a 52-year-old man with Parkinson's disease, 4 months after a right ventral lateral radiofrequency thalamotomy, showing enhancement of the cortical response to stimulation of the left median nerve.

syringobulbia who was found to have cerebellar ectopia and who was studied almost 2 years after surgical decompression of the craniocervical junction the cervical responses were both absent while the cortical responses were within normal limits. In another patient, in whom a diagnosis of atypical cervical syringomyelia was made on the basis of extensive amyotrophy and a neurogenic left elbow joint but with minimal sensory involvement, the ipsilateral cervical response was relatively reduced in amplitude while the cortical response recorded over the contralateral hemisphere was of normal latency but of increased amplitude (fig. 11). In a patient with a slowly progressing non-cystic intramedullary lesion of the cervical cord, thought to be a glioma, the cervical response was absent on one side and normal on the other.

Peripheral Neuropathies

The cervical responses were reduced in amplitude or absent in 2 patients with peroneal muscular atrophy and in 2 other patients with mixed forms of sensorimotor polyneuropathy.

Enhanced Cortical SEPs

The situations in which enhanced cortical responses were found are summarised in table V. The most marked degrees of enhancement were found in 2 patients with long-standing familial myoclonic epilepsy in each of whom responses approximately 10 times greater than the upper limit of normal were recorded. In the other patients the degree of enhancement was much less, responses of up to twice the upper limit of normal being recorded unilaterally or bilaterally. While in some of these the N1-P2 amplitude was increased (figs. 6, 9, 12) in the majority the peak-to-peak amplitude (P1/P2-N3) was increased but the N1-P2 amplitude was normal (figs. 8 and 11). In general, enhanced responses of this type were found in patients without sensory manifestations or with sensory symptoms and minimal or no demonstrable signs on clinical testing. In 1 patient with pontine infarction with a severe right-sided hemisensory loss and an absent response over the left cerebral hemisphere, the response recorded from the right hemisphere on stimulation of the left upper limb was enhanced.

Discussion

The present findings indicate the value of somatosensory evoked potential recording in studying conduction in the somatosensory pathway and particularly as a means of detecting subclinical involvement of this pathway in patients with various types of pathological disturbance. They also provide further insight into the origin of the early subcortical components of the somatosensory evoked potential and into the

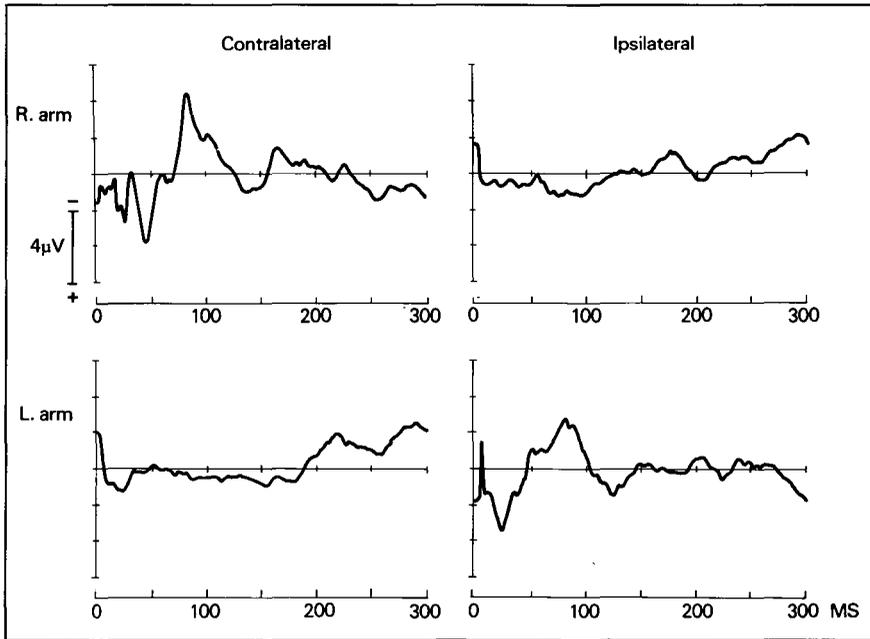


Fig. 10. Cortical SEPs in a 16-year-old boy with a congenital left hemiplegia (see text).

pathophysiological effects of different types of pathological process on conduction in the sensory pathways.

In general, although temporal delays in the evoked responses are characteristic of demyelinating lesions and gross disorganisation or abolition of the cortical response of destructive vascular or neoplastic lesions, the changes in both the cortical and cervical responses are quite nonspecific. In the case of the cervical response delays and changes in configuration are seen in patients with demyelinating disease while in degenerative disorders such as Friedreich's ataxia the size of the response declines without significant delays or desynchronisation.

The site of origin of the so-called cervical response remains uncertain. Small et al. (1978) concluded that it is derived at some point between the lower cervical spine and the brain stem. The fact that 3 or more subcomponents are usually seen under normal circumstances (Small and Jones, 1977) suggests that it is a composite potential derived from more than one source. It has been suggested that the N9 component may be generated in the brachial plexus, the N11 component in the spinal roots or dorsal columns, the N13 component in the spinal cord or brain-stem and the N14 component in the brain-stem or thalamus (Jones and Small, 1977). 3 comparable early potentials with latencies of 3 to 4 msec have been recorded in the rat (Wiederholt, 1975). The first 2 of these are not abolished by high brain-stem transec-

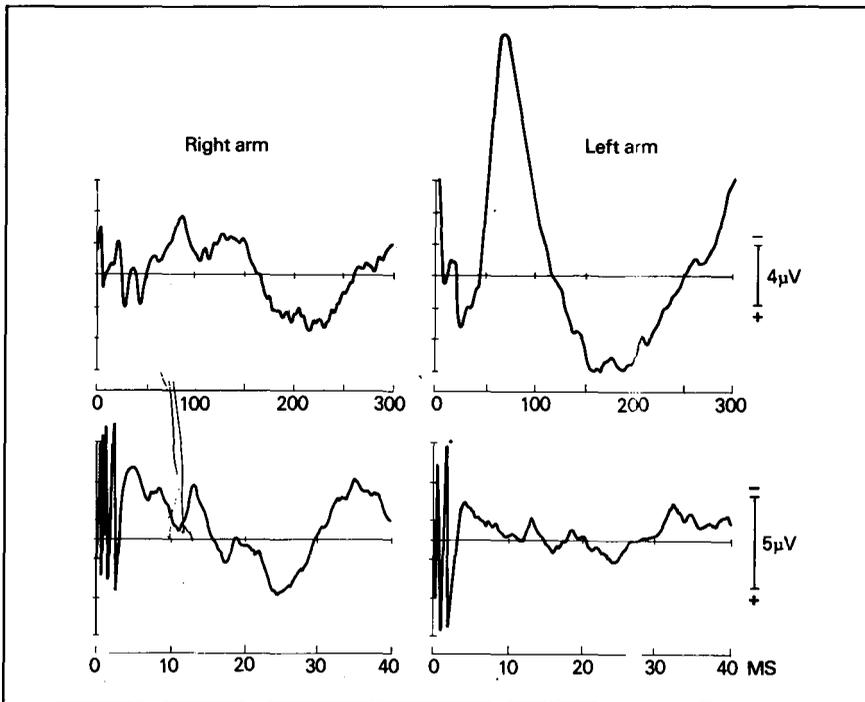


Fig. 11. Cortical (top) and cervical (lower) SEP tracings in a 53-year-old man thought to have syringomyelia (see text).

tion and are thought to be derived from the cuneate nucleus or the medial lemniscus while the 3rd component is probably derived from the thalamus or the sensory radiation. The possibility of a thalamic origin for the N14 component of the cervical response in man is also suggested by the observations of McComas et al. (1970) of thalamic neurones discharging with a latency of 13 to 19 msec after stimulation of the contralateral median nerve at the wrist. Our present findings throw some light upon these questions. The preservation of the cervical response in patients with impairment only of spinothalamic sensory modalities confirms the observations of Small et al. (1978) and suggests that, as in the case of the cortical response, the cervical response is dependent upon the posterior column-lemniscal pathway. The reduction in amplitude or abolition of the cervical response in some patients with non-acute brainstem or thalamic lesions supports the view that it is derived from more central portions of the somatosensory pathway. Further studies in patients with circumscribed lesions at known levels in the sensory pathway are required to clarify this question further.

Little attention has been given to the possible significance of enhanced cortical somatosensory evoked responses. The marked enhancement found in patients with

myoclonic epilepsy is well recognised, particularly since the observations of Halliday (1967a, b, c), who showed that there was a correlation between the severity of myoclonic jerking at the time of the study and the degree of enhancement of the first positive component (P33) of the cortical response. Halliday has also mentioned the finding of lesser degrees of enhancement in patients with a variety of brain-stem lesions but no further details were given (Halliday, 1967a). Our present findings indicate that enhancement may be found not only with brain-stem lesions but also with lesions of the spinal cord, thalamus and cerebral hemispheres and that this is more likely to occur in patients with minor or no clinical signs of involvement of the sensory pathway. It would seem reasonable to suggest that enhancement of the cortical response may occur under a variety of circumstances as a result of interference with the normal inhibitory mechanisms by pathological processes damaging the sensory pathway at one of a number of different levels. Again, further detailed clinical, electrophysiological and pathological studies of patients with well-defined lesions are required to elucidate this question further.

Changes in the amplitude of the cortical somatosensory evoked potential during cryothalamotomy have been studied by Domino et al. (1965) using scalp and epidural recordings. These authors found that lesions of the ventral lateral nucleus did not

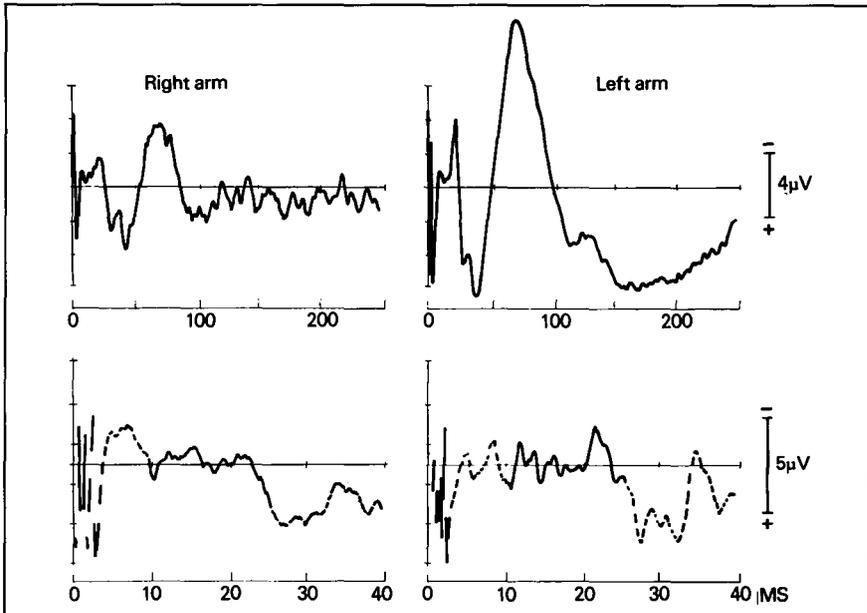


Fig. 12. Cortical (top) and cervical (lower) SEP tracings in a 63-year-old man with progressive supranuclear palsy showing enhancement of the cortical response to stimulation of the left median nerve.

alter the size of the response while combined lesions of the ventral lateral and ventral posterior nuclei caused some reduction in size of the early components, and larger lesions of the ventral posterior nucleus encroaching on the centrum medianum reduced all components of the response. Changes in latency were not commented upon in this study. The authors concluded that the major components of the cortical somatosensory evoked potential are mediated through the ventral posterior nucleus of the thalamus. The present cases were studied at intervals of up to 2 years following placement of unilateral or bilateral radiofrequency lesions in the ventral lateral nucleus followed in some patients by additional lesions in the lateral posterior nucleus or in the pulvinar. The lesions were identified in a high proportion of cases by computerised tomography (Cala et al., 1976) but this technique did not allow confirmation of the precise anatomical position of the thalamic lesions. Abnormalities which took the form of minor delays of the early components (N20, P40) and/or significant amplitude asymmetries, were found in a number of patients without clinical sensory deficits with no apparent correlation with the effectiveness of the procedure.

Summary

The value of evoked potentials in studying conduction in the somatosensory pathway was assessed in patients with various neurological disorders. In patients with multiple sclerosis (MS) abnormalities of the cervical response (N14) were found particularly in longstanding cases but also in the early stages of the disease, even in patients without sensory symptoms or signs, and were reversible in some patients. The cortical response was also abnormal in some cases but the two were not always affected together. In Friedreich's ataxia both the cervical and cortical responses were usually abnormal. Subclinical abnormalities of the cervical responses were found in some patients with hereditary spastic paraparesis or mixed forms of spinocerebellar ataxia. The cervical responses were also abnormal in patients with peripheral neuropathy and cervical radiculopathy, and in some patients with brain-stem or thalamic lesions. Cervical and cortical responses were normal in the lateral medullary syndrome, whereas the cortical response was markedly abnormal in patients with high brain-stem or cerebral hemisphere vascular lesions. Cortical and subcortical responses were abnormal in some patients with stereotactic thalamic lesions.

Enhanced cortical responses were found in patients with lesions at different levels in the CNS. The most marked enhancement was observed in patients with familial myoclonic epilepsy. Lesser degrees were found in some patients with MS, progressive supranuclear palsy, thalamic lesions, brain-stem encephalitis and syringomyelia. Enhanced responses were usually found in patients with minimal or no clinical sensory involvement. It is postulated that this type of abnormality results from an interference to the inhibitory mechanisms which normally operate at various levels in the somatosensory pathway.

It is concluded that evoked potential studies are a valuable adjunct to the clinical evaluation of sensation, and that they may provide useful information on the pathophysiology of conduction in the somatosensory pathway.

Acknowledgements

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Patterns of Response to Levodopa in Parkinson's Disease

*F.J.E. Vajda, G.A. Donnan and P.F. Bladin**

Levodopa therapy has been available in Australia for 8 years. Questions are raised increasingly frequently about the long term efficacy of this drug and the merits of starting levodopa therapy in patients with idiopathic Parkinson's disease immediately on making the diagnosis. Optimal times of starting levodopa, dosage regimens in relation to side effects and the role of ancillary drugs are uncertain.

Modification of levodopa therapy by adding a peripheral decarboxylase inhibitor will diminish the incidence of nausea but it is unlikely to influence significantly other side effects, except for an increase in dyskinesia. Side effects of levodopa occur on prolonged therapy after a number of years and the progress of the disease appears to be inexorable.

This study is an attempt at analysis of broad patterns of response. Categories based on clinical and ancillary occupational therapy assessments may help to define the broad pattern but unless these assessments are made at frequent, pre-set, routine intervals, analysis is difficult.

Patients and Methods

The details of our patients are given in table I. They have all attended the Neurology Unit of a teaching hospital and they were all admitted to the ward initially for assessment of their disease under the care of the same team of neurologists; there the

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Table I. Details of the 50 patients with Parkinson's disease

No. of patients	Mean age (years \pm SEM)	Mean age at onset of symptoms (years \pm SEM)	Interval between onset and treatment (years)	Duration of treatment (years)	Mean duration of disease (years \pm SEM)
50	66.5 \pm 1.33	58.3 \pm 1.46	4.1 \pm 0.65	4.02 \pm 0.37	8.20 \pm 0.87

Table II. Drugs used in 50 patients with Parkinson's disease

Drugs	Number of patients
Levodopa alone	10
Levodopa + amantadine	18
Levodopa, amantadine + anticholinergics	20
Levodopa + anticholinergics	2

diagnosis of Parkinson's disease was confirmed. All patients started levodopa treatment initially in small, though increasing, doses. Since 1976 levodopa has been used combined with a dose of alpha methyl dopa-hydrazine (carbidopa) in a fixed ratio of 10:1. Doses were adjusted as required by each individual patient.

The patterns of treatment are given in table II. 50 patients started levodopa and 44 continued on it up to the time of this review. In 6 patients levodopa was discontinued.

On the basis of clinical assessment and Webster Disability Scores, 3 categories of clinical well-being at the time of review were formulated:

- 1) Responding adequately with or without side effects
- 2) Responding poorly, and
- 3) Ceased levodopa because of side effects.

Each patient was placed into one of the above categories and the relationship of various time factors to clinical state was examined. The factors studied were age, duration of disease, time lag between diagnosis and start of treatment and duration of levodopa therapy. Side effects were analysed and then expressed as a percentage incidence in the total number of patients. Statistical correlations were made between the Webster Disability Score and the time factors under consideration.

Results

The reasons for the cessation of levodopa in 6 patients are shown in table III. Exacerbation of incontinence was noted in 2 and intractable nausea, even on small drug

doses, required the stopping of treatment in a further 2 patients. Psychosis developing during the course of therapy was the cause of the other 2 patients being withdrawn from treatment.

Figure 1 shows the duration of treatment with levodopa in this series of patients. The majority of patients tolerated the drug, only the 6 requiring cessation of therapy at the time periods indicated in the figure.

The patients' states of well-being (as defined above) in relation to their ages are shown in table IV. There is a statistically highly significant correlation between Webster Disability Score at the time of review and patient age ($r = 0.95$, $p < 0.001$).

Table V shows the patients' clinical response in relation to the duration of disease. The correlation between these variables is significant ($r = 0.51$, $p < 0.01$).

The duration of levodopa therapy in relation to categories of response is shown in table VI. The relationship is again significant ($r = 0.41$, $p < 0.01$). The large majority of patients responded well in the first 2 years of treatment. After 3 years, the rate of response declined; however, a significant percentage of patients continued to respond well for up to 8 years.

The relationship between the delay in starting levodopa therapy and the clinical state of the patients at the time of review is shown in table VII. The relationship between delay in starting levodopa therapy after the diagnosis of the disease was established and the clinical state of the patients at the time of review has no discerni-

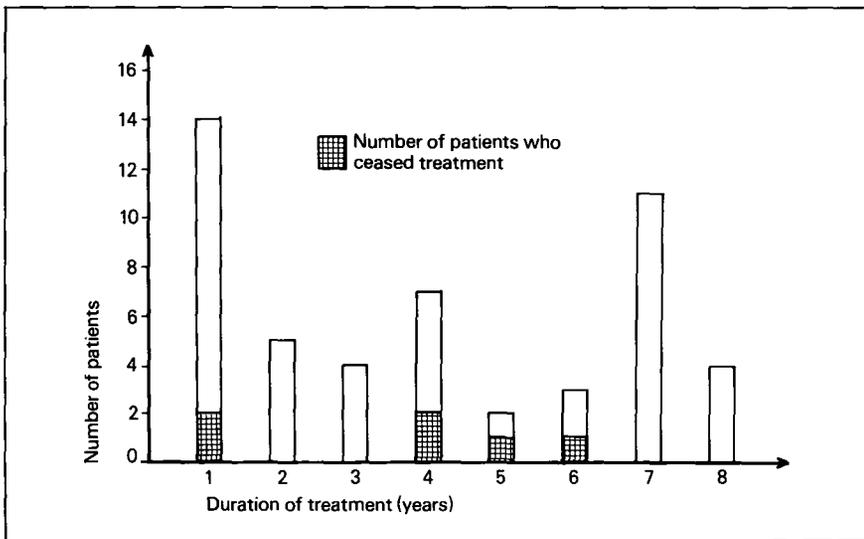


Fig. 1. Duration of levodopa therapy (years) in 50 patients with Parkinson's disease. 6 patients ceased treatment.

Table III. Details of the 6 patients in whom levodopa therapy was discontinued

Duration of levodopa treatment (years)	Reason for discontinuation
5	Nausea, dyskinesia
0	Nausea
6	Psychosis, sexual over-activity
1	Incontinence of urine
4	Psychosis
5	Incontinence

Table IV. Patients' response (well-being and clinical assessment) to levodopa in relation to age

Response	Number of patients	Male	Female	Age (years \pm SEM)
Adequate	33	17	16	60.4 \pm 1.92
Poor	11	4	7	70.8 \pm 1.74
Ceased treatment	6	3	3	65.67 \pm 3.45

ble statistical significance. The number of patients who experienced a long interval between diagnosis and the start of treatment is small. All patients who had Parkinson's disease before levodopa became available continued to do well at the time of review, 10 to 15 years after the diagnosis was made.

The incidence, nature, and time of onset of side effects in this series of patients is shown in table VIII. The most common side effect was nausea, followed by postural hypotension. The other important adverse effects occurred with a lesser frequency.

Discussion

With the advent of bromocriptine, and other dopamine agonists it appears that a new era of drugs similar in action to levodopa is about to begin. For this reason we attempted to review the patterns of response to levodopa in a series of patients with idiopathic Parkinson's disease. Although this study is retrospective, it provides some insight into our progress in treating Parkinson's disease.

It appears that response to levodopa is more closely related to age, duration of disease and period of treatment than to a delay in the introduction of the drug in the

course of the disease in the individual patient. This suggests that levodopa does not maintain its beneficial effect in the majority, and that the disease goes on inexorably although some patients respond well to levodopa even after 8 years. Most people tolerated the drug well, but unacceptable side effects occurred throughout the course of treatment. The nature of the side effects was similar to those in other series, although postural hypotension appeared to be more common in our patients.

From this study no answer can be given to the question of whether early administration of levodopa is to be recommended or whether it is better to wait until the disability from the disease becomes significant. This is important because it seems that the results of treatment are more favourable in the early stages (Fahn et al., 1978). The decline in the effect of levodopa on neurological disability was shown to occur in our study after about 3 years of use. It therefore seems reasonable, as suggested by Fahn et al. (1978), to withhold levodopa until it becomes really necessary and to treat patients with the minimum dosage required to sustain their essential activities.

Table V. Response to levodopa in terms of duration of Parkinson's disease

Disability (years)	Number of patients	Response		
		adequate	poor	ceased treatment
1-4	16	14	2	—
5-9	18	8	6	4
10-14	12	9	2	1
15 +	4	2	1	1

Table VI. Response of patients in relation to the duration of treatment with levodopa

Levodopa treatment (years)	Number of patients	Response		
		adequate	poor	ceased treatment
0-2	19	17	0	2
3-4	10	5	4	1
5-6	5	2	1	2
7-8	16	9	6	1

Table VII. Relationship between the delay in initiating treatment and the response to levodopa

Delay (years)	Number of patients	Response		
		adequate	poor	ceased treatment
0-4	35	23	8	4
5-9	9	5	3	1
10-14	4	4	—	—
15 +	2	1	—	—

Table VIII. The side effects of levodopa and the interval between starting treatment and their onset

Side effect	Number of patients (%)	Onset interval (years)
Nausea	17 (34)	1.0
Postural hypotension	11 (22)	3.0
Psychosis	5 (10)	3.3
'On-off' effect	6 (12)	3.6
Dyskinesia	5 (10)	3.6

Dougan et al. (1975) suggested that the complex metabolites of levodopa may be responsible for the therapeutic failure of long term therapy, and in particular for the 'on-off' phenomenon. Therapeutic failure or success with the drug may depend on the relative rates of production or accumulation of these metabolites in different patients. Levodopa does not influence the underlying pathology of Parkinson's disease. If the drug is stopped, the patient reverts to his pretreatment state, or even more serious disability results (Marsden, 1976). As the side effects of levodopa are moderately frequent and may be difficult to manage there is no clear indication for prescribing it, from the outset, in every patient with Parkinson's disease.

The incidence of 'on-off' phenomena in our series was similar to that in others reported (Calne et al., 1974). This effect represents one of the major problems in the treatment of Parkinson's disease. It has been described as early morning akinesia, freezing episodes and end-dose deterioration; these effects are due to progress of the disease. Peak-dose akinesia and dyskinesia may be due to overtreatment. These two sets of symptoms may overlap (Marsden, 1976).

Shoulson (1975) suggests that a central noradrenergic mechanism, as well as alterations in circulating dopa, may contribute to the 'on-off' response, and it is possible that postural hypotension which is a relatively common adverse effect of levodopa therapy (22% in our series) may be related to abnormal noradrenergic mechanisms.

Tolosa et al. (1975) reported a correlation between Parkinsonian control and plasma levodopa levels. Hornykiewicz (1973) and Rinne and Sonniven (1973) in studies in which plasma dopamine levels were measured, reported a direct correlation between the dose and the time of administration of levodopa and striatal levels of dopamine.

It appears that establishment of methods for plasma levodopa and dopamine measurements may be a useful adjunct to individualising the dose of levodopa for patients with Parkinson's disease. To improve the technique of study it is suggested that regular 6-monthly disability assessments may define more clearly the rate of progress or deterioration of patients with this condition.

Summary

The broad results of the treatment of patients with idiopathic Parkinson's disease who have received levodopa or its variants are reported.

50 patients, 24 males and 26 females, with a mean age of 66.5 years were treated with levodopa, in daily doses ranging from 0.25g to 6.0g or 'Sinemet' in daily doses of 300mg to 750mg. Periods of treatment ranged from 4 months to 8 years, with a mean of 4.02 years. The relationships of patients' age, onset of Parkinsonian symptoms and interval between initial treatment with levodopa and the current clinical state were studied. Patients were classified according to their clinical response into 3 categories: satisfactory response, progressive deterioration or intolerance of levodopa. The proportion of patients in each category was 66%, 22% and 12% respectively.

The clinical results of treatment correlated with those of Webster Disability Testing Scale. Analysis showed that the majority of patients tolerated levodopa and showed an initially satisfactory response. Patients who responded well were considerably younger than those who failed to respond. Patients receiving the drug for a shorter period (< 3 years) showed a better response. After 3 years' treatment, the response declined. Patients who had had Parkinson's disease for more than 4 years appeared to do less well than those with recently diagnosed disease, but many patients responded well even when treatment was initiated 10 years after the onset of symptoms.

Patients discontinued levodopa treatment because of psychoses, nausea, dyskinesia or exacerbation of urinary incontinence. The commonest side effects were nausea (34%), postural hypotension (22%), psychoses (10%) and 'on-off' phenomena in 12% of patients.

Acknowledgements

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Abstract

Immune Lesions of Central Noradrenergic Nerves in the Rat Produced by Antibodies to Dopamine- β -hydroxylase

*W.W. Blessing, M. Costa, L.B. Geffen and R.A. Rush**

Synthesis of catecholamines follows a number of enzymatically mediated steps. Development of antibodies against the enzymes involved in this process facilitated the immunohistochemical localisation of dopamine, noradrenaline and adrenaline-containing neurons. Dopamine- β -hydroxylase (DBH), the enzyme which converts dopamine to noradrenaline, is localised inside noradrenergic synaptic vesicles and becomes exposed to the extra-cellular space during transmitter release. When antibodies to DBH (anti-DBH) are injected *in vivo* they bind to noradrenergic nerve terminals. This suggests the possibility of using anti-DBH to make lesions in noradrenaline containing neurons.

Anti-DBH, mixed with complement, was infused stereotactically into either a lateral or the third ventricle of each of 9 anaesthetised rats. Four control rats received equivalent volumes of non-immune serum and complement. At times varying from 2 to 7 days after infusion the rats were re-anaesthetised and the brain perfused with a buffered mixture of formaldehyde and glutaraldehyde to fix the tissue and convert catecholamines to fluorescent derivatives. Sections were cut on a vibrating microtome and, after air drying, mounted in liquid paraffin and examined with a fluorescence microscope.

Many thick and distorted fluorescent axons were visible throughout the brains of all animals that received immune serum. These were most numerous in the medial septal nuclei, diagonal band of Broca, piriform cortex, rostral corpus callosum, zona

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incerta and posterior commissure. In contrast to the fine smooth appearance of normal catecholamine-containing axons the degenerating fibres were very brightly fluorescent and irregularly swollen. There was also a patchy loss of varicose axon terminals accompanied by occasional swollen varicosities in the neocortex, hippocampus and cerebellar cortex. The catecholamine-containing cell bodies in the brain stem seemed normal. In the control rats there was no detectable loss of varicose axon terminals and the only swollen fibres seen were confined to the area of local necrosis along the pathway of the cannula.

Specific lesioning by antiserum may prove a powerful tool in future studies of the function of the catecholamine systems in the central nervous system. Pathological processes involving transmitter systems may possibly be mediated by autoantibodies to the relevant enzymes.

Abstract

The Medial Pre-optic Area Rhythmically Inhibits a Hypothalamic Pacemaker Stimulating Growth Hormone Secretion

**J.O. Willoughby, Judy Audet and J.B. Martin*

Physiological growth hormone (GH) secretion in mammals is episodic and is mediated in part through a stimulatory neural mechanism in the medial basal hypothalamus (MBH), which probably secretes GH releasing factor (GRF). When this region is experimentally severed from all other brain connections, GH secretion is markedly elevated, and the characteristic troughs between GH secretory bursts are abolished.

Immunohistochemical localisation of GH inhibiting hormone (somatostatin) in neurons of the medial pre-optic area (MPOA) and evidence that electrical stimulation of this region inhibits GH secretion in anaesthetised animals, suggests that the MPOA might have an inhibitory influence on the MBH in the production of physiologic GH secretion. The following study examined this possibility.

Male albino Sprague Dawley rats were anaesthetised and electrolytic lesions or sham lesions were placed in the MPOA. After recovery, animals had chronic indwell-

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ing right atrial cannulae inserted, and 6-hour GH secretory profiles were subsequently constructed from GH concentrations obtained by radioimmunoassay of 15 minute serial blood samples drawn via the cannulae. Histological examination of brains from all lesioned animals confirmed accuracy of lesion placement, or animals were rejected from the study.

Animals with lesions had significantly more frequent GH secretory bursts than controls (2.11 ± 0.74 vs 3.63 ± 0.40 hours; $p < .001$) and GH values between bursts, which are normally unmeasurable, tended to remain elevated. The characteristic rhythmic secretion of GH in normal animals was therefore markedly altered.

This evidence suggests that the MPOA normally inhibits GH secretion in a rhythmic fashion. Both direct MPOA —MBH projections and MPOA — median eminence projections have been described electrophysically and by autoradiography. Thus the inhibitory influence of the MPOA on GH secretion might be mediated by inhibitory neural connections to the MBH pacemaker, or through secretion of somatostatin directly into the portal circulation from MPOA somatostatinergic neurons.

Abstract

Growth Hormone Secretory Rhythms in Rats are Synchronised by the Suprachiasmatic Nucleus

*J.O. Willoughby, * Judy Audet and J.B. Martin*

Growth hormone (GH) secretion in man and experimental animals is episodic and bursts of hormone secretion are generated by hypothalamic mechanisms. GH secretory episodes are sometimes entrained to external stimuli, e.g. meal times, or the commencement of different photo-periods each day.

In the rat, episodic GH secretion has a regular periodicity (approximately 3-hourly) and secretory bursts in different animals are synchronised by the daily light: dark (L : D) schedule. Four anatomically distinct visual pathways have been described which might be implicated in regulating biological rhythms. They are the primary optic pathway, the inferior and superior accessory optic pathway, and the direct retino-hypothalamic projection (DRHP) via the suprachiasmatic nuclei (SCN). Experiments

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were undertaken to determine which visual pathway synchronised episodic rat GH secretion.

Six-hour GH secretory profiles were obtained by radioimmunoassay of 15 minute serial blood samples drawn from operated and control male albino Sprague Dawley rats chronically implanted with right atrial cannulae and acclimatised to isolation and strict 12 : 12 hour L : D cycle. Groups of intact and blind animals, and those with Halasz-type transection of anterior hypothalamic connections, or with SCN electrolytic lesions were tested. These groups provided animals with intact and totally interrupted visual pathways and interrupted DHRP plus inferior accessory optic pathways and selective DHRP lesions, respectively.

In all experimental groups, GH secretion was rhythmic and the periodicity of the rhythms did not differ significantly between groups (3.17 ± 0.36 , 3.32 ± 0.70 , 2.97 ± 0.62 , and 3.00 ± 0.11 hours in intact, blind, anterior hypothalamus transected, and SCN lesioned animals, respectively). Intact animals had GH secretory episodes which were synchronised with the L : D cycle. Blinding, anterior hypothalamic transection and SCN lesions were effective in disturbing entrainment of the GH secretory rhythm to the L : D cycle.

Thus:

- 1) the SCN does not function as a rhythm generator for episodic GH secretion,
- 2) because SCN lesions destroy selectively the DRHP (cf. blinding and transection) which destroy more than one visual pathway.

The SCN or probably the DRHP appears to mediate the effects of the L : D cycle on GH secretory rhythms.

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Subject Index

A

- Acupuncture analgesia
 - for chronic low back pain 182-185
- Anticonvulsant drugs
 - pharmacology of 51-84
- Arachnoid cysts
 - of posterior fossa 159-165
- Autonomic dysfunction
 - in Landry-Guillain-Barre syndrome 197-203

B

- Brachial plexus
 - delayed radiation induced damage 221-227
- Bromocriptine
 - in treatment of Parkinson's disease 228-236

C

- Carotid ulceration
 - experimental detection by radionucleotide labelled particles 174-181
- Causalgia syndrome
 - treated with intravenous guanethidine 166-173

- Cysticercosis
 - spinal 85-91

D

- Dopamine- β -hydroxylase
 - producing immune lesions of noradrenergic nerves 307-308

E

- Electromyographic study
 - of polysynaptic responses 204-214

F

- Fatty acids, free
 - and migraine 190-196

G

- Golden age of neurology 1-10
- Growth hormone secretion
 - inhibited by medial pre-optic area 308-309
 - synchronised by suprachiasmatic nucleus 309-310
- Guanethidine, regional, intravenous

in treatment of causalgia
syndrome 166-173

H

Hypertension

benign intracranial
and primary empty sella
syndrome 248-257

Hypothalamic pacemaker
inhibited by medial pre-optic
area 308-309

I

Immune lesions of noradrenergic nerves
produced by dopamine- β -hydroxylase
307-308

L

Landry-Guillain-Barre syndrome
autonomic dysfunction 197-203

Leukaemia
acute lymphocytic, of childhood
some specific neurological
complications 271-278

Levodopa
patterns of response in Parkinson's
disease 299-306
pharmacology 24-50

M

Memory disorder
in vertebrobasilar disease 215-220

Metastases
vertebral, and spinal cord
compression 98-113

Methylphenobarbitone
pharmacokinetics of 131-144

Migraine
and free fatty acids 190-196

N

Neuralgia, occipital 258-270

Noradrenergic nerves, central
immune lesions produced by antibodies
to dopamine- β -hydroxylase 307-308

P

Pain

central mechanisms 11-23

Pain, chronic low back
acupuncture analgesia for 182-185

Parasitic diseases
in Thailand 92-97

Parkinson's disease
patterns of response to levodopa 299-306
treatment by bromocriptine 228-236

Phenobarbitone
comparison of oral and
intramuscular routes 154-158

Polyarteritis nodosa
neurological features of 237-247

Polyposis coli, familial
with central nervous system
sarcoma 127-130

Potentials, evoked
in assessment of the somatosensory
pathway 279-298

Pre-optic area, medial
inhibitory effect on hypothalamic
pacemaker 308-309

R

Radiation induced damage, delayed
to the brachial plexus 221-227

Radionucleotide labelled particles
detection of experimental
ulceration 174-181

S

Sarcoma of central nervous system
with familial polyposis coli 127-130

Sella syndrome, empty
and benign intracranial
hypertension 248-257

Somatosensory pathway
evoked potentials in
assessment of 279-298

Spinal cord
 compression and vertebral
 metastases 98-113
Suprachiasmatic nucleus
 synchronising growth hormone
 secretory rhythms 309-310

Visual perception
 in left and right handed
 children 186-189
Visuo-motor skill
 in left and right handed
 children 186-189

V

Valproate, sodium
 dose-plasma level relationships 145-153
 interdose fluctuations 145-153
Vertebrobasilar disease
 memory disorder in 215-220

W

Wernicke-Korsakov syndrome
 lesions in coronial necropsies 114-126