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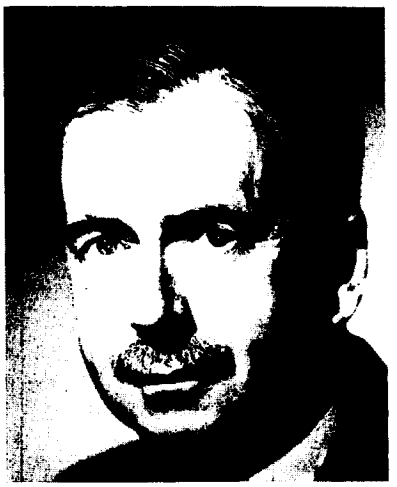

EDWARD GRAEME ROBERTSON
1903-1975

Tribute has been paid to Graeme's life and contributions to world neurology and Australian medicine in other journals, but the dedication of this volume of our Proceedings to him is something different and personal, because this journal is his creation and we are his neurological family.

It frequently happens that what appears to be the product of a group has its origin in the efforts of one man. This is often said but just as often forgotten. There is no doubt that the Proceedings of the Australian Association of Neurologists is Graeme's child. Everything about it—its clear, simple, elegant but unpretentious form and even the standard of its contents—reflects everything that is Graeme and will stand, one hopes, as a fitting memorial to him. Those are outward and visible things. Its real significance as a memorial to him is the motivation for its genesis.

Graeme dedicated himself to the translation to Australia of the spirit and discipline of the school of clinical neurology of Queen Square, into which he had immersed himself until it had become a part of his own being, at the most mature period of the life of that school of thought in London. He had come home in 1934, when he had shown that he could have held a place amongst the great in London. He had set the example in hospital and private practice of neurology in Melbourne and he had shared the lead in creating our Australian Association of Neurologists in 1950. He set the standard of content and discipline of presentation of papers at our annual meetings, he wanted to be sure that the criteria of excellence would be maintained and he saw that publication of our Proceedings—in the full light of day for the whole world to see and criticize—was the surest means of doing that. And so tentatively, and in simple form, the first volume of our Proceedings appeared in 1963. Some of this and the history of our insigne, the Waratah, has been told in last year's volume 12. The second volume and all since have appeared in the present style.

We have had our administrative and, even more, financial vicissitudes in keeping the Proceedings alive,

but now we have an even stronger incentive to ensure its future as a memorial to Graeme. We hope it will one day have pride of place on the shelves of the Graeme Robertson Memorial Library which we hope to establish round the nucleus of Graeme's gift to us, in recent years, of his own neurological library.

In this, our memorial to Graeme, what we want to recognize and to have recognized, is that his greatest contribution was not his scientific work in itself, considerable and significant as that was. It was his personal influence in shaping the course of Australian neurology and neurologists by the example of what he himself did in his daily life and practice, so quietly and modestly and with such discernment and conviction. That was in fact the medium through which he translated to Australia the discipline of the Queen Square school of thought which was a very sound rock on which to build our future. His first duty, indeed, was always to his patients. An no one can give better testimony to this than the patients themselves, whose comments invariably reflect their recognition and appreciation of his human compassion and sensitive and perceptive understanding. His first loyalty was always to neurology. This often found expression in his statement of his basic tenet that we must always be sure to retain control of our own destiny. That is why the Australian Association of Neurologists was so important to him and why he never spared himself in his contribution to the activities of the Association in all the fields of our endeavours, discussed in the review of twenty-five years in our last volume. And that is why he worked so tirelessly as Editor in nurturing the continuing publication of these Proceedings.

Graeme's impact on Australian medicine and neurology began when he returned from England in 1934. School at Scots College, Melbourne, graduation in Medicine with honours from the University of Melbourne in 1927, Doctorate of Medicine in 1930, to London in 1930 and the London Membership, these paved the way to Queen Square. Then followed what I think would have been one of the very happy periods in his life. He found fulfilment of his intellectual and personal talents and inclination in the ordered discipline of neurology, then probably at its peak at Queen Square, and in the stimulating personal associations and treasured friendships which lasted all his life. Amongst his seniors my impression is that he formed the closest bond with Gordon Holmes, and amongst his contemporaries Denis Brinton and "Denny" Denny-Brown became his lifelong friends. Above all he met his future wife, Jane Duce.

Return to the Royal Melbourne Hospital in 1934 showed where his loyalties lay. He served that great hospital for the rest of his life. There he began to build a neurological department—belatedly recognized as such by his appointment as Honorary Neurologist ten years later in 1944. Well before that, however, work on his major scientific contribution was begun, in circumstances and conditions where, to use his own words, "the specialist was forced to shift for himself if, without assistance, he was to develop a satisfactory service." His first monograph of pneumoencephalography was published in 1941, but the quest for perfection went on until the classic volume of 1967. There were sixty-eight other papers and monographs. Amongst the early ones were those in memorable and very personal association with Denny-Brown on the physiology of micturition, which remained the authoritative work on the subject for many years. But the majority of later papers came from his own work and own hand. Amongst these the most notable contributions after encephalography were on photogenic epilepsy and cerebral aneurysm.

Graeme's life in neurology in Australia is too well known to most readers of this journal to need any recitation here, as was his participation in all activities of the A.A.N. He was a Foundation Member in 1950, our most distinguished President in those important years of maturation from 1962 to 1966, and later Honorary Member Emeritus, the highest honour our Association can confer in recognition for personal service to the Association. He never missed a meeting until once, towards the end, due to ill health.

With Professor Shigeo Okinaka he shared the formation of the Asian and Oceanian Association of Neurology in 1962 and was President of the Second Congress in Melbourne in 1966. He became a prominent and active figure in the World Federation of Neurology serving a time as Vice President and on several of the important policy committees where his advice was often sought and followed. All these brought great credit to Australia. Our own Royal Australasian College of Physicians also recognized his standing in Australian medicine by electing him Vice President in 1962. Space does not allow reference to all his other neurological appointments and accolades.

But there must be room to speak of quite another aspect of his life—his hobbies which like his work reflected his personality and also became a contribution to the cultural life of the community in which he lived. A love of beauty and a flair for perceiving it in the perfection of simple ordinary things led his eye to

the early cottages and houses of Tasmania, built of a soft sandstone in simple Georgian style. Having learned to use the camera in his work, he photographed these early cottages in off duty hours during regular professional visits to Tasmania. He studied their history and wrote about them. In Melbourne, originally settled some decades later than Tasmania and soon flourishing from the "gold rush", the more flamboyant style of common domestic architecture was frequently decorated with ornamental cast iron, hanging like lace from balconies. It was really the soft tracery of the shadows of this, thrown on the walls behind, especially by the morning and evening sun, which caught his eye. The result was ten superb books, and one more still in the press (prepared together with his daughter Joan, who shared his gifts and skill). These beautiful volumes are already greatly valued as a record of an era of building, now often falling under the wrecker's hammer and apparently strangely neglected in architectural historical works.

The most treasured aspects of his personal life were the peace and beauty created in the privacy of his own home, shared, until her sudden death a few years ago, with his wife Jane and their two children Denis and Joan, whose devoted care was his main support until the end.

JOHN A. GAME

HENRY MILLER

"Henry Miller M.D., Vice-Chancellor, University of Newcastle-upon-Tyne, Professor of Neurology 1964-68, Dean of Medicine 1966-68, Neurological Physician and Education Administrator"—how inadequately this describes a man who in truth became a legend in his own life time! Others will do justice to his outstanding academic and clinical career and to his abilities in many fields. I shall write only of Henry Miller in Australia and of the high regard, respect and affection in which he was held by his Australian colleagues.

I first met Henry in 1961 as his guest at Newcastle-upon-Tyne and in 1963 he accepted an invitation to Brisbane to be the Sir Edwin Tooth Visiting Professor, the first of his three visits to Australia. To say that his visit was a signal success would be an understatement. He was no cold, sterile academician. Rather, he imparted knowledge and wisdom with consumate oratory, both at formal lectures and at teaching rounds. Those privileged to hear him were regaled with a remarkable mixture of astute clinical observations ("A fit during sleep is epilepsy unless proved otherwise"), stimulating Millerisms ("the ignition key of a Bentley is the best instrument for eliciting a Babinski reflex"), and profound philosophic comments ("A curiously moralistic attitude—probably Scottish in origin—makes tractotomy morally acceptable and heroin morally wrong for the treatment of intractable pain in carcinoma").

In 1963, Henry Miller delivered lectures in many Australian centres on "Accident Neurosis" (the subject of his Milroy Lectures before the Royal College of Physicians of London in 1961). The views he expressed, by design provocative, created such interest that the Editor of the Australian Medical Journal did not terminate the lively correspondence which followed until June 1964.

Henry Miller's criticisms were sometimes trenchant (" ... it is still difficult to regard psychiatry as in any way a science, or even as belonging to that rather small sector of Medicine which can at the present time be regarded as reasonably scientific"), but the flashing smile and invariable good humour which accompanied such comments robbed them of innuendo or hurt. Socially, Henry was tremendous company. His ability as a raconteur, his skill in friendly debate, his tolerance and good humour made him the most pleasant of companions.

In the years following Henry Miller's first visit to Australia, further bonds between Newcastle-upon-Tyne and various neurological centres in Australia were forged and strengthened by many of our younger neurologists and neurosurgeons spending periods of post-graduate training at Newcastle-upon-Tyne. Indeed, it can be said that over the past decade the Newcastle-upon-Tyne School of Neurology under the leadership of Henry Miller and Professor John Walton has had a profound influence on Neurology throughout Australia.

Henry Miller paid two further visits to Australia, the last one in 1975, when he was accompanied and supported by his wife, Eileen. On this occasion, although in failing health, he undertook the arduous task

of officially launching the Australian Neurological Foundation. Only his indomitable courage and spirit and his wife's unfailing care enabled him to carry out the onerous duties of a commitment he regarded as being of immense importance.

Henry Miller was a big man in every way. He was big physically, he painted on a broad canvas; he enjoyed life hugely; he had an immense influence on all who knew him. His Australian friends and colleagues salute his memory and offer their sincere sympathy to Eileen and their four children.

JOHN M. SUTHERLAND

HENRY MILLER—AN APPRECIATION

Henry George Miller was born at Stockton-on-Tees in December 1913 and graduated in medicine from the University of Durham in 1937. He obtained his early postgraduate training in the Royal Victoria Infirmary, Newcastle, going on to posts at the Hospital for Sick Children, Great Ormond Street, and the Johns Hopkins Hospital, Baltimore, just before the Second World War. After war service in the Royal Air Force as a neuropsychiatrist under the aegis of Sir Charles Symonds, he obtained further experience at the Hammersmith Hospital and the National Hospital, Queen Square, returning to Newcastle in 1947 as an Assistant Physician to the Royal Victoria Infirmary. He then commenced the long and distinguished career in consultant practice and research with particular interest in demyelinating diseases and forensic neuropsychiatry which culminated in his appointment to a personal Chair in Neurology in 1964. During this time, he laid the foundation of what has become one of the most influential neurological departments in the English-speaking world. There can be no doubt of the significance of his many contributions to clinical and academic neurology but those of us who had the privilege of working with him will remember him with affection and gratitude for much more personal reasons. It would be difficult if not impossible to choose one outstanding aspect of this great man's often bewilderingly varied personality although his quite extraordinary generosity and kindness never failed to impress the young neurologists working in his unit. Henry also was an extremely funny man who never failed to enliven the most dull conference or committee proceedings. His mastery of the English language with respect to both the written and the spoken word was complete and an inspiration to junior and senior colleagues alike.

Australian neurology and neurologists owe a considerable debt to Henry Miller. Many of us have been influenced directly or indirectly by his approach to neurology and his robust enjoyment of life generally, and we have every reason to be grateful to him for this. He in turn liked Australia and greatly enjoyed his three visits in 1963, 1968 and 1975. The last visit, undertaken when he was already a sick man, was at the behest of the Australian Neurological Foundation to stimulate an appeal for research funds and was to be his last contact with many old friends. He was delighted with the success of the tour and recounted many amusing tales of his experiences on returning to Newcastle, being particularly satisfied with the public outcry excited by his more scathing criticisms of Australian medicine generally. There will never be another Henry Miller and the Australian Association of Neurologists would like to take this opportunity to record its enduring appreciation of his life and work. We are all going to miss him badly.

PETER HUDGSON

BRYAN COOPER

Bryan Cooper came to Sydney from Forbes and was educated by the Christian Brothers at Lewisham, becoming dux of his class in 1948 and the winner of a university exhibition and a state bursary. He graduated in medicine with honours and became a resident at St. Vincent's Hospital where he came under the influence of Sir Douglas Miller who stimuated his interest in the neurological sciences. He undertook

postgraduate work in England where he obtained his F.R.C.S. in 1961. He worked at the Sunderland Eye Infirmary and Birmingham Eye Hospital before being appointed Chief Clinical Assistant at Moorfields Eye Hospital in 1960 and Senior Registrar at the Western Ophthalmic Hospital, London, in 1961. In England he married Mary Kevans and he and his wife returned to Australia where he established an ophthalmological practice in Penrith. He obtained his F.R.A.C.S. in 1962.

Although extremely busy in private practice, he became Honorary Neuro-ophthalmologist to the Prince of Wales and Prince Henry Hospitals, Sydney, which gave him the opportunity to pursue the aspect of his work which had fascinated him most during his years in England. His work necessitated his beating a triangular track across Sydney from his home at Strathfield to his consulting rooms in Penrith, then to Macquarie Street in the centre of the city and on to The Prince Henry Hospital. In spite of the enormous strain on his constitution which this must have imposed, Bryan was always a very helpful and friendly consultant who contributed enormously to the neurological life of this hospital group. He played an important part in the education of registrars and neurological trainees as well as of the consultant staff itself. It was never too much trouble for him to see a patient and his view was always soundly reasoned, playing a very important part in the management of the patient. He was responsible for the training in neuro-ophthalmology of an Indonesian neurologist who is now developing this specialty in Djakarta and he stimulated some of his ophthalmological colleagues to take a particular interest in neuro-ophthalmology which enabled the continuation of the clinic after he was appointed to the Sydney Eye Hospital where he continued the same high standard of service that characterized his postgraduate career.

Bryan detected in himself an increasing hesitancy of speech and increasing headache which marked the onset of his final tragic illness. He was well aware of the diagnosis and of its likely outcome but faced this with equanimity, strength of mind and religious faith. His only concern was for his wife and children.

Bryan became an Associate Member of the Australian Association of Neurologists because of his devotion to neuro-ophthalmology, a subject to which he gave so much during his professional life. Bryan had much more to give and it is a great sadness to us that his life was cut short at so early an age. He will always be remembered by his neurological colleagues who extend their deep sympathy to his wife and children.

JAMES W. LANCE

PATTERN VISUAL EVOKED POTENTIALS IN THE DIAGNOSIS OF MULTIPLE SCLEROSIS AND OTHER DISORDERS

ANN L. HUME and B. R. CANT#

The diagnosis of multiple sclerosis remains difficult. Despite the development of various laboratory techniques, primarily involving the immune system, the diagnosis still largely depends on clinical methods and it is frequently made by excluding other conditions. According to Lumsden (1970), the optic nerves are one of the most common sites for plaques in multiple sclerosis, but patients frequently present without clinical evidence of visual impairment.

In 1962, Hubel and Wiesel demonstrated that the mammalian visual system is specifically organized for the recognition of contours. In 1967, Cobb, Morton and Ellinger showed that very reproducible cortical evoked potentials with a narrow range of peak latencies could be obtained in human subjects by reversing a black and white chequer pattern. Each time the pattern is reversed, so that black squares become white and white squares become black, a small cortical potential is evoked. If the pattern is repeatedly reversed at a rate of 1 or 2 per second, an averaged evoked potential can be recorded from an electrode placed over the mid-occipital area and an indifferent electrode.

Halliday and his colleagues at Queen Square (Halliday, McDonald and Mushin, 1972), were among the first to look at pattern evoked potentials in a clinical context. In patients with a history of optic neuritis the response was delayed in almost all cases when the affected eye was stimulated. These delays persisted even when the eye was again clinically normal and were found in some patients in whom the attacks had occurred up to 5 years previously. A year later Halliday, McDonald and Mushin (1973) described pattern potentials in a series of 51 patients with multiple sclerosis. Ninety-six per cent of the patients had delayed responses in one or both eyes, and more than half of these patients had no clinical history of optic neuritis. Two other groups have recently presented similar findings (Milner, Regan and Heron, 1974; Asselman, Chadwick and Marsden, 1975). The present paper describes results from a developmental study of this technique.

METHODS

Procedure

Patients fixated visually on a small green light in the centre of a chequer pattern at a distance of 2.8 m. The total stimulating field of the pattern subtended 20° and each chequer subtended 40′ at the eye. The luminance of the white squares was 15 cd/m^2. The projected chequers were moved repetitively through one square to produce an appearance of pattern reversal. Each movement, alternately to the right and left, occurred every 590 m.sec (reversal time less than 5 m.sec). Evoked potentials were recorded from silver-silver chloride electrodes placed over the mid, right and left occipital areas (O_z, O_2, O_1, International 10-20 system) referred to linked ears. A PDP-8L computer was used to average potentials evoked by 200 pattern reversals and each average potential was printed out on an X-Y Plotter.

Department of Clinical Neurophysiology, Auckland Hospital, New Zealand.

Normal subjects and patients

Pattern evoked potentials were recorded in 11 healthy control subjects (median age 27 years). Twenty-two patients with multiple sclerosis were tested (age range 25-65 years). They were diagnosed on the basis of clinical information and, in some cases, on the basis of negative information from radiological investigations. Using the diagnostic criteria of McAlpine, Lumsden and Acheson (1972), the patients were classified as having definite (7), probable (5) and possible (10) multiple sclerosis. Nineteen other patients with a variety of neurological conditions which may or may not involve the visual system were also studied.

RESULTS

Multiple sclerosis

Figure 1 shows the latency of the major positive component of the pattern evoked potential for normal subjects and patients with multiple sclerosis. In the group of 11 normal subjects (22 eyes), the latencies all fell within a narrow range and none exceeded 120 m.sec (mean latency—110.4±5.3 m.sec). Because of the small number of normal eyes tested, the upper limit of normal latency was defined at 3 standard deviations above the mean (126.6 m.sec). The average latency difference between the two eyes for the normal group was 2.2 m.sec (± 2.2 m.sec).

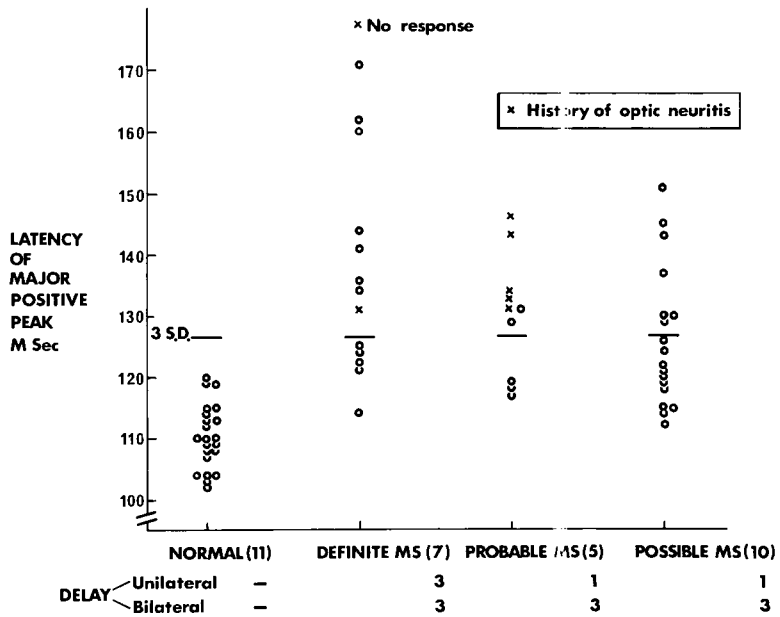

Fig. 1. Latencies of the major positive peak of pattern evoked potentials for each eye of normal subjects and patients with definite, probable or possible multiple sclerosis. The upper limit of normal latency is indicated at 3 S.D. from the mean (126.6 m.sec). The numbers of patients with unilateral or bilateral dealys are summarized at the bottom of the Figure.

The latencies of the evoked potentials were increased in some patients of each group with multiple sclerosis. Five patients had a history of unilateral (3) or bilateral (2) optic neuritis and the latency of the evoked potential was abnormal for each affected eye. In one case, with an unresolved episode occurring 2 months before the test, no response could be recorded. In some patients, episodes of optic neuritis had occurred and resolved 18 months to 5 years previously.

Table I summarizes the results and shows the number of patients in each group who had a history of optic neuritis. Overall, 6 of 7 definite multiple sclerosis patients had unilateral or bilateral delays, 4 of 5 probable patients had delays and 4 of 10 possible patients had delays, a total of 14 of 22 patients having had delayed evoked potentials. One other patient from the possible group, whose latencies fell within the normal range, was also classified as having abnormal evoked potentials. His responses were of very low amplitude and there was a significant latency difference between the two eyes.

Table 1. Incidence of delayed pattern visual evoked potentials (PVEP) and history of optic neuritis in 22 patients with multiple sclerosis.

	Total	History of optic neuritis	Delayed PVEP / optic neuritis	Delayed PVEP / no optic neuritis	Total Delayed PVEP
Definite MS	7	2	2	4	6
Probable MS	5	3	3	1	4
Possible MS	10	–	–	5*	5
	22	5	5	10	15

* In one patient the evoked potential latencies for both eyes fell within the normal range but were significantly different.

Figure 2 reproduces pattern evoked potentials obtained from a normal 35 year old subject and from two patients with possible multiple sclerosis. For the normal subject (two upper traces), the latency of the major positive component of the potential was 112 m.sec when the right eye was stimulated and 113 m.sec when the left eye was stimulated.

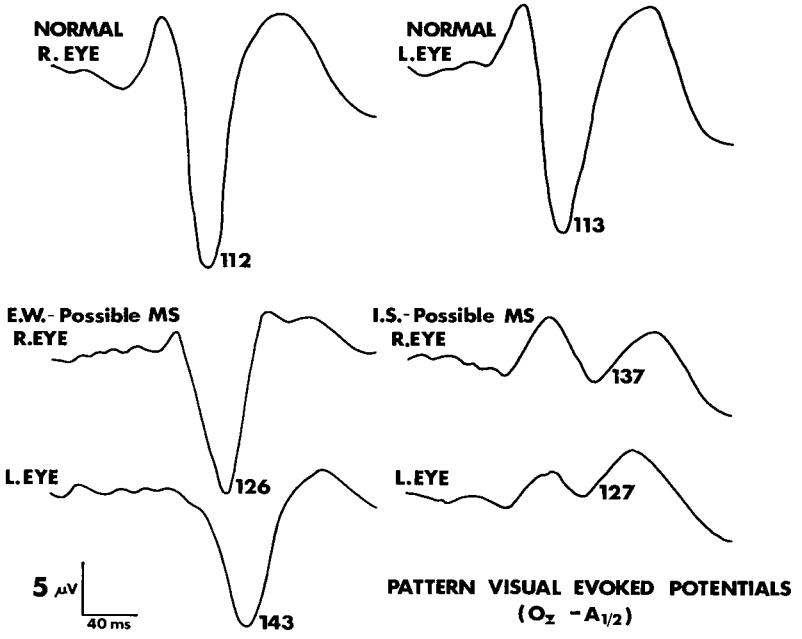

Fig. 2. Pattern visual evoked potentials recorded from the mid-occipital area of a normal subject (two upper traces) and two patients with possible multiple sclerosis. Each eye was stimulated independently. The latency (m.sec) of the major positive peak (downward deflection) is indicated.

CASE I.

E.W., whose evoked potentials are shown on the left of Figure 2, was a 56 year old lady who present with a 2 year history of

progressive spastic paraparesis. Two years earlier she had also had hesitancy and frequency of micturition which had largely resolved. She had no other symptoms or sensory changes and her visual system was normal. A myelogram showed no significant abnormalities and a lumbar air encephalogram was normal. The latency of the evoked potential obtained when her right eye was stimulated lay at the upper end of the normal range (126 m.sec). The response obtained when her left eye was stimulated was delayed (143 m.sec).

CASE II.

I.S., whose evoked potentials are shown on the right of Figure 2, was a 25 year old lady who presented with a 3 day history of double vision and severe headache behind her right eye. She had no previous history of neurological disturbance. Her right pupil was dilated and fixed and she had a right III nerve palsy and a probable right IV nerve palsy. A right carotid angiogram was normal, as also were subsequent left carotid and vertebral angiograms. On testing, 8 days after admission, her diplopia had largely resolved and her visual acuity, visual fields and fundi were normal. The evoked potential obtained when her right eye was stimulated was delayed (137 m.sec). The response obtained when her left eye was stimulated had a latency at the upper end of the normal range (127 m.sec) and it was of slightly abnormal form.

Of the 3 other patients in the possible multiple sclerosis group with delayed potentials, 2 presented with a history of progressive spastic paraparesis and no other signs or symptoms, and the third was a 25 year old girl with a one year history of varying neurological symptoms.

If the criterion for abnormal delay had been the more commonly used one of two standard deviations from the mean, placing the upper limit of normal latency at 120.7 m.sec, 9 more eyes including 3 additional patients would have been classified as having abnormally delayed responses. One of these patients had a diagnosis of definite multiple sclerosis and the other two had diagnoses of possible multiple sclerosis.

Other neurological conditions

Pattern potentials were studied in patients with a variety of conditions including isolated spinal cord lesions, cerebellar degeneration, and alcoholism with associated peripheral neuropathy. Because of the small number of patients in each category no definite conclusions concerning specific conditions can yet be drawn.

Two patients with intracranial hypertension and visual involvement had abnormal evoked potentials which improved after treatment.

CASE III.

This 22 year old lady was admitted with gross bilateral papilloedema, more severely affecting the right eye. She had a latent right convergent squint and a slight left VI nerve palsy. Her visual acuity was normal but she had enlarged blind spots and constriction of her peripheral fields, also more severe on the right. Radiological investigation excluded obstructive hydrocephalus and a diagnosis of benign intracranial hypertension was made. She was treated with dexamethasone, in decreasing doses, and pattern potentials were recorded over this period (Figure 3). One week after admission, the evoked potential recorded when her left eye was stimulated was of normal latency and form and remained so. The evoked potential recorded when her right eye was stimulated was slightly delayed. The positive peak had a latency of 129 m.sec and, over a period of 2 months, it became further delayed (152 m.sec). Four months after treatment began, the potential returned to normal latency. The patient's papilloedema gradually improved although her right eye still showed mild involvement at day 68. Her diplopia resolved by day 45 and her visual fields were almost normal by day 60.

Two patients with pituitary tumours and evidence of optic nerve compression were studied preoperatively and post-operatively.

CASE IV.

This 41 year old lady presented with amenorrhoea and a 6 month history of impairment of vision in her left eye (visual acuity: left eye 6/18; right eye 6/5). The visual fields showed marked bitemporal defects and an arcuate scotoma on the left encroaching onto the fixation region. A lumbar air encephalogram demonstrated a pituitary tumour with a large suprasellar extension. Pattern evoked potentials were recorded from the right and left occipital areas before surgery. The two upper traces in Figure 4 were recorded when the right eye was stimulated: the latency of the major positive peak over the left hemisphere was normal (114 m.sec) while the latency of the peak of the simultaneous response over the right hemisphere was delayed (153 m.sec). When the

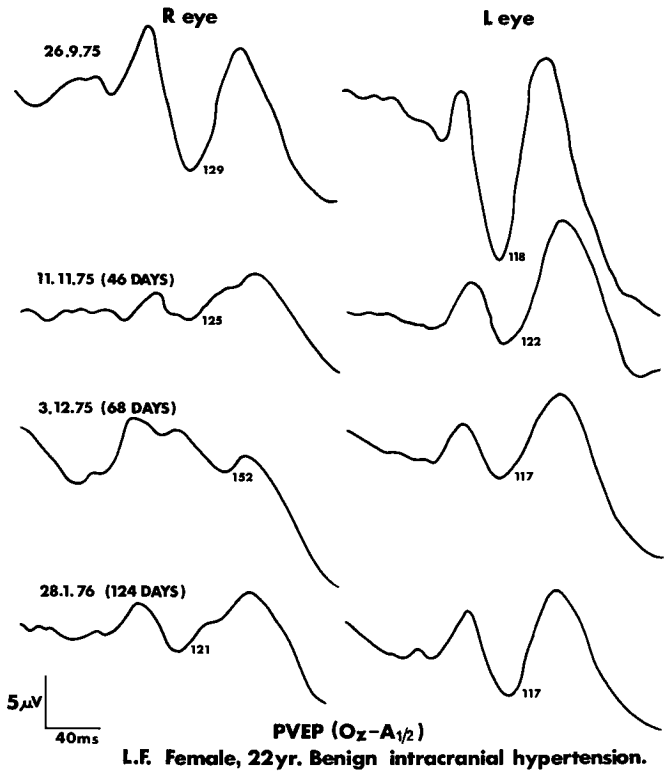

Fig. 3. Pattern evoked potentials recorded from a patient with benign intracranial hypertension during treatment with dexamethasone. Latencies (m.sec) of the major positive peak following stimulation of either eye independently are indicated.

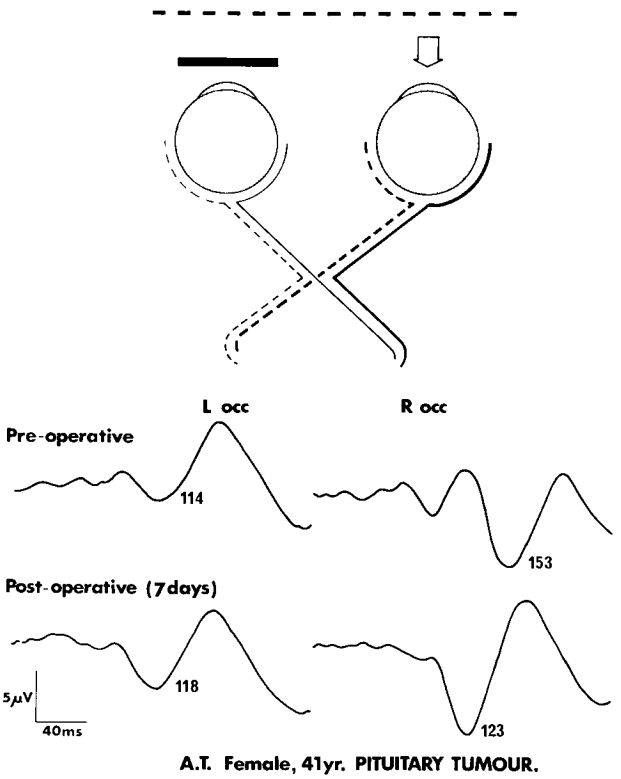

Fig. 4. Pattern evoked potentials recorded from the right and left occipital areas following stimulation of the right eye in a patient with a pituitary tumour. The upper traces were obtained before surgery, and the lower traces were obtained 7 days after surgery. Latencies (m.sec) of the major positive peak are indicated.

left eye was stimulated (not shown), the major positive peak over the right hemisphere was normal (120 m.sec) and over the left hemisphere was delayed (156 m.sec). These results suggested that while conduction in the crossing fibres from each eye was normal, conduction in the non-crossing fibres from each eye was impaired. At surgery, long optic nerves with a well post-fixed chiasm were exposed. Elevation was principally of the right optic nerve and the chiasm itself. The left optic nerve was not under tension. A cystic pituitary adenoma was removed. Seven days later, the evoked potentials were recorded again (Figure 4, two lower traces). When the right eye was stimulated, the latencies of the evoked potential were normal over both hemispheres (123 m.sec on the right; 118 m.sec on the left). A similar improvement occurred for left eye stimulation: the response over the right hemisphere remained normal, while the latency of response over the left hemisphere decreased from its pre-operative value of 156 m.sec to 129 m.sec. Three weeks after surgery, the patient's visual fields were normal although some red desaturation persisted in the left paracentral area.

DISCUSSION

Increases in the latency of evoked potentials to pattern reversal stimulation were found in 15 of 22 patients (68%) with proven or suspected multiple sclerosis. Five patients had a history of optic neuritis, each having delayed evoked potentials, while 10 patients had no such history. Six of the seven patients with definite multiple sclerosis had delayed potentials and a relatively high incidence of delays also occurred in patients for whom the clinical picture justified only a probable or possible diagnosis (4 of 5 and 5 of 10, respectively). These findings are similar to those of Halliday, McDonald and Mushin (1973) and of Asselman, Chadwick and Marsden (1975).

The demonstration of delayed potentials in patients with proven multiple sclerosis is not of diagnostic significance. The test is of most value for patients in whom there is otherwise insufficient clinical evidence to establish a diagnosis of multiple sclerosis, i.e. for patients within the probable or possible category. If the results of this method are valid, 9 of 15 patients in these categories have evidence of optic nerve pathology and the probability that they have multiple sclerosis is greatly increased by this knowledge. Long term studies are needed to determine what proportion of patients with clinically silent delayed potentials subsequently develop visual symptoms as, in fact, 2 patients of this series did.

An important issue concerns the specificity of delayed potentials for multiple sclerosis and optic neuritis. Intracranial hypertension with visual involvement and optic nerve compression affect the pattern evoked potential. Delays have also been described in glaucoma (Cappin and Nissim, 1975) and in optic atrophy due to a variety of causes (Halliday *et al.*, 1973). If, however, disease of the eye is excluded, a delayed evoked potential can be reasonably assumed to indicate a lesion of either the optic nerve or of more posterior parts of the visual system. Its exact interpretation must depend on the clinical context.

The mechanism of delay in patients with optic neuritis or multiple sclerosis remains uncertain. Experimental studies suggest that slowing or blocking of conduction in fibres through the demyelinated region may contribute to the delay (McDonald and Sears, 1970), but whether such local slowing can account for delays of 50-100 m.sec is uncertain. Alteration of retinal processes and central synaptic transmission may also contribute to the delay, as is suggested by changes in the latency of the normal pattern potential with changes in stimulus intensity and retinal locus.

If the results of this study are substantiated, the analysis of pattern evoked potentials would appear to be a valuable and objective test in the early diagnosis of multiple sclerosis. In patients with a doubtful diagnosis, a delayed potential may substantiate the diagnosis. In particular, in patients with symptoms or signs of a single brain stem or spinal cord lesion, a delayed potential demonstrating the presence of multiple lesions may be decisive in establishing a diagnosis of multiple sclerosis. The value of the test must depend on determining if false positive results can be obtained.

SUMMARY

The diagnostic value of pattern visual evoked potentials has been assessed in a pilot study of 22 patients with proven or suspected multiple sclerosis.

Of 7 patients satisfying McAlpine's criteria for diagnosing definite multiple sclerosis, 6 had delayed potentials. Four of 5 patients with probable multiple sclerosis, and 5 of 10 patients with possible multiple sclerosis, had delayed potentials. Ten patients with delayed potentials had no history of optic neuritis.

Changes in the evoked potential with other neurological conditions that may affect the visual system are also described.

ACKNOWLEDGEMENT

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EVOKED POTENTIAL STUDIES IN NEUROLOGICAL DISORDERS

F. L. MASTAGLIA†, J. L. BLACK* and D. W. K. COLLINS*

INTRODUCTION

Cerebral and spinal evoked potential studies have found increasing application in the assessment of patients with neurological disorders in recent years (Halliday and Wakefield 1963; Richey *et al.*, 1971; Halliday *et al.*, 1972; Namerow and Enns 1972; Halliday *et al.*, 1973; Feinsod *et al.*, 1973; Tsumoto *et al.*, 1973; Nakanishi *et al.*, 1974; Milner *et al.*, 1974; Asselman *et al.*, 1975; Robinson and Rudge 1975; Feinsod and Hoyt 1975). These techniques add an additional dimension to the evaluation of central nervous system function as they allow an objective assessment of conduction in specific sensory pathways to be made. Over the past two years we have applied these techniques to a group of subjects with a variety of neurological disorders in an attempt to evaluate the diagnostic role of these techniques more fully. We have been particularly interested in the relative value of the visual and somatosensory evoked responses in the detection of subclinical involvement of sensory pathways in patients with suspected demyelinating disease. The present paper reports our experience to date.

MATERIALS AND METHODS

Visual evoked responses (VER)

In the first group of 17 patients studied, VERs to 150 randomly delivered flash stimuli from a red light emitting diode were recorded. Subsequently, recording of the flash VER was discontinued because of the inconsistency of the responses obtained even among normal subjects and the pattern-reversal technique as described by Halliday *et al.* (1972) has since been employed. The subject was seated 140 cm from a semi-transparent screen onto the back of which was projected a 2 x 2 inch slide of a black and white checkerboard pattern via a mirror which rotated through a small angle sufficient to produce side-to-side movements of the pattern through one square. The screen subtended an angle of 6° at the patient's eye and each square an angle of 12'. Movements of the mirror were effected by a Devices function generator in turn triggered randomly by a purpose designed pseudo-random timer. Pattern reversals occurred approximately once every 1.7 seconds and 125 cycles were averaged. Each eye was stimulated separately. The patient fixated on an illuminated spot on the centre of the screen throughout the recording, the room otherwise being in darkness. Responses were recorded from scalp electrodes, the active electrode being at Oz, the reference electrode at Pz (10-20 system), and the earth electrode on the forehead.

Somatosensory evoked responses (SER).

Two 3-times threshold 100 μsec electrical shocks were delivered to the median nerve at the wrist through padded silver electrodes at a non-randomized rate of 1.1 per second for the cortical somatosensory evoked response, and 3 per second for the spinal somatosensory evoked response. Spinal responses

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were recorded from a surface electrode placed over the spinous process of C2, referred to an electrode at the vertex. Contralateral cortical evoked responses were recorded from a scalp electrode placed over the hand area of the sensory cortex (2.5 cm behind and 7 cm lateral to the vertex), the reference electrode again being placed at the vertex.

Analysis

Responses were collected and analysed on line using a PDP 1/40 computer, 125 responses being averaged for the pattern VER, 300 for the spinal SER and 200 for the cortical SER. Data appeared dynamically throughout the study on a digital to analog convertor driven refresh oscilloscope and at the end of the run on a Tektronix 4010 graphics terminal. With the aid of the cursor facility provided with the graphics terminal it was possible to mark points of interest and to read absolute magnitude and time-since-stimulus co-ordinates off the displayed graph. The computer also automatically calculated the mean voltage over the time region of interest (4-500 m.sec for the pattern VER, 9.6-25.6 m.sec for the spinal SER, 15 to 250 m.sec for the cortical SER) in addition to the RMS voltage (defined as the square root of the mean of the sum of the square of the data points) and the "energy index" which is a number proportional to the total electrical energy. It also searched automatically for the highest and lowest points in the data set and calculated the difference between these, yielding a figure for response amplitude. A correlation programme was used to calculate the cross-correlation coefficient between data sets (e.g. pattern VER's obtained by stimulation of the left and right eyes) and the cross-correlation function where one data set was shifted in time steps relative to the other. This yielded the delay difference between data sets which allowed a more objective comparison to be made between responses from the two eyes for the visual studies or the two arms for the somatosensory studies.

RESULTS

Normal Controls

Flash VER The great variability in the configuration and timing of the sub-components of the flash evoked VER did not allow the establishment of a clearly defined range of normality for latency and response size with which to compare findings in abnormal subjects.

Pattern VER While the pattern VER also showed a good deal of variability between different subjects in terms of overall response configuration, the configuration of the responses and the latencies of sub-components for the two eyes in the same individual were remarkably constant even when the test was repeated on different occasions (Figure 1). Moreover, the latencies of the first negative (A) and positive (B) peaks proved to be remarkably consistent with a fairly narrow range of variability among different subjects. Normal ranges for latency and response size are shown in Table I.

Spinal SER While there was some variability in the early (< 10 m.sec) and late (> 15 m.sec) components of the response, the major component which consisted of a monophasic or less often a diphasic complex with a predominant negative peak at 11.4-15.8 m.sec was remarkably reproducible (Figure 2). In the majority of subjects, 3 separate sub-components could be recognised within the major negative peak. As shown in Table II the amplitude of the response varied over a reasonably narrow range.

Cortical SER The overall configuration of the response was essentially the same as described by previous workers and showed a good deal of variability between different subjects. The most consistent components were N1 (20 m.sec), P1 (25 m.sec), N2 (32 m.sec), P2 (44 m sec), N3 (65 m.sec) and P3 (98 m.sec) (Figure 3). The highest peak-to-peak amplitude found in normal subjects has been 14 μV.

Multiple Sclerosis (Tables 3 and 4)

Flash VER's were considered to be abnormal in 7 of the 17 cases, comprising definite or probable MS

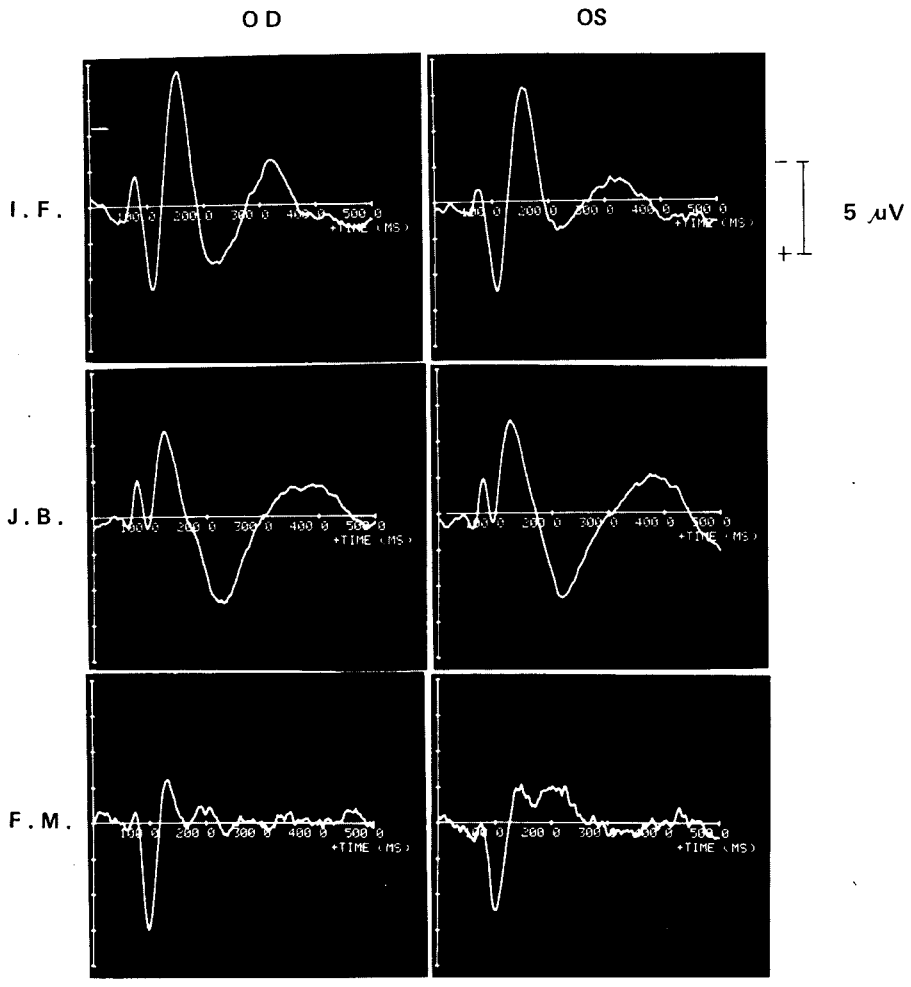

Fig. 1. Pattern visual evoked responses from right (OD) and left (OS) eyes of 3 normal subjects.

TABLE I

Spinal evoked responses
Normal Ranges (13 studies)

	Latency (M.SEC)	Primary Peak Amplitude (μV) (B–A)
Mean ± S.D.	13.6 ± 0.9	2.5 ± 0.9
Lowest Observed	12.6	1.14
Highest Observed	15.8	4.53
Normal Range (Mean ± 2½ S.D.)	11.4 – 15.8	< 4.8

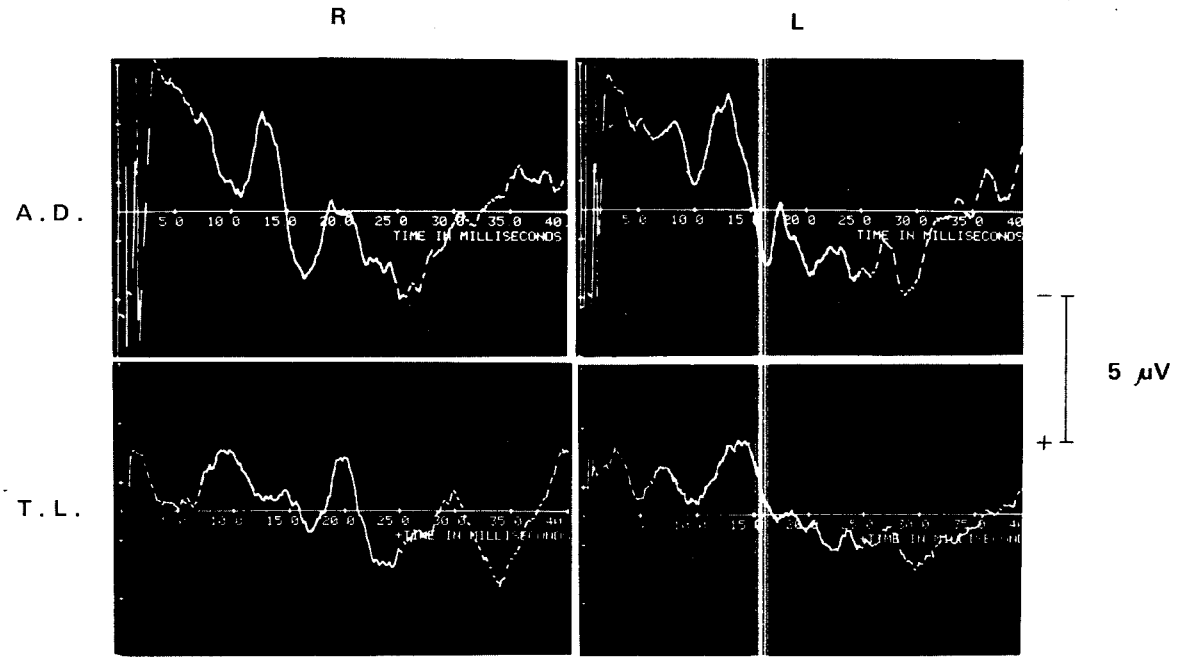

Fig. 2. Spinal somatosensory evoked responses recorded during stimulation of the right (R) and left (L) median nerves. A.D. – normal responses in a 40-yr old female with a simulated sensory deficit in the upper limbs. T.L. – abnormally delayed responses in a 23-yr old male with possible multiple sclerosis who presented with internuclear ophthalmoplegia without sensory symptoms or signs.

TABLE II

Pattern Evoked Responses
Normal Ranges (22 studies)

	Latency (M. SEC)		RMS Voltage (μV) (4 – 50 M. SEC)	Primary Peak Amplitude (μV) (B–A)
	Peak A	Peak B		
Mean ± S.D.	75.1 ± 3.6	101 ± 6.6	1.6 ± .6	4.8 ± 1.9
Lowest Observed	68	90	0.82	2.2
Highest Observed	82	112	2.91	8.6
Normal Range (Mean ± 2½ S.D.)	66 – 84	85 – 118	<3.2	<9.65

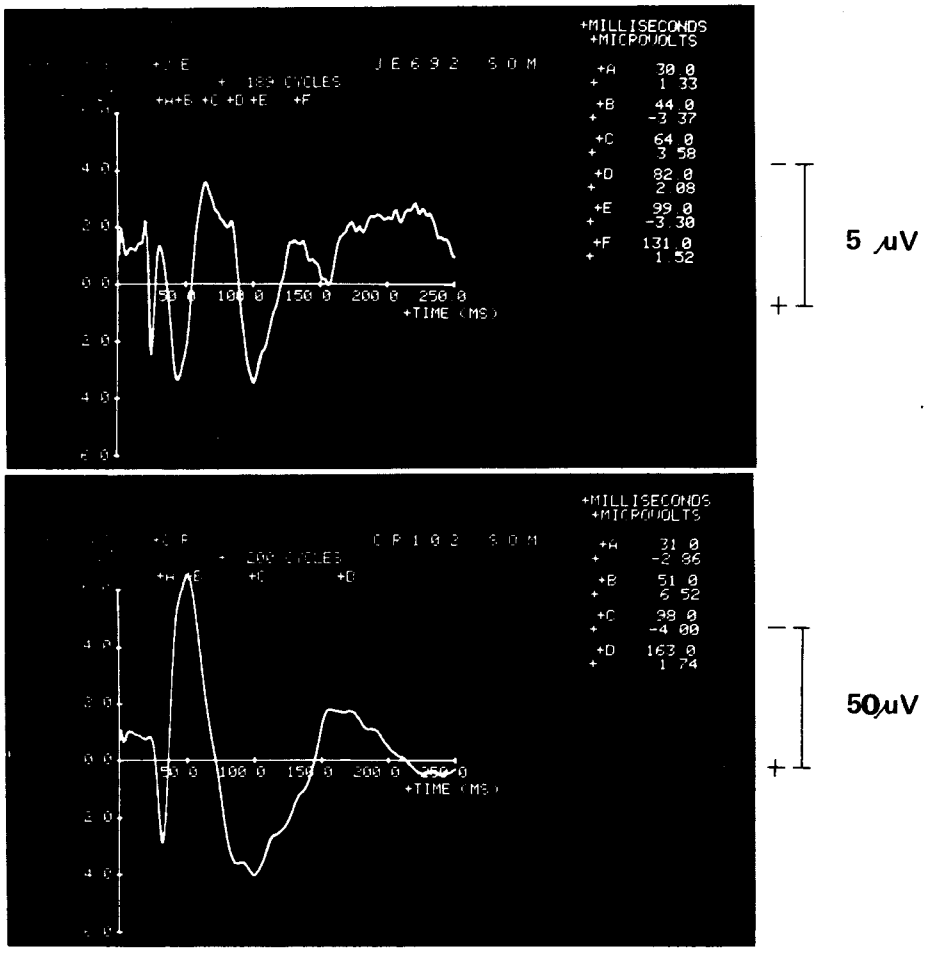

Fig. 3. Cortical somatosensory evoked responses. Top – normal response. Bottom – simplified and greatly enlarged response in a 16-yr old boy with myoclonic epilepsy.

TABLE III

MS – Definite or Probable
(14 cases)

	Normal	Abnormal
Flash VER (6)	3	3 (50%)
Pattern VER (12)	6	6 (50%)
Spinal SER (8)	5	3 (38%)
VER + Spinal SER (8)	3	5 (63%)

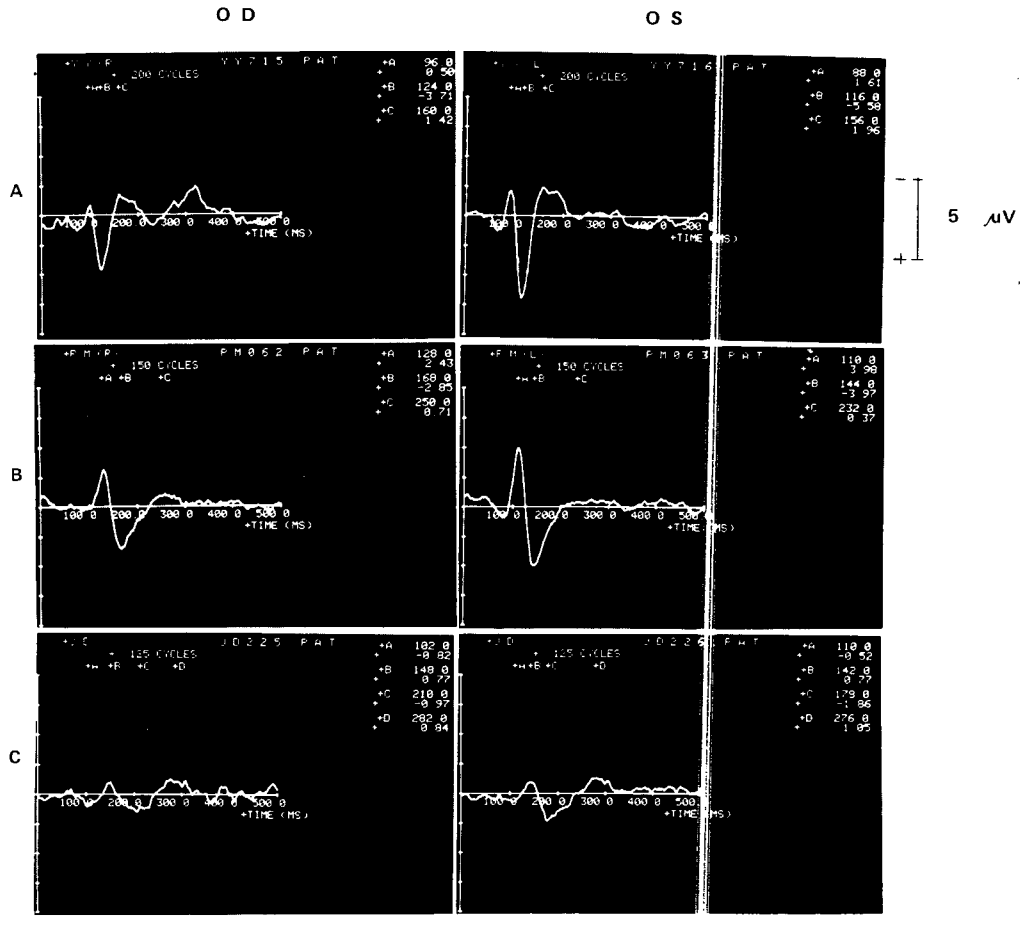

Fig. 4. Abnormal pattern visual evoked responses from right (OD) and left (OS) eyes in 3 patients with multiple sclerosis: (A) A 56 year old female: the response from the right eye shows a delayed primary positive peak (124 m.sec) and is reduced in amplitude. (B) A 44 year old male: positive and negative peaks for both eyes are significantly delayed. (C) A 29 year old female: both responses are markedly delayed and reduced in amplitude.

TABLE IV

MS – Possible
(33 cases)

	Normal	Abnormal
Flash VER (11)	7	4 (36%)
Pattern VER (24)	17	7 (29%)
Spinal SER (19)	11	8 (42%)
VER + Spinal SER (19)	10	9 (47%)

(3), and possible MS (4), including one case of monocular optic neuritis. The commonest abnormality was a reduction in response size. Less often a delay in the primary negative component of the response was noted. The abnormality was confined to one eye in 6 cases and was bilateral in 1. Pattern VER's were also performed in 3 of these cases and confirmed the abnormality in 2.

Pattern VER's were recorded in 36 patients with definite or probable MS (12) or possible MS (24) including one case of resolving optic neuritis. Abnormal responses were found bilaterally in 6 of the definite or probable group of cases (50%). Seven of the 24 possible cases (29%) had an abnormal response; in 4 the abnormality was bilateral while in the other 3 it was monocular. The most significant abnormality in the MS group consisted of a change in latency of peaks A and B, which could be significantly prolonged even when the response size remained normal and the configuration of the response was preserved (e.g. Figure 4). Latencies in excess of 200% of normal were encountered in some cases. As shown in Figure 4 response size was also reduced in cases showing the more marked delays.

Spinal SER's were recorded in 27 cases, including definite or probable MS (8) and possible MS (19). A bilateral abnormality was found in 3 of the definite cases (38%). Abnormal responses were found in 8 of the possible cases (42%), the abnormality being unilateral in 3 and bilateral in 5. In some cases there was a delay in the latency of the major negative peak while in others response size was also reduced (Figure 2). In the more abnormal responses none of the normal features could be identified. Seven of the 11 cases with abnormal responses had normal VER's. Conversely, 3 of the cases of possible MS with normal spinal SER's had abnormal VER's. The cortical SER was recorded in 12 of this group of cases and was abnormal in only one. Twenty-seven patients (8 definite or probable MS, 19 possible MS) had both VER's and spinal SER's. Five of the 8 definite or probable cases (63%) and 9 of the 19 possible cases (47%) had abnormal responses with one or other or both techniques.

Compressive Lesions of the Optic Nerve and Chiasm

Grossly abnormal responses with no recognizable normal components were found unilaterally in single patients with optic nerve glioma, pre-sellar carotid aneurysm, and extension of a pituitary adenoma. A response of reduced size but with normal latency was recorded from one eye in a patient with a nasopharyngeal carcinoma.

Pattern VER's were performed pre-operatively and post-operatively in an 18 year old woman with a bitemporal hemianopia (visual acuity: left eye 6/18; right eye 6/24), due to a pituitary adenoma. Pre-operatively the response from the right eye was delayed and markedly reduced in amplitude while that from the left eye was within normal limits. By the third post-operative day when the left field was full and the right showed only a residual upper temporal defect (visual acuity: left eye 6/6; right eye 6/24), the response from the right eye was of higher amplitude and showed a normal configuration but was still significantly delayed (by approximately 30 m.sec). The delay was still present but less marked 1 week later and again 4 weeks later.

Two patients with normal vision studied $2\frac{1}{2}$ and 3 years following the removal of supra-sellar craniopharyngiomas which had previously caused an incongruous right hemianopia in one and a bitemporal hemianopia in the other were found to have normal responses, as was a patient with intermittent visual loss arising as a result of an anterior communicating artery aneurysm.

Hysterical Sensory Deficits

Normal spinal and cortical SER's were recorded in 2 patients with global hysterical sensory loss in the upper limbs.

Miscellaneous

Grossly impaired VER's were found in patients with ischaemic optic neuropathy, cataracts, post anoxic brain damage and bilateral occipital cortical infarction complicating migraine. Responses of normal latency but reduced amplitude were found in patients with uncorrected refractive errors and amblyopia ex

anopsia. Normal VER's, spinal and cortical SER's were recorded in a patient with familial spastic paraplegia. Greatly enlarged cortical SER's (27 and 60 μV) were recorded in 2 patients with familial myoclonic epilepsy (Figure 3).

DISCUSSION

The present study emphasises the value of visual and somatosensory evoked responses in neurological diagnosis. Because of its consistency in the same subject and within a group of subjects, the pattern reversal VER is a far more valuable technique than the flash VER for detecting abnormalities of conduction in the visual pathways. The technique is of greatest value in detecting lesions involving the optic nerve or chiasm. The fact that abnormalities may be detected even when visual acuity, colour vision, visual fields and optic discs are normal makes this a very sensitive technique for detecting the presence of lesions in the anterior visual pathways in patients with suspected demyelinating disease. Our incidence of abnormal responses in patients with definite or probable MS (50%) is lower than that reported in previous studies from the United Kingdom. Thus Halliday *et al.* (1973) found abnormal responses in 49 out of 51 cases of multiple sclerosis (96%), while Asselman *et al.* (1975) reported an incidence of 84% of abnormal responses in a group of 31 patients with definite multiple sclerosis. Our incidence of abnormal responses in the possible MS group (29%) is comparable to that of Asselman *et al.* who found an incidence of 25% in this group of cases. The number of cases of definite MS in the present study is clearly small and it will remain to be seen whether the figure of 50% still applies after we have examined a larger series of cases.

It is clear that an abnormal VER is not in any way specific for lesions of the optic nerve or chiasm. In the present as in previous studies abnormal responses were also found in patients with cataracts, refractive errors and amblyopia ex anopsia. The importance of excluding the presence of significant ocular disease before attaching too much significance to an abnormal response is obvious. The question arises as to whether there are any patterns of abnormality with sufficient specificity to be of diagnostic value. While our experience with different types of optic neuropathy is limited, it does nevertheless, support the observation by Halliday *et al.* that significant delays in the major components of the response with preservation of response configuration and little or no fall off in amplitude is highly suggestive of a demyelinating neuropathy. We have also observed delays in patients with compressive lesions but, in general, the size and configuration of the response is also markedly abnormal in this group of neuropathies. In our experience a response of reduced amplitude but with normal configuration and peak latencies usually results from poor fixation by the subject during the procedure or from an uncorrected refractive error.

Our findings with the spinal somatosensory evoked response are comparable to those of Matthews *et al.* (1975). Abnormal responses are again non-specific and may occur in patients with radiculopathies or peripheral neuropathies and it is clearly important that such peripheral disorders should be excluded by careful clinical examination and, if necessary, by conventional electromyography and nerve conduction studies before an abnormal response is attributed to a spinal cord lesion. In the present series abnormal responses were found in 41% of cases of established or suspected MS even in some patients without symptoms or signs referable to the sensory pathways. Like the VER, this technique is therefore also of value in detecting sub-clinical involvement of sensory pathways in patients with suspected MS. Our incidence of abnormal responses in this group of patients compares with the 56% incidence reported by Small and Matthews (1974) in a group of 26 cases of MS. It is noteworthy that the cortical evoked response did not show any significant abnormality in most patients with an abnormal spinal response, suggesting that the latter is the more sensitive of the two techniques in patients with demyelinating disease. Of considerable importance was the finding of abnormal spinal responses in some patients with normal VER's, and vice versa, suggesting that the two techniques have a complementary role in the investigation of suspected MS.

One of the most useful roles of the visual and somatosensory evoked responses is in confirming the functional nature of sensory abnormalities in patients with simulated or hysterical deficits. Of particular interest in the present series was the demonstration of normal VER's in a case of "chronic MS" of many years standing who professed to being blind, and of normal spinal evoked responses in a similarly long standing "known case of MS" professing to have impairment of all sensory modalities in the upper limbs.

SUMMARY

Techniques for recording and analysing visual and somatosensory evoked responses using an on-line PDP 11/40 computer have been developed and applied to a group of subjects with established or suspected multiple sclerosis as well as to patients with a variety of other lesions of the visual pathways, myoclonic epilepsy and functional neurological deficits. The most consistent responses were obtained using the pattern reversal visual evoked response and the spinal somatosensory evoked response, abnormal responses being found with both techniques in a significant number of patients with suspected demyelinating disease even in the absence of symptoms or signs referable to the visual or somatosensory pathways. The complementary role of these techniques in the detection of sub-clinical abnormalities of conduction in sensory pathways in patients with suspected MS is emphasized.

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COMPUTERIZED AXIAL TOMOGRAPHY FOR INTRACRANIAL DIAGNOSIS

LESLEY A. CALA*

INTRODUCTION

Several authors have demonstrated the versatility of computerized axial tomography for intracranial diagnosis (Ambrose, 1973; Ambrose, 1974; Baker *et al.*, 1974; New *et al.*, 1974; Scott *et al.*, 1974; Gawler *et al.*, 1975; New *et al.*, 1975). The present paper outlines our local experience with conditions described by other workers, and touches on a few areas that have not been dealt with previously.

PATIENTS AND METHODS

Table I shows the number of patients the author personally supervised on an E.M.I. brain scanner during a six month period. The patient who had 6 examinations was having a radiotherapy programme monitored in relation to a solitary melanoma metastasis. The patient who had 7 examinations was being monitored throughout the various stages of a sub-arachnoid haemorrhage.

TABLE I

Case Material used in this series

Total number of examinations = 936				
Comprised of	809	patients	who had	one scan
	46	"	"	2 scans
	4	"	"	3 "
	1	"	"	4 "
	1	"	"	5 "
	1	"	"	6 "
	1	"	"	7 "

Table II shows analysis of the work into pathological conditions diagnosed. The data are presented as pathological conditions diagnosed as it is felt that it is too early to present a follow up that could be in any way comprehensive. False positives were encountered, especially in the posterior fossa, where normal variants were misinterpreted in the early months due to lack of personal experience. By the same token, false negatives also occurred, the lesion having been diagnosed by other neuroradiological methods. However, Ambrose (1974) considered that assessment of the results of computerized axial tomography (C.A.T.), weighed against results from other tests, may bring in a number of factors which for various

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reasons cannot easily be compared. He quoted an example "why any particular investigation is being requested in addition to others". Apart from C.A.T. the only other investigation that all patients in this series had performed was plain radiography of the skull.

TABLE II

Pathological conditions diagnosed in this series

Normal	239		
Abscess	21		
Atrophy	191	Primary Tumours:–	156
Hydrocephalus	36	Central	14
Orbit	30	Frontal	27
Trauma: oedema	1	Occipital	7
intracerebral haematoma	7	Parietal	16
subdural haematoma	17	Posterior fossa	36
infarction	36	Suprasellar	22
Vascular: post-convulsive oedema	1	Temporal	32
migraine	44	Multiple Secondary Tumours:–	36
intracerebral haematoma	25	Single	23
infarct	63	Multiple	13
aneurysm	29		
Post-stereotaxy	3		

RESULTS

Vascular lesions

Aneurysms in differing locations can be examined. The first patient had rupture of an anterior communicating aneurysm and the haematoma could be identified in the interpeduncular cistern, the white of the haematoma being separated from the white of the adjacent bone by the μ values.

The second case was a 36 year old female who had presented with sudden onset of homonymous hemianopia. An angiogram performed at Fremantle Hospital showed a large aneurysm arising from the right posterior cerebral artery after it completed its arc around the tentorial edge. The scan was requested to establish the presence of co-existent haematoma around the aneurysm. The scan showed a large blood pool which was a combination of aneurysm and haematoma, as well as a track of blood passing towards the quadrigeminal cistern, so it was possible to conclude that the aneurysm had bled.

The third case was a 43 year old female patient who had a ruptured middle cerebral artery aneurysm. On the initial examination, well defined blood clot was seen tracking along the Sylvian fissure (Figure 1 a). A slice taken higher in the cranium (Figure 1 b), also demonstrates the haemorrhage and, in addition, some blood in the midline, presumably being located in the interpeduncular cistern. A higher slice still (Figure 1 c) discloses early ventricular dilatation which is symmetrical. Six days later this patient was re-examined and most of the haemorrhage was found to have disappeared. The ventricular system was a little more dilated than on the previous examination. The same afternoon, the patient collapsed, becoming unrousable. Repeat lumbar puncture found no evidence of another haemorrhage. The operation planned for the following day was postponed, and an E.M.I. brain scan was performed. This third scan revealed extensive oedema throughout the left temporal lobe, considerable shift of the ventricular system to the right but no evidence of haemorrhage. These findings confirmed, therefore, the clinical suspicion that the deterioration in the patient's clinical state was attributable to secondary vaso-spasm alone, on the 8th day after the initial subarachnoid haemorrhage. A week later, the patient was still rather drowsy but otherwise much improved on clinical grounds. A fourth E.M.I. scan revealed further dilatation of the ventricular system, including the fourth ventricle (see Figure 2). The most cranial slice showed scattered areas of

reduced density consistent with moderately severe oedema. A shunting procedure was carried out and two further E.M.I. scans performed. The seventh and final scan showed the ventricles returned to normal size.

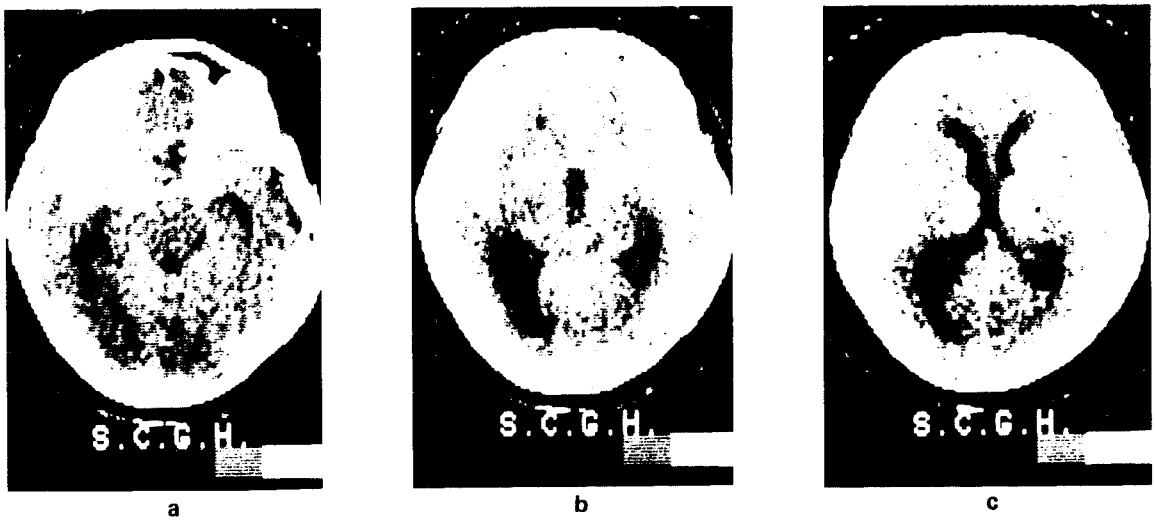

Fig. 1. A 43 year old female examined for clinically proven subarachnoid haemorrhage. The polaroid pictures demonstrate extravasated blood in the left Sylvian fissure and early hydrocephalus.

Fig. 2. Same patient as in Fig. 1. 4th examination. There is well-developed hydrocephalus, probably of the communicating type. Complete resorption of the haemorrhage.

Three patients were examined who were considered to have arterio-venous malformations.

The first case was a 21 year old female who suddenly lost consciousness shortly after delivery of a full-term infant. The patient was deeply stuporose, with one fixed dilated pupil. There was gross papilloedema and hyperreflexia of the right limbs. E.M.I. scanning revealed a large, irregularly shaped haematoma in the left frontal region, with gross displacement of the ventricular system to the right. The patient was given

high doses of steroids during the night and a left common carotid angiogram was performed the following morning. No evidence of an aneurysm or arterio-venous malformation was found so the haematoma was evacuated. Repeat examination three days after operation showed the ventricles to be normal in position and a small residue of blood at the surgical site.

Similarly, an occult arterio-venous malformation was suspected in a 10 year old boy who suffered visual hallucinations following an influenza like illness some weeks previously. An almost spherical area consisting of a peripheral zone of increased density around a central lucency was found at the junction of the temporal with occipital region, on the right side. At operation, this was found to consist of old haematoma with a well formed capsule. The differential diagnosis of the lesion on the E.M.I. scan had, therefore, to include an abscess, the capsule of which would have had a similar appearance.

In the group of infarction, the first example was found in a 42 year old female who had had an embolus from a mitral vaive prosthesis to the frontal lobe. Apart from the large area of infarction in the left frontal lobe, there were many smaller areas of infarction scattered through both hemispheres.

The next case was a 62 year old male who had collapsed on the day of admission and was found to be stuporose. The polaroid film showed a large area of reduced density corresponding to the territory of supply of the left middle cerebral artery. The print-out showed minus values of fat, indicating brain necrosis in the acute stage. This was proven at operation to attempt decompression.

Trauma

This group constituted only 2.5% of all the cases in the present series due to a community arrangement whereby head injuries, in the acute stage, are taken to other hospitals. However, an 82 year old gentleman was examined. He had fallen from a ladder, causing it to strike his head. There was no evidence of skull fracture but as was discovered after the E.M.I. scan, he did have a moderately large intracerebral haematoma surrounded by a zone of oedema.

Another case was an 18 year old male who had sustained an extensive occipital fracture in a road traffic accident. He was found to have bilateral frontal lobe haematoma.

Some patients with a head injury were only examined in the stage of rehabilitation. This was the case with a 19 year old male who had been the victim of a hit and run accident. He had bilateral frontal lobe necrosis and it was tempting to postulate that this was the cause of his inability to deal with the rehabilitation programme planned.

In one patient who had a very severe head injury, E.M.I. scanning revealed extensive loss of brain tissue in the right occipital region with dilatation of the occipital horn of the lateral ventricle filling the available space.

Hydrocephalus

The EMI scanner has proved very useful for patients suspected of having raised intracranial pressure and to assess ventricular size in patients who have had a ventricular shunt. However, there were some unexpected findings. One such was a 36 year old male who had been extensively investigated in the gastrointestinal unit for intractable vomiting. There were no neurological signs. The EMI scan was requested as no diagnosis had been reached. The fourth ventricle was found to be grossly dilated, whilst there was a lesser degree of dilatation of the other ventricles. After other radiological investigations this case was thought to be due to acquired adhesions around the exit foramina of the fourth ventricle. A ventricular shunt was performed with good results.

For comparison there was the case of a 11 year old female who had a long standing deformity of her neck and hydrocephalus for which a shunting procedure had been carried out some years before without a definitive diagnosis being reached. The EMI scan showed gross dilatation of the fourth ventricle, as well as of the lateral and third ventricles. This patient could probably be classified in the Dandy-Walker syndrome.

In the group of raised intracranial pressure is the category of benign intracranial hypertension, which is said characteristically to have ventricles of normal or reduced size There were more than a dozen such cases in the present series, the EMI scan being requested to assess ventricular size, in atypical cases, prior to performing lumbar puncture in a patient with gross papilloedema.

Infection

Several cases were examined, where the isotope brain scan had been normal. These were patients who had either a temporal lobe abscess or an abscess in the posterior fossa.

Suprasellar masses

The EMI scanner is very useful in this region but unfortunately cannot reliably distinguish between giant aneurysm with laminated thrombus and tumour, so it is still necessary to perform angiography. Nevertheless, in the case of tumour, a knowledge of the consistency of the lesion has proved helpful prior to surgery. An 18 year old male had a well defined tumour mass seen on a scan and it was possible, by referring to the print-out, to establish that the posterior wall was solid, uncalcified tumour, the right lateral wall was calcified and the centre of the tumour was filled with fluid. This was proven to be the situation at operation.

Similarly, an 11 year old female was investigated for the finding of bitemporal hemianopia. It was found that there was a solid mass of calcification in the anticipated location of the pituitary fossa but, extending laterally, was a zone of reduced density where the μ values were consistent with fluid containing cholesterol. This was also proven at operation.

Intra-cerebral masses

All masses are not solid as was the case with a 48 year old female demonstrated to have a large cyst in the right frontal lobe. The μ values were those for cerebro-spinal fluid.

The scanner is particularly useful to show the characteristics of a tumour, such as ventricular encasement, crossing of the midline or multiplicity. It has been found necessary to use contrast medium for enhancement, in all cases suspected of tumour.

Sometimes, tumour definition is not so straight forward. This was the situation with a 19 year old female whose only complain was right homonymous hemianopia. An ill-defined area of increased density was present in the vicinity of the left thalamus, with no change occurring after injection of contrast medium. Following angiography, the patient was explored neurosurgically but this failed to locate a tumour and the operation had to be abandoned due to the patient's clinical condition. However, post-operatively she continued to have a progressive neurological deficit so a further attempt was made and on this occasion, infiltrating glioma in the left parietal and occipital regions was found.

It is also difficult to diagnose infiltrating glioma in the frontal region. Another 19 year old female presented with mild hemiparesis and headache. The EMI scan on his patient was unequivocally normal, even in retrospect. However, angiography and air encephalography provided the diagnosis.

Small focal lesions

There has been occasion to perform an EMI scan on a few patients after a radio frequency stereotactic lesion had been made, and it has been possible to identify the lesion.

A lesion, of similar size and identical μ values, is a lacunar infarct. The periphery of such a lesion is usually sharply defined, as is the stereotactic lesion. On the other hand, a lesion of similar size but with an ill-defined perimeter, is the plaque found in multiple sclerosis. This has an average μ value comparable to that of a lacune. Serial examinations on patients with multiple sclerosis have enabled mapping of the evolution of their cerebral disease. It has also been found possible to locate plaques in the optic nerves.

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The author wishes to thank all Members of the Neurological Services Committee of Western Australia for referring cases for study, and would like to acknowledge the assistance afforded by radiological colleagues. The author also wishes to thank Mr. B. A. R. Stokes for permission to report the three cases of intracranial aneurysm. Mr. K. Fellowes prepared the photography.

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HEREDITARY HYPERTROPHIC NEUROPATHY IN THE TREMBLER MOUSE: ELECTROPHYSIOLOGICAL STUDIES

P. A. LOW and J. G. McLEOD*

INTRODUCTION

Electrophysiological studies have been performed in experimental demyelinating neuropathies such as experimental allergic neuritis (Cragg and Thomas, 1964), demyelination due to the focal application of diphtheria toxin (Rasminsky and Sears, 1972) and circumscript neuritis (Lehmann, 1967). However, the studies were all performed during the acute stage of the neuropathy and the experimental lesions bore little resemblance to the pathological changes in chronic and naturally occurring neuropathies such as Déjerine-Sottas neuropathy, hypertrophic Charcot-Marie-Tooth disease and chronic relapsing polyneuropathy.

The Trembler mouse suffers from a dominantly inherited hypertrophic neuropathy, the pathological features of which resemble Déjerine-Sottas neuropathy (Ayers and Anderson, 1975). It was decided to perform detailed electrophysiological studies in this naturally occurring and chronic hypertrophic neuropathy, in order to examine whether the electrophysiological findings in experimental acute demyelination apply also to a naturally occurring chronic demyelinating neuropathy.

MATERIALS AND METHODS

Motor conduction velocities were studied on the sciatic, median and tail nerves of control and Trembler mice. Each animal was anaesthetized with intraperitoneal pentobarbitone 50 mg/Kg, following which its hind and forelimbs were shaved. The temperature of the animal, which was monitored by means of a rectal thermistor probe, was maintained at 37-38°C by means of a heated stage and radiant heat. For tail recordings the temperature of the tail was maintained at the same level. For sciatic nerve studies stainless steel recording electrodes were inserted into the small muscles of the foot and the nerve was stimulated at the knee and hip. For median nerve recordings, the recording electrodes were inserted into the small muscles of the forefoot, and the nerve stimulated at the elbow and axilla. For tail recordings, recording electrodes were inserted into the middle third of the tail and the stimulating electrodes were placed at 2 sites, one at 1 cm from the recording site and the second at either 3 or 4 cm away.

In a second series of experiments, the refractory period of the sciatic tibial nerve trunk, its ability to conduct rapid trains of stimuli and the effect of temperature on conduction were studied. The animal was anaesthetized as before, following which the sciatic and posterior tibial nerves were exposed in the thigh and tibial regions respectively, under a dissecting microscope. The animal was stretched out on cork in a perspex box containing liquid paraffin and the temperature of the bath was maintained at 36°C. The sciatic nerve was stimulated through paired silver electrodes and the stimulus intensity was set at twice that required to evoke a maximal response. The recording electrodes were placed under the posterior tibial nerve.

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RESULTS

The amplitude of the muscle action potential (MAP) of the sciatic, tail and median nerves of Trembler mice were below the control range for each nerve examined (See Table I). The terminal latencies of the MAP of the sciatic, median and tail nerves were above the control range for each nerve examined. The motor conduction velocity (MCV) for Trembler sciatic, tail and median nerves fell below the control range in each instance and did not exceed 6 M/sec in any of the nerves. When the MCV of the sciatic nerve was related to age, the mean conduction velocity in control mice increased with age until the age of 4 months, after which it remained constant. By contrast, the MCV in Trembler sciatic nerves was grossly reduced from the earliest recordable age and did not increase with age (Figure 1).

TABLE I

Motor Conduction Studies in Trembler and Control Mice

	Compound Muscle Action Potential (mV)			Distal Latency (m.sec)			Motor Conduction Velocity (M/sec)		
	Sciatic	Median	Tail	Sciatic	Median	Tail	Sciatic	Median	Tail
CONTROLS									
Range	1.3 – 5	2.7 – 5	0.5 – 5	0.6 – 1.35	0.7 – 1.6	0.6 – 1.7	35 – 60	40 – 57	25 – 50
Mean ± S.D.	3.18±1.15	3.90±1.08	1.69±1.58	0.92±.21	1.13±.37	1.00±.26	45.92±7.21	47.80±8.47	34.30±6.50
No. of animals	25	5	17	25	5	17	25	5	17
TREMBLERS									
Range	0 – .40	0.25–1.0	0 – .18	1.87 –7.7	3.0–6.2	4.5–6.7	0 – 6	3.3–5.2	0 – 6
Mean ± S.D.	0.21±.13	.53±.32	0.07±.07	4.16±2.01	4.16±1.13	5.98±1.05	2.51±1.34	4.22±.82	1.13±1.95
No. of animals	14	6	9	14	6	5	14	6	9
SIGNIFICANCE OF DIFFERENCE (Student's t test)	ALL HIGHLY SIGNIFICANT ($P < .001$)								

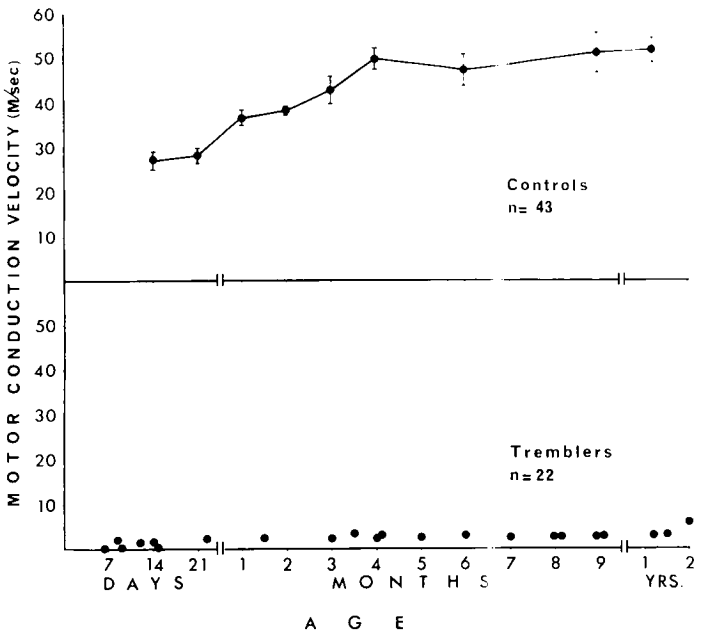

Fig. 1. Sciatic nerve motor conduction velocity related to age in control and Trembler mice. (From Low and McLeod, 1975).

The refractory period of the sciatic tibial nerve was studied in 8 control and 11 Trembler mice. The refractory period of transmission (RPT) (which is that interval following a conditioning stimulus when the nerve will not propagate a response, no matter how strong the second stimulus might be) ranged from 0.6 to 0.9 m.sec (mean 0.7; SD, 0.1). By contrast, the RPT of Trembler mouse nerves ranged from 1.5 to 5 m.sec and in each instance fell outside of the control range (Figure 2). The relative refractory period (RRP) was determined using 2 methods. The conditioning and test stimuli were both twice maximal. The amplitude method, RRP (A), was based on the time taken for the amplitude of the test response to equal that of the conditioning response (Figure 2A). The latency method, RRP (L), was based on the time taken for the latency from stimulus to the onset of the first negative deflection of the test response to return to that of the conditioning response (Figure 2B). The results based on these 2 different methods were not significantly different for controls or for Tremblers. When the RRP of Trembler mice was compared with that of control mice, it was significantly greater ($P<0.001$).

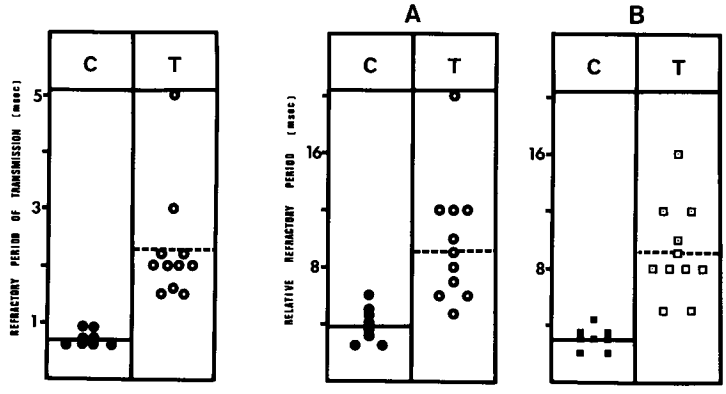

Fig. 2. The refactory period of transmission and relative refractory period of control (C) and Trembler (T) nerves. Results in A have been obtained using amplitude measurements and in B, latency measurements.

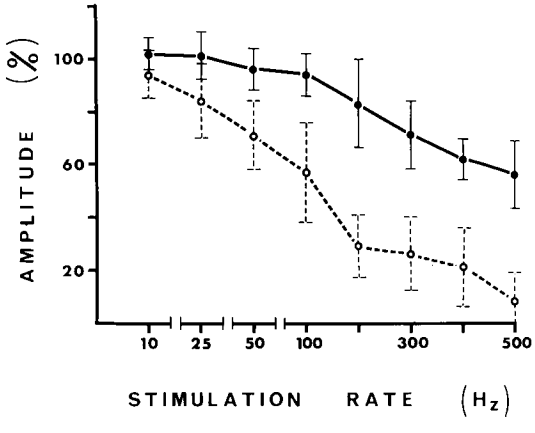

Fig. 3. The mean amplitude (%) of the compound nerve action potential of the 10th response relative to the first in control (closed circle) and Trembler (open circle) sciatic-tibial nerve. Bars represent 2 SD.

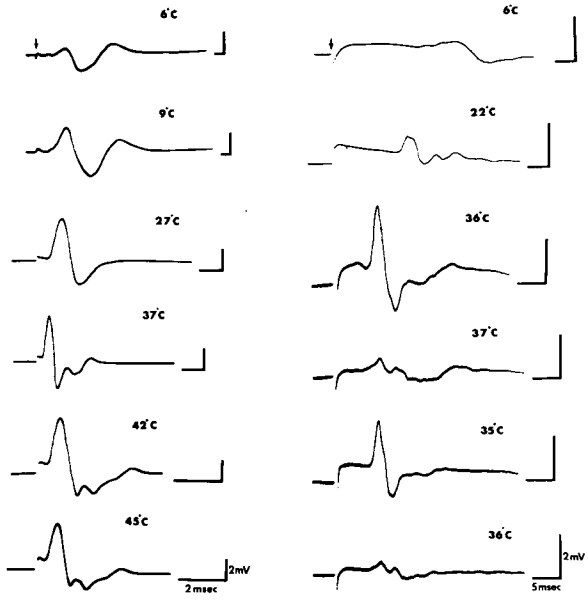

Fig. 4. The diphasic compound nerve action potential of control (left column) and Trembler (right column) sciatic-tibial nerves in response to temperature change.

The ability of the sciatic tibial nerve trunk to conduct trains of impulses was studied in 13 control and 17 Trembler mice. The amplitudes of successive responses underwent marked decrement in Trembler mice at stimulus frequencies as low as 25 Hz (Figure 3) in contrast to those of control mice which underwent little change below 100 Hz. When the amplitude of the 10th response was expressed as a percentage of that of the first, it was more severely reduced in Trembler mice than in control mice at all stimulus frequencies (Figure 3). The effect of temperature on conduction in the sciatic and tibial nerves was studied in 9 control and 10 Trembler mice. Conduction block was a prominent feature in Trembler nerves and occurred with minor alterations in temperature (Figure 4).

DISCUSSION

It has been shown by Kaeser and Lambert (1962), McDonald (1963) and by others that marked slowing of conduction occurs through demyelinated segments of nerve. Similar conclusions have been reached in man. The findings of gross slowing of conduction and a very long distal latency in the peripheral nerve of Trembler mice, where severe abnormalities of the myelin sheath have been demonstrated (Ayers and Anderson, 1973; Low and McLeod, 1975) confirm in a naturally occurring neuropathy, the relationship between marked slowing of conduction and demyelination.

The peripheral nerves of Trembler mice did not conduct trains of impulses and underwent conduction block at stimulus frequencies and temperature that were well within the physiological range. These findings are similar to the observations of failure to conduct rapid stimulus trains (Cragg and Thomas, 1964; Rasminsky and Sears, 1972) and of warm block (Davis and Jacobson, 1971; Rasminsky, 1973), which were observed in acute demyelinating neuropathies.

The mode of conduction in Trembler peripheral nerves is uncertain. Unmyelinated fibres have refractory periods of about 2 m.sec (Gasser, 1950), are unable to conduct rapid trains of stimuli (Iggo, 1960; Torebjörk and Hallin, 1974), and undergo abrupt conduction block on warming (Gasser, 1950). All these features resemble the findings in the peripheral nerves of Trembler mice. The definitive answer will have to be provided by single fibre studies using methods similar to those of Rasminsky and Sears (1972).

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COMPUTERIZED AXIAL TOMOGRAPHY FINDINGS IN A GROUP OF PATIENTS WITH MIGRAINOUS HEADACHES

LESLEY ANN CALA* and FRANK LOUIS MASTAGLIA#

INTRODUCTION

A personal communication from Dr. J. Ambrose and Dr. J. Gawler to the authors suggested the possibility that the finding of cerebral oedema on computerized axial tomography (CAT) might support the diagnosis of migraine in patients presenting with recurrent headaches or with focal neurological symptomatology. The subsequent unexpected finding of a significant degree of cerebral atrophy in a 35 year old female migraine sufferer further prompted our interest in the changes which may be demonstrated by CAT in this group of subjects. A systematic survey of all patients with migrainous headaches examined over the past 9 months was therefore undertaken. Our findings are summarized in the present report.

PATIENTS AND METHODS

The series consisted of 46 patients (16 males and 30 females), ranging from 17 to 53 years in age, who were referred for examination because of increasing severity or frequency of their headaches or because of an initial severe attack of migraine associated with alarming focal neurological manifestations. All had been assessed by a neurologist or a neurosurgeon. The length of history in those with recurrent headaches was up to 18 years. In 13 patients there was a history of a clear cut visual or other sensory aura preceding or accompanying the headache, while focal neurological signs were present in 14 patients at the time of the examination (Table I). Twelve patients were examined by CAT during a headache while the remainder were in a headache free period at the time.

TABLE I

Focal neurological symptoms and signs in patients with normal and abnormal CAT findings

CAT findings	Visual or other sensory area	Focal signs*
Normal (9)	–	–
Infarcts (6)	4	4
Oedema (21)	6	8
Atrophy (8)	2	1
Tumour (2)	1	1

* Visual field defect, lateralized motor, sensory or reflex changes.

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The original report made from the cathode ray tube display, the polaroid picture taken from it, and the computer print out of the 46 patients examined were analysed and similar record material was analysed from 23 control subjects. The latter were patients who had been referred for other reasons and who were considered to have unequivocally normal CAT findings as recently outlined by Gawler, Bull, de Boulay and Marshall (1975). Unfortunately, to date it has not been feasible to collect data from a group of normal volunteers, a limitation which also existed in the study of the normal EMI scan by Gawler *et al.* (1975).

Previous workers have used a variety of criteria to assess cerebral atrophy on CAT. Gawler *et al.* (1975) relied on deepening of the cerebral convexity sulci, widening of the lateral and inter-hemispheric fissures together with prominence of the insular (Sylvian) cisterns, and dilatation of the ventricles as criteria of atrophy but did not make a quantitative assessment. On the other hand, Huckman, Fox and Topel (1975) utilised the span of the ventricles at the level of the frontal horns together with a measurement at the level of the caudate nuclei and a measurement of 4 cortical sulci. In the present study the following indices were evaluated on the polaroid photograph : the width of the third ventricle at its mid antero-posterior point, the span of the lateral ventricles at the level of the tips of the frontal horns, the width of the Sylvian cistern, the width of the inter-hemispheric fissure at a level 10mm internal to the inner table of the skull, the width of the ambient cisterns at their mid-antero-posterior point, and the average width of 4 cortical sulci or, of as many as were visible if this was less than 4. In the control series of 23 patients, the figures obtained for bi-frontal ventricular span were 8.0-14.0 mm, the 3 patients exceeding 12.0 mm being males. The indices of normality chosen are summarized in Table II.

TABLE II

Normal Indices

	Polaroid Measurement (mm.)	True Value (mm.)
Ventricular span	<14.0	<51.0
Third ventricle	<1.5	<5.5
Cortical sulcus	<1.25	<4.5
Sylvian cistern	<1.0	<3.6
Ambient cistern	<1.0	<3.6
Inter-hemispheric fissure	<1.0	<3.6

RESULTS

The incidence of abnormal findings is summarized in Table I. Abnormalities fell into 4 categories.

Infarction

Six patients (20-49 years) had circumscribed areas of low μ numbers (average 8) as seen in patients with infarction due to athero-thrombotic cerebrovascular disease. In 4 of these patients the area of infarction was in the medial occipital region within the territory of supply of the posterior cerebral artery and was bilateral in 2 patients (e.g. Figures 1 and 2). All of these patients had a demonstrable fixed visual field defect either in the form of a homonymous scotoma, or a homonymous hemianopia, or tunnel vision in one of the patients with bilateral infarction. The remaining 2 patients had unexpected small areas of infarction in the temporal region without detectable clinical accompaniments.

Atrophy

As shown in Table I, 8 subjects had indices outside the normal range and were therefore considered to have some degree of cerebral atrophy. The ventricular span in these subjects varied from 9.0-15.5 mm.

Fig. 1. Right occipital infarct in a 20-yr old male with classical migraine and a left homonymous hemianopia (polaroid).

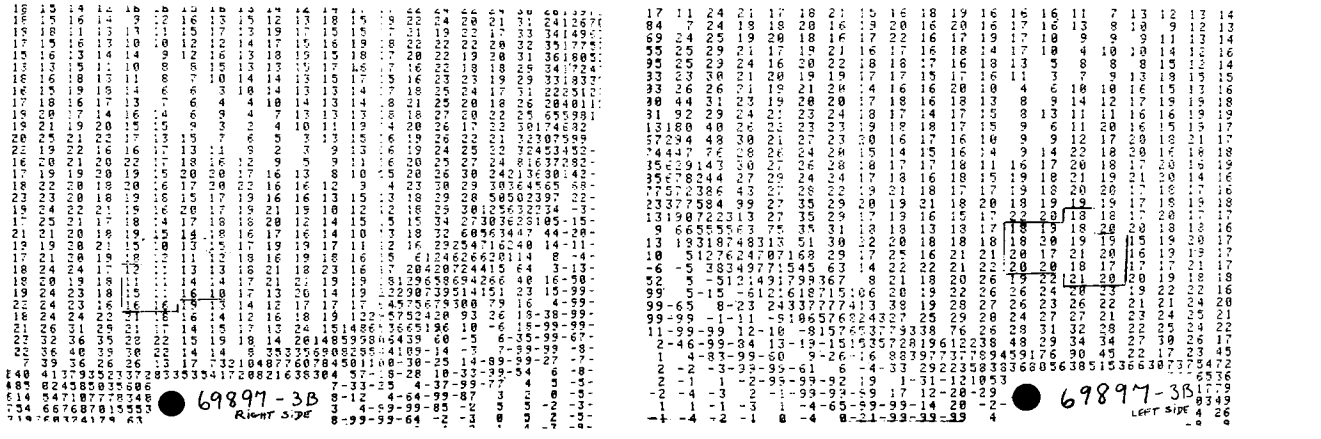

Fig. 2. Computer print-out of occipital regions in the same patient as in Figure 1: a. right side showing area of infarction; b. normal left side.

When one considers the minification factor involved, namely 3.63, this gives an actual measurement of between 32.7 and 56.3 mm for these patients, the highest figure in the controls being 51.0 mm. Only one of the 8 had an excessively wide bi-frontal ventricular span but in 6 of the 8 the third ventricular measurement was 2.0 mm. The width of the cortical sulci fell within the normal range in each of the 8, but 5 showed widening of the Sylvian and ambient cisterns and of the inter-hemispheric fissure. The majority of these subjects therefore showed what may be interpreted as a mild degree of cortical and/or central atrophy. A more marked degree of atrophy was found in 2 patients, one a 35 year old female with a history of frequent severe attacks of classical migraine for several years, the other a 36 year old female

with mitral stenosis who had suffered from intractable migrainous headaches for the previous 10 months (Figure 3).

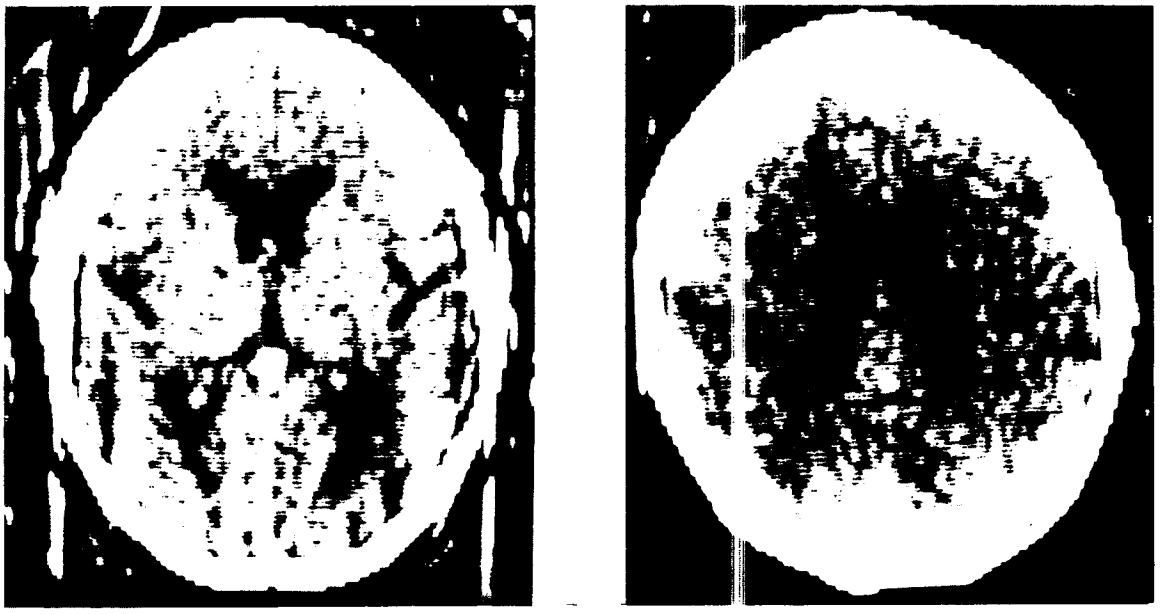

Fig. 3. Atrophy in a 36-yr old female with migrainous headaches and mitral stenosis: a. central slice; b. top slice.

Oedema

Forty-five percent of the series showed appearances considered to be suggestive of mild cerebral oedema (Table I). This was initially recognised as an appearance of slightly increased blackening, i.e. reduced density, on the polaroid photograph and was confirmed on examination of the computer printout by the finding of scattered matrix cells with values of 2 or more units less than their immediately contiguous cells. As the absolute μ values are modified by the thickness of the cranial vault in any particular subject, it is not possible to derive an absolute figure for oedema since, in a sense, each patient must act as his own control. The lowest figure for oedema in the 21 cases was 7 and the highest figure was 13. The appearance of oedema was bi-frontal in 15 patients (Figure 4), right frontal in 3, left frontal in one and was more extensive throughout the left hemisphere in 2 cases. There was no consistent correlation between the hemisphere showing oedema and the lateralization of the headache in patients with unilateral symptoms, although the 2 patients with extensive oedema in the left hemisphere did have either symptoms or signs referable to that hemisphere. Seven of the 21 patients in this group underwent CAT during an attack. Comparison was made with 7 patients who had evidence of oedema due to other causes—5 with proven primary or secondary brain tumours, one with suspected encephalitis and one examined by CAT immediately following a grand mal convulsion. The degree of cerebral oedema in this group was more marked and was therefore much more evident on the polaroid. The lowest figure in the oedema area was 7 and the highest figure was 10. Repeat EMI scans 2 weeks and 4 months later respectively in the latter 2 patients were normal supporting the validity of the criteria for cedema.

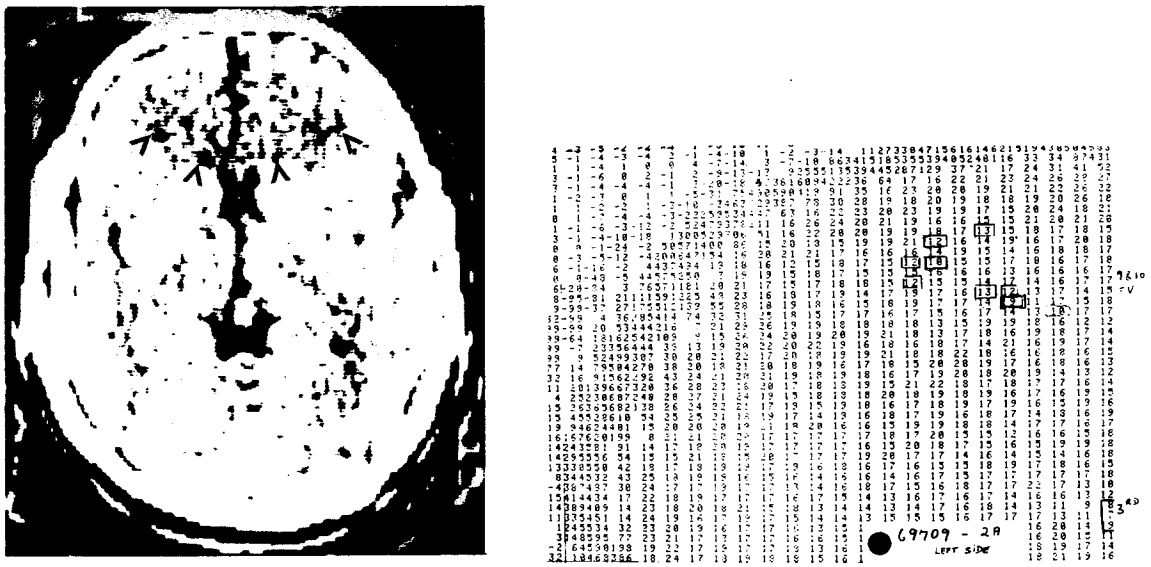

Fig. 4. Appearance of bi-frontal oedema in a 47-yr old male with classical migraine: a. polaroid; b. computer print-out of left frontal region.

Tumours

Two patients were found to have tumours. One was a 26 year old male with a parieto-occipital glioblastoma who had suffered from classical migraine with teichopsia for 2 years (Figure 5). The other was a 32 year old woman who had suffered from common migraine for many years and had more recently developed adversive seizures, who had an extensive calcified tumour in the left cerebral hemisphere.

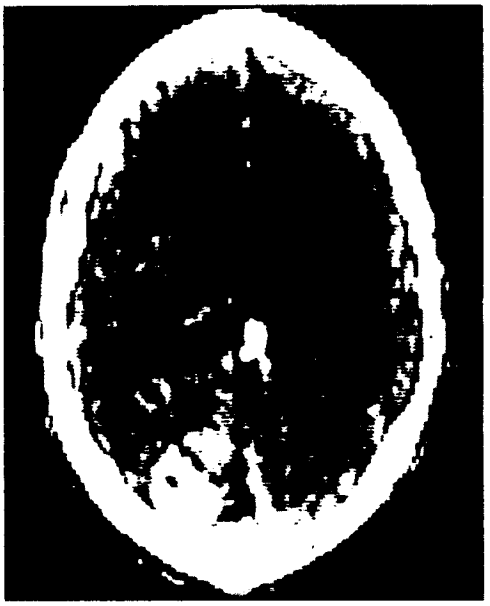

Fig. 5. Left parieto-occipital glioblastoma in a patient with a 2-yr history of classical migraine (polaroid, contrast slice).

DISCUSSION

The present findings draw attention to the possibility of detecting relatively subtle abnormalities such as mild white matter oedema, early cerebral atrophy and small areas of cerebral infarction by computerized axial tomography of the cranium. The findings highlight the importance of establishing indices of normality, with which to compare findings in abnormal subjects. On the other hand, the discovery of tumours in 2 of the present cases indicates that unexpected gross lesions may at times also be detected and emphasizes the value of CAT as a screening investigation in patients suffering from recurrent migrainous headaches particularly when there are atypical features or when there is a change in headache pattern.

The demonstration of areas of infarction in the posterior cerebral artery territory in patients with permanent visual defects is not unexpected. However, the finding of small clinically inapparent areas of infarction in the temporal lobe does suggest that focal areas of brain damage due to migrainous vasospasm may occur more frequently than is appreciated.

While the degree of oedema found in migraine subjects is of a different order of severity to that found in relationship to cerebral metastases, acute vascular lesions or other focal destructive processes, it is nevertheless felt that this is a significant finding which, when present, may provide an additional clue to the migrainous nature of a headache syndrome. Two possible explanations for an appearance suggestive of oedema need to be considered. The first is that the reduction in μ values is due to an increased fluid content of brain tissue (i.e. true oedema) on the basis of regional cerebral ischaemia due to vasospasm. Alternatively, a reduction in μ values and increased blackening on the polaroid photograph might also be expected if regional cerebral blood flow were reduced at the time of scanning implying a reduced content of fluid blood per unit volume of brain tissue at any one time. Extrapolating from the results of regional cerebral blood flow (CBF) studies in migraine subjects (O'Brien 1970) it might be anticipated that true oedema would be more likely to occur in the prodromal stage when regional cortex perfusion rates are decreased. Further observations employing both CAT and CBF techniques in patients in the prodromal, the headache and the post-headache phases of migraine are required to throw further light on the significance of these findings.

The significance of the mild atrophic process found in some patients in this series is uncertain. Although no correlations with the length of history or frequency and severity of headaches were apparent in these subjects it is tempting to consider the possibility that some degree of atrophy may result from recurrent episodes of regional cerebral ischaemia on the basis of migrainous vasospasm. A prospective study of a larger group of subjects and a more detailed correlation with the migraine history are clearly necessary to throw further light on this possibility. It would also be of importance to carry out prospective psychometric studies in patients with frequent migrainous attacks to determine whether there is a functional correlate to the atrophic process. An alternative explanation which needs to be considered is that the migrainous headaches were in fact symptomatic of the atrophic process in the patients with the more marked degrees of atrophy. It is noteworthy in this regard that we have seen comparable examples of intractable headaches with migrainous characteristics in some elderly patients with advanced cerebral atrophy of presumed Alzheimer type.

The patients included in the present study represent a selected group and are clearly not representative of the migrainous population in general. The incidence of abnormal findings in this group of patients would therefore almost certainly be an over-estimate for the general migraine population. Nevertheless, the present findings do suggest that CAT is useful not only as a screening investigation in selected patients with migraine but also for studying the pathogenesis of the cerebral changes in migraine.

SUMMARY

Computerized axial tomography of the cranium has been carried out in 46 patients referred because of recurring migrainous headaches. Increasing frequency or severity of headaches or a change in headache pattern were the usual reasons for referral. Abnormalities were found in 37 cases and fell into 4 categories. The most frequent (21 cases) consisted of a mild degree of oedema in the white matter of one or both cerebral hemispheres. This was usually bi-frontal (15 patients) but was more extensive in 2 patients. Varying degrees of cerebral atrophy, as determined by widening of the Sylvian, brain-stem and in-

terhemispheric cisterns, and/or widening of the third and lateral ventricles as compared to a group of normal scans, was found in 8 cases. Areas of occipital infarction were found in 4 patients with permanent visual field defects.

Unexpected small areas of infarction were found in the temporal lobe in 2 other cases. Cerebral tumours were found in 2 cases. The significance of these findings is discussed, as well as the possible role of migrainous vaso-spasm with consequent changes in cerebral blood flow in the pathogenesis of oedema and atrophy in migraine subjects.

ACKNOWLEDGEMENTS

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NEUROPHYSIOLOGICAL ASPECTS OF PERIPHERAL NEUROPATHIES

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INTRODUCTION

The development of the technique of recording from individual nerve fascicles with tungsten micro-electrodes (Vallbo and Hagbarth, 1968) has allowed study in conscious human subjects of the activity of fibres of all conduction velocities. The technique has obvious advantages in the investigation of patients with peripheral neuropathy, since only the fastest fibres can be recorded by conventional surface electrodes.

Since 1974, the Unit of Clinical Neurophysiology at the Prince Henry Hospital has carried out more than 100 micro-neurographic studies on normal subjects and patients with various peripheral nerve disorders. This paper reports our findings in those patients who had unequivocal evidence on sural nerve biopsy of segmental demyelination or axonal degeneration.

MATERIAL AND METHODS

Surface sensory action potentials (SAPs) from the median and sural nerves were recorded using conventional techniques (for details, see Burke, Skuse and Lethlean, 1974a). The refractory period was determined for both nerves when possible, or from the median nerve only when sural nerve responses were of low amplitude or absent. Conditioning stimuli were delivered from 1.0-6.0 m.sec before the test stimulus, and latency measurements were made to the onset of the negative deflection of the conditioning and test response. Values were obtained from 12 normal nerves, 10 nerves with chronic axonal degeneration and 6 nerves with segmental demyelination found on sural nerve biopsy (Dr John Walsh).

Microneurographic techniques were similar to those described previously (Burke, Skuse and Lethlean, 1974b; Burke, Mackenzie, Skuse and Lethlean, 1975). Insulated tungsten micro-electrodes with a tip diameter of 1 μm were manually inserted percutaneously into the median nerve just proximal to the wrist, or into the subcutaneous segment of the sural nerve just lateral to the tendo Achilles. Paraesthesiae induced by stimulating through the micro-electrode were used to guide the tip into sensory fascicles supplying the distal finger pulp (median nerve) or the lateral aspect of the foot (sural nerve). The lowest voltage perceived was recorded as the intrafascicular threshold, Tfi. Needle electrodes were inserted 1 cm. apart into similar skin sites in each subject, and single square wave pulses of 0.1 m.sec duration were delivered. The applied voltage at which fibre responses were first recorded (threshold of fibre activation, Tfa) and the voltage level first perceived (perceptual threshold, Tp) were noted. Responses to single electric shocks at various stimulus levels, delivered at 1.0/sec, were electronically averaged and photographed. Changes in the evoked response after the delivery of a supramaximal stimulus train at 500/sec for 2 minutes were also assessed. Discomfort was reduced by first delivering the stimulus train at low voltage and increasing stimulus strength over 1 minute to the previously determined level. Two stimulus trains were delivered in

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each subject, the first when skin temperature of the limb had been allowed to fall to 27-28°C and the second after it had been restored to 32-33°C by radiant heat. Responses to single electric shocks at 1.0/sec immediately after the stimulus train were photographically superimposed on 35 mm film, and latency measurements made to the peak of all consistently recorded potentials. Responses from all fibre potentials in each of the 3 groups of subjects were pooled, and final comparisons made in terms of percentage change in conduction velocity.

Thirty-three median nerve and 15 sural nerve penetrations were performed in 10 normal subjects aged 24-57 years, mean age 37.2 years. Three sural nerve and 11 median nerve penetrations were carried out in 5 patients aged 18-63 years, mean age 43 years, with biopsy evidence of chronic axonal degeneration. Three had hereditary spino-cerebellar ataxia and two had idiopathic neuropathy. Eight sural nerve and 18 median nerve penetrations were done in 11 patients aged 36-53 years, mean 43 years, with demyelinating neuropathy. Eight of these had the dominantly inherited form of hypertrophic Charcot-Marie-Tooth (CMT) disease and 3 had idiopathic neuropathy; all had extensive segmental demyelination shown on sural nerve biopsy.

Experiments were conducted in an air conditioned room. Skin temperature was monitored during all phases of an experiment with a thermocouple, and usually maintained at 32-33°C with radiant heat.

There were no permanent sequelae related to the intrafascicular penetrations. Complications following the procedure were limited to transient paraesthesiae induced by tapping over the site of penetration, as has been described previously.

RESULTS

Intrafascicular Threshold (Tfi)

There was no significant difference between Tfi in normals (0.44 ± 0.06v, mean ± SD) and in patients with chronic axonal degeneration (0.55 ± 0.22v) or demyelinating neuropathy (0.50 ± 0.28v). Tfi was always less than 1v.

Perceptual Threshold (Tp)

In normal subjects, Tp was 0.94 ± 0.2v for median nerve, and 1.50 ± 0.52v for the sural nerve. Median nerve Tp was 4.0 ± 2.2v in the axonal neuropathy group and 3.0 ± 0.5v in demyelinating neuropathy, both significantly greater than normal ($P < 0.025$). Sural nerve Tp in the demyelinating neuropathies was 7.8 ± 2.6v, again significantly greater than normal ($P < 0.01$).

Fibre Activation

In normal subjects, 1.0 Tp stimulation evoked 1-4 fibre potentials (mean 1.8) with similar conduction velocity (31-45 m/sec, mean 39.6 m/sec). Patients with axonal neuropathy had 1-8 fibres (mean 3.5) recorded at 1.0 Tp with a wide range of conduction velocity, 16-39 m/sec (mean 31 m/sec). The number of fibres activated and their conduction velocity were significantly different from normal ($P < 0.05$). A greater number of fibres was also recorded at 1.0 Tp in demyelinating neuropathy (range 1-10, mean 4.2 fibres), and conduction velocity was considerably slower (range 2.1-22 m/sec, mean 13 m/sec) (Figures 1&2).

It has been shown previously that, in normal subjects, fibre responses may be recorded at stimulus levels just below perceptual threshold, but such stimuli are always felt if delivered at high frequencies (Burke, Mackenzie, Skuse and Lethlean, 1975). In neuropathic subjects, fibre responses could still be recorded at 0.5 Tp and even 0.3 Tp, and these stimuli were not felt even when delivered at high frequencies (Figure 3).

Tfa was greater in both neuropathic groups than in normal subjects. Responses were first recorded at 2.2 ± 0.4v in axonal neuropathy and 1.8 ± 0.52v in demyelinating neuropathy, significantly greater than the 0.76 ± 0.14v required in normal subjects ($P < 0.05$).

When stimulus strength was increased in multiples of Tp, there was always an increase in the absolute amount of neural activity and in the range of recorded conduction velocities. With supramaximal stimulation, the maximum conduction velocity of recorded responses in normal nerves was 41-60 m/sec (mean 52.6 m/sec) compared with 31-46 m/sec (mean 38.6 m/sec) in axonal neuropathy ($P < 0.001$). Responses were more dispersed, and total amount of neural activity was less in nerves with axonal degeneration as compared with normal nerves (Figure 2). In demyelinating neuropathy, supramaximal stimulation evoked dispersed fibre responses with a maximum conduction velocity of 8-29 m/sec, mean 18.1 m/sec. The absolute amount of recorded neural activity was consistently less than in normal nerves (Figures 1&4).

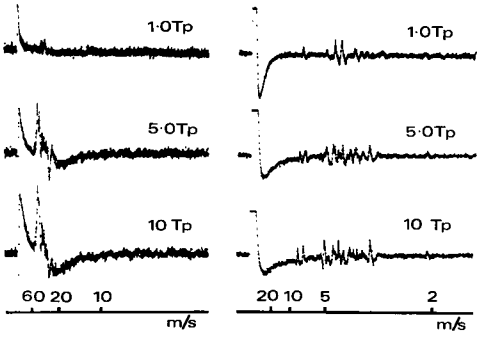

Fig. 1. A fibre activity in sural nerve of normal subject (left column) and patient with hypertrophic Charcot-Marie-Tooth disorder (right). 100 averaged responses to single electric shocks at 1.0/sec. Note: normal nerve-initial compound response, velocity 30–50 m/sec.; pathological nerve-dispersed discrete fibre potentials, velocity 2.1–8.0 m/sec. Input gain 50,000. Some display gain in this and all averaged recordings.

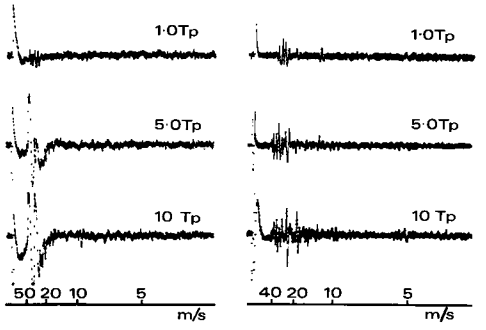

Fig. 2. A fibre activity in median nerve of normal subject (left column) and patient with chronic axonal degeneration (right). 100 averaged responses to single electric shocks at 1.0/sec. Fibre responses in the pathological nerve are more dispersed at all stimulus levels, and conduction velocity is slower.

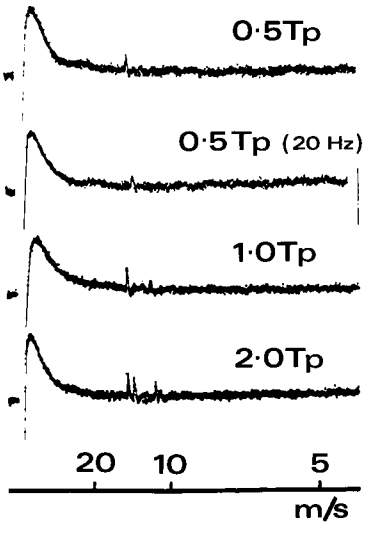

Fig. 3. A fibre activity in median nerve of patient with hypertrophic Charcot-Marie-Tooth disorder. 100 averaged responses to single electric shocks at 1.0/sec and 20/sec (line 2). Fibre response is recorded at stimulus level which is not felt, even at 20/sec. Note prolongation of latency and duration of single fibre response at 20/sec. Velocity of "touch" fibres 10.5–13.2 m/sec.

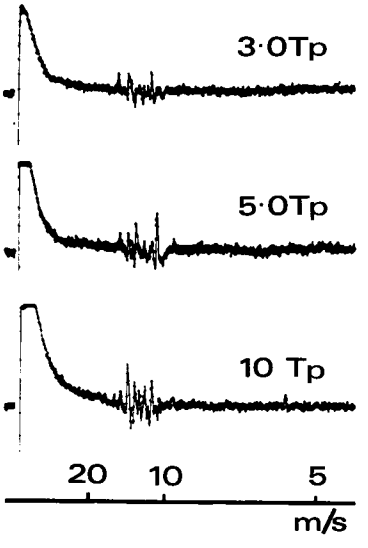

Fig. 4. Same subject and recording conditions as in Fig. 3. Higher stimulus levels evoke a burst of low velocity fibre potentials, with recruitment of a very slow single fibre at 10Tp.

Trains of stimuli at frequencies from 2-100/sec were delivered, and the effects on the evoked neurogram were studied. Although considerable latency change occurred in the demyelinating neuropathies at high frequencies (Figure 3), complete conduction block was not observed.

Assessments were made of the evoked neurogram before and after the delivery of a supramaximal stimulus train at 500/sec for 2 minutes. Immediately after the conditioning stimulus there was dispersion of the initial compound responses, with an associated drop in amplitude, and the latencies of all fibre responses were increased. These changes were much more conspicuous in patients with neuropathy, especially demyelinating neuropathy, than in normal subjects (Figures 5&6). However in no experiment was complete abolition of neural activity observed. Conduction velocity changes of individual fibres following repetitive stimulation are shown in Figure 7. Mean conduction velocity of normal fibres dropped to 90% of their control value, and returned to pre-stimulus levels in less than 3 minutes in all cases. No significant functional change, apart from increased conduction velocity, occurred after the limb was heated. In patients with axonal neuropathy, conduction velocity immediately after the repetitive stimulus was 88% of control and remained significantly more depressed than normal for 3 minutes ($P < 0.05$). Recovery was also more prolonged, not being complete until almost 4 minutes. Heating did not cause any further changes. Fibres affected by segmental demyelination showed depression of conduction velocity to 83% of control at 27-28°C, and had not recovered to control values after 5 minutes. Differences from both normal and axonal neuropathy group were significant at all times ($P < 0.01$). At 32-33°C the changes were significantly greater than those obtained at the cooler temperature ($P < 0.5$) and after 5 minutes mean fibre conduction velocity had reached only 91% of control value. Original conduction velocities returned in all cases after a 5 minute interval without stimulation. Refractory period changes were assessed from surface SAP recordings in the groups already outlined. Latency changes in the 3 groups for stimulus intervals from 1.0 to 2.0 m.sec are shown in Table I. There is no significant difference between the normal and the axonal degeneration groups. However the values for the demyelinating neuropathies differ from both of the other groups at 1.0 and 1.5 m.sec ($P < 0.01$) and from the axonal degeneration group at 2.0 m.sec ($P < 0.05$).

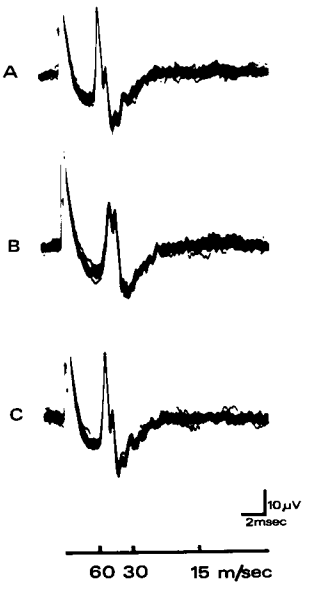

Fig. 5. Superimposed intrafacicular responses to 10 supramaximal stimuli at 1.0/s in a normal subject, before (A) and immediately after (B) the delivery of a stimulus train at 500/sec for 2 minutes. Recording C taken 5 minutes after the end of the stimulus train. Input gain 50,000, display gain 0.1 v/cm, sweep time 2 m. sec/cm.

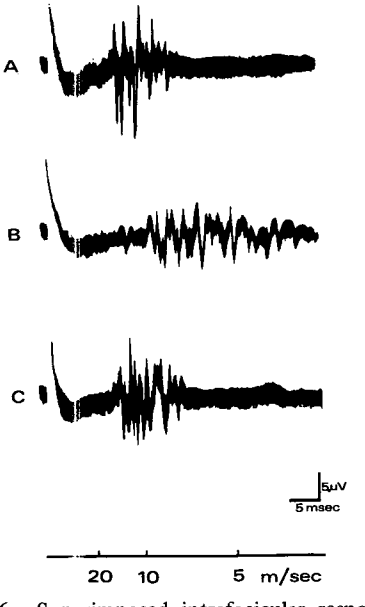

Fig. 6. Superimposed intrafacicular responses in a patient with demyelinating neuropathy at similar times in relation to the stimulus train as in Fig. 5. Input gain 50,000, display gain 0.05 v/cm, sweep time 5 m. sec/cm.

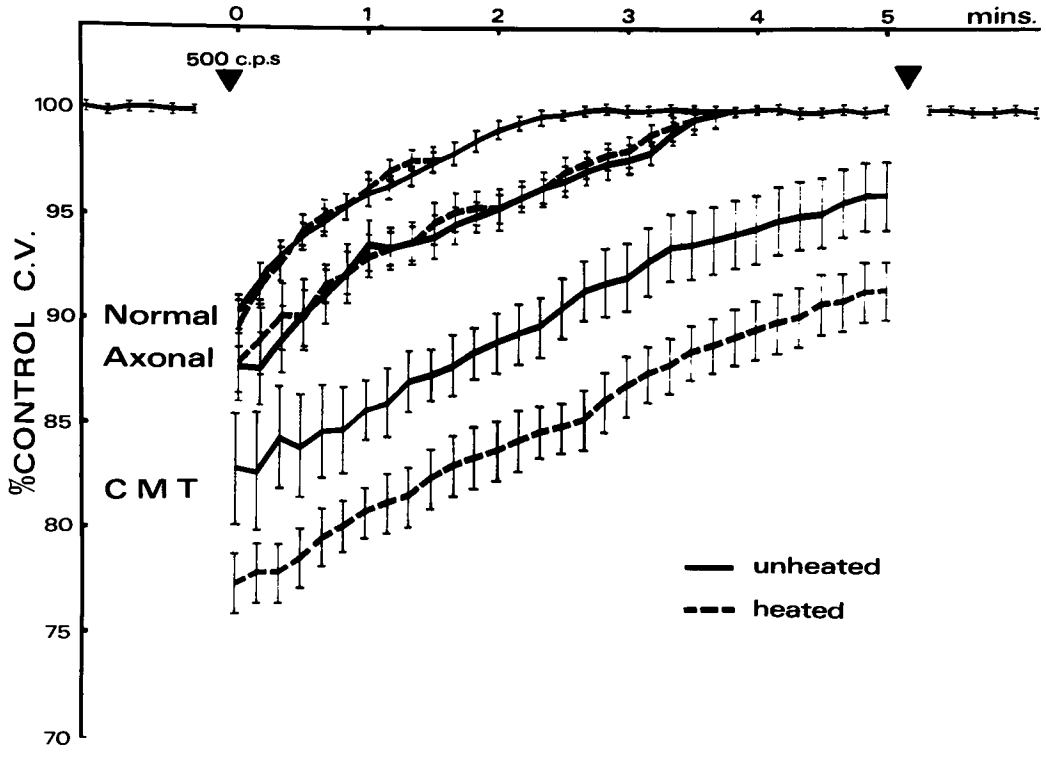

Fig. 7. Changes in conduction velocity of fibres in the three groups after the stimulus train, measured at 10 sec intervals for 5 minutes, and again after a 5 minute interval without stimulation. Skin temperature of unheated run 27–28°C, heated run 32–33°C. Bars represented 2 standard errors above and below the mean.

TABLE I

Median and Sural Surface S.A.P.: Prolongation of Relative Latency

	Stimulus Interval (m.sec)		
	1.0	1.5	2.0
Normals (12) (% Control ±SD)	131.7 ± 7	121.8 ± 6	114 ± 6
Axonal Neuropathy (10)	133 ± 10	120.2 ± 4	111.4 ± 4
Demyelinating Neuropathy (6)	152 ± 17	138 ± 10	121 ± 10

DISCUSSION

Penetration of median and sural nerve sensory fascicles was achieved without technical difficulty or excessive discomfort, and satisfactory recordings of multi-unit activity were obtained in all patients. The length of time (1-3 hours) required for the procedure and the necessity of the patient's co-operation limited to some extent the range of patients studied, but all those selected tolerated the procedure well.

Stimulus voltage delivered through subcutaneous electrodes was higher than normal for both perception

and fibre activation in neuropathic subjects. However there was no difference in the stimulus levels required for perception when the stimulating electrode was intrafascicular. This suggests that either there is drop-out of nerve fibres and end-organs distally, or that these structures require a greater stimulus for activation of nerve trunks and central perception to occur.

When distal stimulation was sufficient to reach conscious perception, more volleys were recorded in pathological than in normal nerves, suggesting that more fibre activation was required for central appreciation of the stimulus in these subjects. This may be due to conduction block during central transmission, or the volleys may become so dispersed that they no longer constitute a perceptible stimulus. The latter explanation seems the more likely, since no evidence of conduction block was found, even at high frequencies in demyelinating neuropathy, while a wide range of conduction velocities for "touch" fibres was observed in both varieties of sensory neuropathy.

Stimulation for 2 minutes at very high frequencies has been shown to cause varying degrees of conduction block in experimental demyelinating neuropathy while causing little change in nerves undergoing Wallerian degeneration (Cragg and Thomas, 1964). In the present study, post-tetanic slowing of conduction velocity occurred in demyelinating neuropathy, although this did not progress to complete conduction block. Significant changes were also found in the axonal neuropathy group, despite the finding of a normal refractory period with surface SAP recordings. One possible explanation for this is the change in fibre population which occurs in chronic neuropathy (McLeod, 1971; McLeod, Prineas and Walsh, 1973). The largest fibres are reduced in number and smaller, sometimes regenerating fibres with short internodal lengths, probably contribute more to the test population. These fibres have a decreased safety factor (Tasaki, 1955). According to this explanation, the refractory period remained normal because the surface electrodes used for the recordings allowed measurement of only the largest (fastest) fibres. The other possible explanation for the differences is that such pathological fibres do not show a significant decrease in nodal current with two shock stimulation, but when activated repetitively, intracellular sodium accumulates and there is sufficient change in transmembrane concentration gradient to cause a critical decrease in nodal current and associated conduction slowing.

It is proposed to investigate further the extent of receptor and fibre dysfunction in peripheral neuropathy. However it is already apparent that axonal neuropathy can no longer be regarded as a simple "drop out" of some fibre groups, leaving normally functioning small fibres. Both receptor and nerve fibre abnormalities appear to contribute to sensory dysfunction in degenerative and demyelinating neuropathies.

SUMMARY

1. Eighty-eight intrafascicular neural recordings were obtained in 10 normal subjects, 5 patients with axonal degeneration and 11 patients with demyelinating neuropathy.
2. Stimulus levels required for perception and fibre activation were higher in neuropathic subjects. Fibres transmitting touch perception had significantly lower conduction velocities in both patient groups, but were very much lower in the group with demyelinating neuropathy than the group with axonal degeneration. Maximum electrical stimulation evoked dispersed fibre responses in the axonal degeneration group and more dispersed, slowly conducting fibre potentials in the demyelinating group. In patients with hypertrophic Charcot-Marie-Tooth disorder, usually only a small group of slowly conducting low amplitude potentials was recorded.
3. Delivery of a train of supramaximal stimuli caused prolongation of latency and dispersion of fibre potentials in all microneurographic recordings. The changes were significantly greater in the axonal neuropathy group than in normals, and recovery was slower. The demyelinating neuropathies showed significantly greater changes than both the normal and the axonal neuropathy groups, and post-tetanic conduction slowing became even more marked after limb temperature was raised.
4. Surface SAP recordings showed normal refractory period in chronic axonal neuropathy but significant latency prolongation occurred in demyelinating neuropathy.
5. It is concluded that both receptor and nerve fibre abnormalities contribute to sensory dysfunction in degenerative and demyelinating neuropathies.

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THREE CASES OF POST TRAUMATIC VASCULAR HEADACHE TREATED BY SURGERY

JOHN TERENCE HOLLAND*

"There is probably no harm and occasional benefit in the judicious use of an operation performed as a therapeutic trial; but the indiscriminate use of operations on patients ... is out of keeping with the sound principles that characterise most of the rest of our neurosurgical effort." (Ray, 1954).

The history of surgery in the treatment of vascular headache has not been a rewarding one. With the exception of biopsy of a temporal artery for the diagnosis of cranial arteritis or the correction of a stenotic lesion causing transient ischaemic attacks which sometimes are associated with extracranial throbbing headache, surgery for vascular headache is not recognized as having a place. It is now possibly of no more than historical interest to recall that Cushing (1910), Gordon Holmes (1933) and Critchley and Ferguson (1933) recommended right subtemporal decompression, Dandy (1931) recommended cervical and first thoracic sympathetic ganglionectomy and Watts, Wiley and Groh (1944) recommended multiple resections of scalp vessels for selected cases, and all for the treatment of migraine. Wolff (1963) reviewed the literature up to that time in depth and listed other procedures tried for the relief of migraine such as resection of the supraorbital artery and nerve, ligation of the external carotid artery and destruction of the trigeminal ganglion or its sensory root with disappointing results. Nonetheless the occasional patient apparently did obtain dramatic and prolonged relief.

Haynes (1948) reported the results of surgery for vascular headaches other than "pure migraine." His group 1, characterised by "severe unilateral temporo-orbital pain, reddening of the conjunctiva, tearing of the eye and tenderness of the temporal artery" sounds much like cluster headache. He reported complete relief of the headache in 13 of the 17 cases following ligation of the superficial temporal artery. Unfortunately details of other than a few selected cases are not given, nor follow up indicated. Interestingly, one of the reported cases followed a penetrating scalp injury over a superficial temporal artery. With the number and variety of drugs now available for the medical treatment of vascular headaches one, nevertheless, does still see occasional patients incapacitated with pain, unresponsive to or only partially controlled by medication.

The three cases here presented all suffered severe vascular headaches, following localized trauma to the region of a single extracranial artery in two cases, and a more diffuse injury to the head and neck in the third. In each case medication was either not successful, or only barely so, in controlling the pain which was significantly interfering with the patient's life. The result of local surgery to the involved artery in each case was dramatic, although the follow-up, as yet, has not been very long in one of the cases.

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CASE REPORTS

CASE 1

Female, born in 1945. In 1973 she presented with a history that ten years previously she had fallen off a horse and struck her right temple, though she was not knocked out. Approximately two weeks later she developed her first attack of severe throbbing right sided headache in the region of the right superficial temporal artery. Following this she experienced almost monthly attacks, not related to her menstrual periods and often associated with photophobia and/or vomiting. The attacks lasted between 3 and 21 days. The pain could be relieved early in the attacks by pressure applied to the artery. There was no previous history or family history of migraine, travel sickness or bilious vomiting. "Periactin", "Deseril" and "Catapres" were tried as prophylactic agents without success. If given early, I.M. ergotamine tartrate would often give relief. In August, 1973 ligation of the right superficial temporal artery was performed. Since this time she has not had a single headache and has taken no medication.

CASE 2

Male, born in 1939. He presented in mid 1974. Twelve months previously he had undergone surgery to a middle cerebral aneurysm. In May 1974 a tantalum plate was inserted in the right side of his skull. Two weeks following this operation he began to notice severe throbbing headache, localized to the right superficial temporal artery where it ran across the lower edge of the plate. The headache was strictly related to exercise or bending when it would last only a matter of minutes. He learnt to prevent the pain on bending by applying pressure to the artery beforehand. There were no associated phenomena. There was no previous history or family history of migraine, travel sickness or bilious vomiting. "Sandomigran" and "Catapres" failed to prevent the headaches.

Five months after the onset of the headaches the right superficial temporal artery was ligated. From the time of this procedure he has not had a single headache and has had no medication for headache. (He is taking phenytoin for sensory fits following the original operation for the aneurysm.)

CASE 3

Male, born in 1939. Towards the end of 1972 he had fallen off a water ski, at speed, on to the right side of his head and neck. He was not knocked out. The following night he was awoken from sleep with very severe throbbing pain involving the right side of his head. The pain lasted approximately one hour. From this time he experienced nightly attacks lasting 1-3 hours, eventually (over a few weeks) spreading to involve, and to commence in, the right side of his neck but rapidly spreading to involve the whole of the right side of his neck and scalp. As a rule this was associated with lachrymation and blurred vision of the right eye, nasal congestion of the right nostril and his wife often noted that the right pupil became constricted during the attacks. Over the next 2½ years he lost over one stone in weight. The attacks were not prevented by "Catapres" but eventually were partially controlled by 4 mgm daily of "Deseril". He was unable to take more than this because of vertigo and parasthesiae of his extremities. He learnt also to take "Ergodryl" on retiring at night and for any attack that did occur. It was not possible during the 12 months before surgery to reduce his "Deseril". There was no past history or family history of migraine, travel sickness or bilious vomiting. Because the pain commenced in the distribution of the right thyrocervical trunk vessels, in June 1975 this artery was ligated in the neck at its origin. Immediately following this operation he lost all his headaches for a few weeks at which time it recurred but only in the right temple and forehead. In November 1975, at his persistent request, the right superficial temporal artery was ligated but above an anastomotic branch with the supraorbital artery. Following this procedure he lost all headaches in the distribution of the superficial temporal artery but has continued to have pain strictly localised to the anastomotic branch described. This is again just controlled by prophylactic "Deseril" and "Ergodryl". If this pain also persists it is planned to ligate the anastomotic artery in the future.

DISCUSSION

Vascular headache following trauma has been recognised for years. Simons and Wolff (1946) classified post-traumatic headache into 3 types:—

Type 1—the most frequent—of the muscle contraction variety;

Type 2—due to local tissue and nerve injury;

Type 3—a more typical vascular variety which would fit the description of common migraine.

Type 3 was found in 4 of the 63 cases studied, and all were relieved by ergotamine tartrate. Hass and Sovner (1969) and Matthews (1972) have reported what must be accepted as attacks of classical migraine related to head trauma with trauma as the precipitating factor on each occasion and Whitty (1967) and Morris (1972) also reported classical migraine precipitated by head trauma, identical to subsequent, spontaneously occuring episodes. A similar pattern has been described even more recently by Haas, Pireda and Louri (1975). In the present series Case 1 would perhaps fit to some degree with this group. However

the first attack did not occur until 2 weeks after the head trauma, and the attacks were always localized to the same artery without further precipitating trauma on each occasion.

It is difficult to know where to fit in Case 2. The headaches were certainly vascular in origin but there were never any associated features to characterize them as migraine. They were strictly related to posture and exercise and again to one single artery.

Case 3 would appear to be an example of cluster headache precipitated by trauma and of a distribution wider than usual. However, this seems not to have been described in the literature except for the single case reported by Haynes (1948) and mentioned above. It differs from the usual pattern of cluster headache in that, once the attacks commenced, there was not any period of relief (the headache occured every night). However, one does occasionally see cluster headaches behave like this. From the history, at least, there was evidence to suggest episodes of temporary paralysis of the oculosympathetic pathway, and this too is well documented with attacks of cluster headaches. (Alpers and Yaskin, 1951; Nieman and Hurwitz, 1961). Recently Vijoyan and Dreyfus (1975) described 5 cases of what they called "post traumatic dysautonomic cephalalgia" characterised by "severe episodic, throbbing, unilateral headaches, accompanied by ipsilateral mydriasis and excessive sweating of the face, following an injury to the neck that involved the region of the carotid artery sheath." These 5 cases are remarkably similar to Case 3 except for the presence of sympathetic overactivity rather than paresis with the attacks, although the authors reported that between attacks there was some evidence of mild sympathetic paresis. All their cases responded very satisfactorily to propranalol.

The mechanisms of vascular headache and migraine are not well understood. However it seems reasonable to believe that the triggering factor in the cases described was local trauma to the artery or arteries involved, resulting in disturbance to the anatomy and/or neurochemical control of the autonomic plexus. Factors involved have been recently reviewed by Lance (1972) and Anthony (1972) and others, but in addition Adams, Orton and Zilkha (1968) found an abnormality in the binding of noradrenaline to the adventitia of arteries involved in an attack of migraine and which had been excised during an attack. One of the interesting facets of this report is that the 6 cases were reported as having recurrent attacks involving a single artery which was painful to touch on each occasion. Unfortunately there is no comment on any follow up as to the effect of the surgery on the prevention or otherwise of subsequent attacks.

Concerning the resort to surgery described in the present paper, it seemed reasonable to try this in the first two cases on the basis that the attacks were wholly confined to one vessel, the vessel in each case was superficial and it could easily and safely be ligated. By thus reducing flow and pressure in the part of the vessel involved, the presumed localized autonomic defect would, to some extent, be protected. There had been no significant benefit from medical prophylaxis.

In Case 3 surgery was approached with considerably more caution. The distribution of the arterial disturbance was much greater, the anastomoses were likewise much greater which would tend to annul the effects of ligation. However the pain and the amount of continued medication were such as to make surgery a reasonable therapeutic trial. I would emphasize that the patient himself asked for the second operation and, indeed, persisted with his request until it was agreed upon. Likewise he is eager to go ahead with a projected ligation of the remaining involved vessel.

In conclusion then, it would seem that trauma can give rise to vascular headache which may conform to the pattern of classical migraine, common migraine, cluster headache or simply just headache localized to an artery at the site of the trauma itself. Such a headache may not always respond to accepted medical management. Ligation of the involved artery may give dramatic and prolonged relief. It is emphasized that it is not intended to suggest that surgery necessarily has a place in the treatment of vascular headache as a whole, but that in the uncommon case of persistently localized superficial arteralgia, especially following localized trauma, and when such a headache remains unresponsive to medical management, surgery should not be forgotten.

SUMMARY

Three cases are reported of vascular headache following trauma and which failed to respond adequately

to standard therapy for migraine. In each case the effect of ligation of the arteries involved has been dramatic, with complete and lasting relief in two cases.

ACKNOWLEDGEMENTS

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THE INFLUENCE OF PREVIOUS STEREOTACTIC THALAMOTOMY ON *l*-DOPA THERAPY IN PARKINSON'S DISEASE

GEORGE SELBY*

INTRODUCTION

After almost 20 years of stereotactic surgery for Parkinson's disease, there is a consensus of opinion that a surgical lesion placed correctly in the lateral ventral nucleus of the thalamus can abolish—or at least significantly diminish—rigidity and tremor of the limbs contralateral to this lesion. It is similarly agreed that thalamotomy has no influence on akinesia, speech disorders and postural dysequilibrium and improves the Parkinsonian gait only to the extent by which it was impaired through rigidity of the lower limbs. During the past decade it has become obvious that neither unilateral nor bilateral thalamotomy can retard or alter in any way the natural progression of Parkinson's disease, apart from the persisting improvement in rigidity and tremor. Consequently the majority of Parkinsonian patients, who had been subjected to stereotactic procedures in the past, required treatment with *l*-DOPA since this drug became freely available.

Among the few published reports dealing with the long term effect of *l*-DOPA therapy in large series of patients (Hunter *et al.*, 1973; Markham *et al.*, 1974; Barbeau, 1975), only one has paid any attention to the possible influence of prior thalamotomy on the slow, gradual and relatively slight progression of Parkinson's disease which occurs in spite of treatment with *l*-DOPA (Presthus and Holmsen, 1974).

PATIENTS AND METHODS

This study is concerned with 148 patients, who have taken *l*-DOPA for the treatment of Parkinson's disease for periods ranging from two to five years. The aim of the study was to ascertain if prior thalamotomy had any influence on the therapeutic results achieved by *l*-DOPA or on the side effects produced by this drug.

Stereotactic thalamotomies had been performed on 67 of the patients in this series; only 17 of those had had bilateral operations. The remaining 81 patients had not been subjected to surgery. The time interval from thalamotomy to the institution of *l*-DOPA therapy ranged from 1-15 years:

Time interval	Number of patients
1 – 5 years	40
6 – 10	22
11 – 15	5

The site of the surgical lesion was the lateral ventral nucleus of the thalamus (v.o.a. and v.o.p. of Hassler) in all cases.

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Selection of patients was solely on the basis of sustained treatment with *l*-DOPA under the regular supervision of the author. The aetiology of Parkinson's disease was idiopathic in 144 patients, post-encephalitic in one, and familial in three cases. The sex distribution did not differ significantly between the operated and non-operated groups, but there was a larger proportion of patients over the age of 70 years in the group who had not been subjected to surgery (Table I). As one may anticipate, the duration of Parkinson's disease before *l*-DOPA was first administered was significantly longer in those who had prior thalamotomies (Table II). The duration of treatment with *l*-DOPA ranged from two to five years. In the operated group 45% of patients had taken the drug for more than four years, compared with only 31% of those who had no surgery (Table III). The majority of patients (80%) continued to take one or more anticholinergic drugs and 49 patients (33%) received Amantadine, mainly when drug induced dyskinesiae or other side effects demanded a reduction in the dose of *l*-DOPA. Peripheral decarboxylase inhibitors were not used in this study.

Before treatment with *l*-DOPA was begun, the severity of specific Parkinsonian symptoms and of the patients' functional incapacity was recorded in four grades, and a total disability score was calculated from the Webster Rating Scale (Webster, 1968). At each subsequent attendance the effect of treatment on the cardinal symptoms and on the patients' working capacity and dependence on help in daily activities were assessed—some by standardised tasks—and the total score of the Webster Rating Scale was again calculated for each patient.

TABLE I

	Operated 67 patients	Non-Operated 81 patients
Male	57%	62%
Female	43	38
Age:		
< 50	10%	11%
51 – 70	85	70
> 70	5	19

TABLE II

	Operated 67 patients	Non-Operated 81 patients
Duration of Disease:		
< 5 years	11%	52%
6 – 10	49	37
11 – 20	34	11
> 20	6	–

TABLE III

	Operated 67 patients	Non-Operated 81 patients
Duration of therapy:		
24 – 36 months	25%	31%
36 – 48	30	38
> 48	45	31

RESULTS

In a previous study, designed to determine the influence of the severity and duration of Parkinsonism on the progress of the disease during long term *l*-DOPA therapy (Selby, 1975), the patients were considered in four groups of which the first two groups distinguished the severity of the disease at the beginning of treatment, the third described patients who developed severe *l*-DOPA induced dyskinesiae, and the fourth group was concerned with those who experienced marked diurnal fluctuations (the 'on-off' phenomenon) in performance. As it was found that all these factors had some influence on the success of *l*-DOPA therapy, a division into these four groups was adopted also in the present investigation of the effect of stereotactic operations.

Group 1: 41 patients were severely disabled with an average pre-treatment Webster Rating Score of 17.63. The maximum disability rating attainable on this score is 30. Twenty-seven patients (66%) had had previous stereotactic procedures, 12 of them bilateral.

During the first two years of treatment with *l*-DOPA there was a significant improvement in all symptoms of Parkinson's disease and the Webster Rating Score fell by 43% to an average of 10.05. Then a gradual and modest decline appeared and, during the third to fifth years of sustained treatment, 63% of these patients scored a little worse than in the first two years, but only 5% were worse than they had been before taking *l*-DOPA. While rigidity, tremor and akinesia increased to only a slight to moderate degree, there was a more marked deterioration in the patients' gait and equilibrium. Start hesitation, shuffling with small steps and "freezing" reappeared and occasionally resulted in falls.

Group 2 comprised 89 patients who were only moderately disabled with an average Webster Rating Score of 9.39 when treatment with *l*-DOPA was begun. Twenty-nine of them (33%) had been previously subjected to thalamotomies, of which only five were bilateral.

A good response to *l*-DOPA was maintained during the first two years of treatment when the Webster Rating Score improved by 54% to an average of 4.36, but it then regressed to 4.65 during the third and fourth years and declined further to an average of 6.54 in the 37 patients of this group who had taken the drug for longer than four years. While there was no significant difference between the two groups in the Webster Disability Ratings, which include some minor and relatively insignificant symptoms, such as loss of arm swing, the degree of progression of gait disorders was materially less in Group 2: the gait of only 20% of patients deteriorated after the second year of treatment compared to 55% of patients in Group 1 ($p < .0005$).

Neither the number of patients affected, nor the clinical features and severity of these progressive gait disorders in Groups 1 and 2, were influenced by a previous thalamotomy.

Group 3 included only 10 patients. All of them showed an initial rapid and spectacular improvement on relatively small doses of *l*-DOPA, but soon developed violent and distressing choreiform movements of the limbs and painful dystonic postures of the feet and toes. These demanded a reduction in the dose of *l*-DOPA to sub-optimal levels. Six of these patients (60%) had had previous thalamotomies (all unilateral). The drug induced abnormal movements were either completely absent or greatly diminished in the limbs for which the thalamotomy had been performed.

These dyskinesiae cannot be attributed to structural lesions in the extra-pyramidal system and their cause remains undetermined. The more attractive hypotheses include abnormal receptor sensitivities outside the nigro-striatal pathway, the action of O-methylated derivatives of dopamine (Ericsson, 1971), or the displacement of transmitters of the autonomic nervous system (Barbeau, 1975).

Group 4 refers to only eight patients who experienced marked diurnal fluctuations in performance (the 'on-off' phenomenon), alternating from periods of almost normal motor performance to periods of hypotonia and severe akinesia. These fluctuations appeared only after 18-24 months of continuous treatment with *l*-DOPA, usually recurred regularly at a specific time of day and persisted for 2-4 hours. In some of these patients severe dyskinetic movements occurred only during the periods of akinesia. Stereotactic thalamotomies—all unilateral—had been performed on five patients (62.5%) and three of these had suffered from Parkinson's disease for more than 11 years. Anomalies in the absorption of *l*-DOPA from the gut, or in the rate of metabolic turnover of dopamine may be the cause of these striking fluctua-

tions in the patients' physical capabilities; the periods of hypotonia and severe akinesia may be attributed to a temporary deprivation of dopamine at the nigro-striatal synapses or receptor sites.

The 18 patients in Groups 3 and 4 were separated from the remaining 130 patients of this study because their clinical status was greatly influenced by pharmacokinetic factors, due entirely to the administration of *l*-DOPA and in no way related to the pathological process which causes the natural progression of Parkinson's disease. Comparing the proportion of patients who had a prior thalamotomy in Groups 3 and 4 with the first two groups it may be concluded that stereotactic surgery protected the patient only from drug-induced dyskinetic movements in the limbs for which the thalamotomy had been performed, and had no influence on the occurrence of the 'on-off' phenomenon.

The distribution of the 67 patients who had had stereotactic thalamotomies before receiving *l*-DOPA in the four groups described in this report is as follows:

	Prior thalamotomy	No thalamotomy
Group 1	27 (66%)	14 (34%)
2	29 (33%)	60 (67%)
3	6 (60%)	4 (40%)
4	5 (62.5%)	3 (37.5%)
	67	81

It is not surprising that the largest proportion of operations was performed on the most severely disabled patients of Group 1. This has to be taken into account when comparing the progress of the operated with the non-operated patients of the entire series.

An analysis of the severity of specific symptoms and of the Webster Rating Scale before *l*-DOPA therapy was instituted shows that the patients who had a prior thalamotomy were more severely disabled than those who had not been subjected to surgery (Table IV). Although tremor was almost always confined to the non-operated side, or involved the head, it was still a little more severe in the patients who had unilateral thalamotomies only. Gait disabilities were scored from 0 (normal gait) to 4 (unable to walk unaided). The figures shown in Table IV are the average gait disability score for each group. As the Webster

TABLE IV

Severity of Symptoms and Disability Scores before l-Dopa Therapy

	Operated 67 patients	Non-Operated 81 patients
Rigidity:		
None – Mild	58%	74%
Moderate – Severe	42	26
Tremor:		
None – Mild	61	69
Moderate – Severe	39	31
Akinesia:		
None – Mild	25	22
Moderate – Severe	75	78
Average Gait Disability Score:	2 (50% disability)	1.3 (32.5% disability)
Average Webster Rating Score:	12.8 (42.7% disability)	11.2 37.3% disability)

Rating Score includes relatively minor disabilities, such as the degree of facial immobility, loss of associated movements during walking, and seborrhoea, the small difference in this score does not give a true picture of the greater severity of Parkinson's disease in the group of patients who had had prior stereotactic procedures.

It was mentioned earlier that a slow, gradual progression of Parkinson's disease appeared in from 50-60% of patients during the third to fifth years of sustained *l*-DOPA therapy. The extent of this deterioration varied a little for the specific symptoms of Parkinson's syndrome, but the patients' gait showed the greatest decline. Prior thalamotomy appeared to have little or no effect on this natural progression of the disease. The proportion of patients who obtained marked improvement in rigidity fell from 17% during the second year to 7% during the fifth year of treatment in the operated group, compared with a slight fall from 24% to 21% in those who had not been subjected to surgery. In 7% of patients who had had thalamotomies rigidity was worse during the fifth year than before they received *l*-DOPA, compared with only 3% in the non-operated group. The same did not apply to tremor where the proportion of patients markedly improved was maintained in both the operated and non-operated groups. None of those who had had a thalamotomy were worse than before they received *l*-DOPA, in contrast to 3 of the 33 non-operated patients (9%) who had taken the drug for more than 4 years. Improvement in the severity of akinesia due to *l*-DOPA was also maintained a little better in patients with a prior thalamotomy: the proportion of patients with marked improvement fell from 16% to 10% in the operated group compared to a fall from 28% to 18% in those who had no surgery. During the fifth year of treatment with *l*-DOPA the degree of akinesia was worse than before the drug was given in one of 30 operated and in 2 of 33 non-operated patients.

No significant difference between the two groups was observed in the progression of gait disorders. The gait disability score prior to *l*-DOPA therapy fell by 50% from a score of 2.0 to 1.0 during the first two years of treatment with *l*-DOPA in the operated group, compared with a fall of 69% from a score of 1.3 to 0.4 in those who had no prior surgery. During the fifth year of treatment the gait deteriorated to a score of 1.3 (35% improvement on pre-treatment disability) in patients who had had a thalamotomy, and it declined also to a score of 0.7 (46% improvement on pre-treatment disability) in the non-operated group.

When the overall improvement during *l*-DOPA therapy was calculated from the Webster Rating Scale, the operated patients had a score of 12.8 before treatment, which fell to 7.4 during the first two years and then rose again to 8.4 in the fifth year of treatment—an improvement of 41% and 34% respectively. In comparison, the non-operated group prior to *l*-DOPA therapy had a lower Webster Score of 11.2, which fell by 53% to 5.3 and then rose to 7.0 (improved by 37.5% on the initial score) during the fifth year (Figure 1).

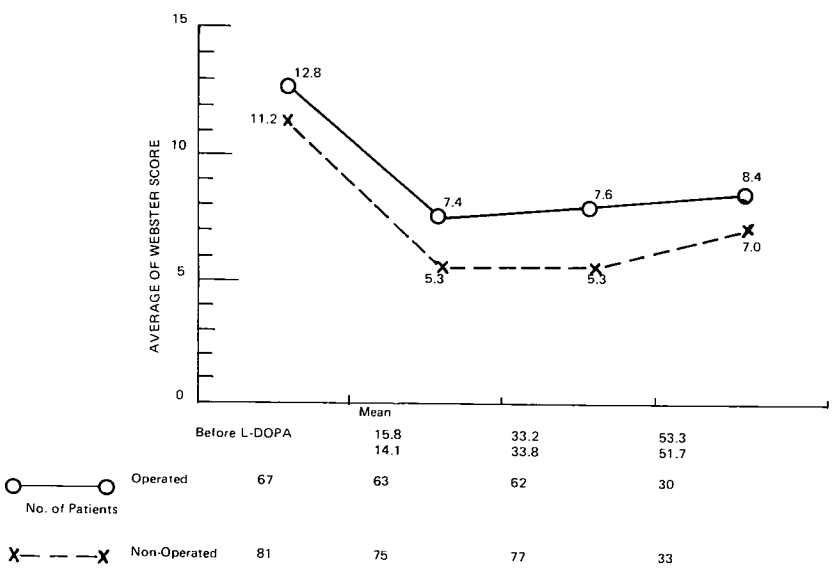

Fig. 1. Influence of stereotactic surgery on long-term l-DOPA therapy in Parkinson's disease. See text.

The intellectual state of the patients before and during *l*-DOPA therapy did not differ in the two groups, nor did a prior thalamotomy appear to contribute to the infrequent occurrence of hallucinations, confusion, or psychotic states during treatment with *l*-DOPA (8% of the operated compared with 11% of the non-operated patients). The average daily doses of *l*-DOPA taken by the patients were similar for the two groups.

Apart from the protection which a prior thalamotomy afforded against *l*-DOPA induced involuntary movements and dystonic postures, this operation had no influence on gastro-intestinal side effects or on the postural hypotension occasionally aggravated by *l*-DOPA.

SUMMARY AND CONCLUSIONS

It is generally recognised that stereotactic thalamotomy is an excellent operation for the relief of rigidity and tremor, while it has little or no effect on the akinesia, dysarthria and disorders of gait and equilibrium in Parkinson's disease. The discovery of *l*-DOPA was a major step towards a more complete therapy of Parkinsonism with a beneficial effect on those disabilities which are not alleviated by surgery. As the majority of Parkinsonian patients who had had a thalamotomy in the past required treatment with *l*-DOPA in later years, it is no longer possible to study the long-term results of thalamotomy alone.

The observations presented in this report show that the group of patients who had had prior stereotactic procedures were generally more severely disabled before *l*-DOPA treatment was begun than the non-operated group. It is impossible to calculate how much this difference in severity influenced the patients' subsequent progress during sustained *l*-DOPA therapy. It is, therefore, of considerable interest that the proportion of patients who showed a progression of their Parkinson's disease, and the extent of their decline during the third to fifth years of *l*-DOPA treatment, did not differ significantly in the operated and non-operated groups.

Based on the Webster Rating Scale, 30 of the 56 patients (53.6%) in Groups 1 and 2 of this study who had had a thalamotomy were worse during the third to fifth years than they had been during the first two years of treatment with *l*-DOPA. This is not significantly different from the 45 patients of 74 (60.8%) in these two groups who had not been subjected to stereotactic surgery.

The necessity of regular supervision of patients receiving *l*-DOPA provided an opportunity for study of the long-term effect of thalamotomy. This established that neither tremor nor rigidity recurred after a correctly placed lesion in the lateral ventral nucleus—at least during the 5-15 years post-operative observations of this study. Furthermore, during treatment with *l*-DOPA, finger dexterity was usually better in the limb for which a unilateral thalamotomy had been performed. It is now becoming clear that thalamotomy is a more effective treatment for rigidity and tremor than *l*-DOPA alone. This operation also inhibits the *l*-DOPA induced involuntary movements and could be considered in selected patients with severe Parkinsonism where these dyskinesiae preclude the use of optimal doses of *l*-DOPA.

Although treatment with *l*-DOPA has improved both the duration and quality of life of the vast majority of Parkinsonian patients, it has now become obvious that this drug can only retard, but not arrest, the natural progression of Parkinson's disease.

Dopamine deficiency is only the result of a progressive pathological process, which includes a loss of pigmented cells in the compact zone of the substantia nigra and in the locus coeruleus but, in spite of the great therapeutic advances in recent years, the primary cause of Parkinsonism remains an enigma.

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A UNIQUE CASE OF DERANGEMENT OF VITAMIN B12 METABOLISM

MICHAEL ANTHONY and ALAN C. McLEAY*

Vitamins are essential precursors of coenzymes, the latter acting as acceptors or donors of chemical groupings or atoms that are removed from, or contributed to, the substrate during an enzymatic reaction. Inherited disorders of vitamin metabolism are rare and result in disturbance of some step that makes the coenzyme form of the vitamin accessible to the enzyme. Vitamin responsiveness, either biochemical or clinical, indicates that a block in biosynthesis is 'leaky', or that an unfavourable relationship between enzyme and coenzyme can be overcome.

In mammals there are only two enzymes known to require vitamin B12 derivates as coenzymes for catalytic activity. One is N5-methyltetrahydrofolate homocysteine methyltransferase, required for the conversion of homocysteine and homocystine to methionine, and the other is methylmalonyl coenzyme A mutase, necessary for the conversion of methylmalonate to succinyl coenzyme A, for the latter's entry into the Krebs (tricarboxylic acid) cycle. The first enzyme requires as coenzyme methylcobalamin (Me-B12) and the second adenosylcobalamin (Ado-B12). The metabolic abnormalities resulting from defects in vitamin B12 coenzymes are shown in Figure 1.

So far, there have been four reported cases of deficiency of both vitamin B12 coenzymes in the same patient. Two of these patients have died before proper treatment was instituted and two others are still alive and in them the defect is quite mild. (Levy *et al.*, 1970; Goodman *et al.*, 1970; Dillon *et al.*, 1974).

As far as we are aware, the patient described in the present paper is the first with a severe form of the disease, who has been treated successfully over the last three years and whose condition has improved significantly since the beginning of therapy.

CASE REPORT

History

The patient was a female born in July 1969, the fifth child of unrelated parents. The mother's pregnancy was normal and the patient was delivered by planned Caesarean section. She sat up, crawled and walked a few months later than her siblings. At 18 months the mother noted that the child was not comprehending spoken words normally since, although able to do such things as open and close doors, use keys, get toys out of boxes etc., she would not respond to verbal commands to go and do these tasks. At the age of 2 years her speech consisted of only a few isolated words. At the age of 18 months and again at 2 years she had had periods of several days during which she was pale, tired, unsettled and lethargic, sleeping for long periods, 14 to 20 hours at a time. On both occasions she was treated with iron-containing tablets and improved. At the age of 3 years she had a severe attack of influenza, following which she developed episodic lethargy, became hyperactive, developed drooping and fluttering of her eyelids, the latter particularly in bright sunlight. She seemed to have poor control of her legs whilst walking and was somewhat clumsy. The mother considered that the volume of her speech and vocabulary were reduced following a recent episode of influenza and that there had been some degree of regression in the child's mental state. She related poorly to other children. There had been two episodes of jerking of limbs, both whilst travelling in a car, without loss of consciousness or other associated epileptic phenomena.

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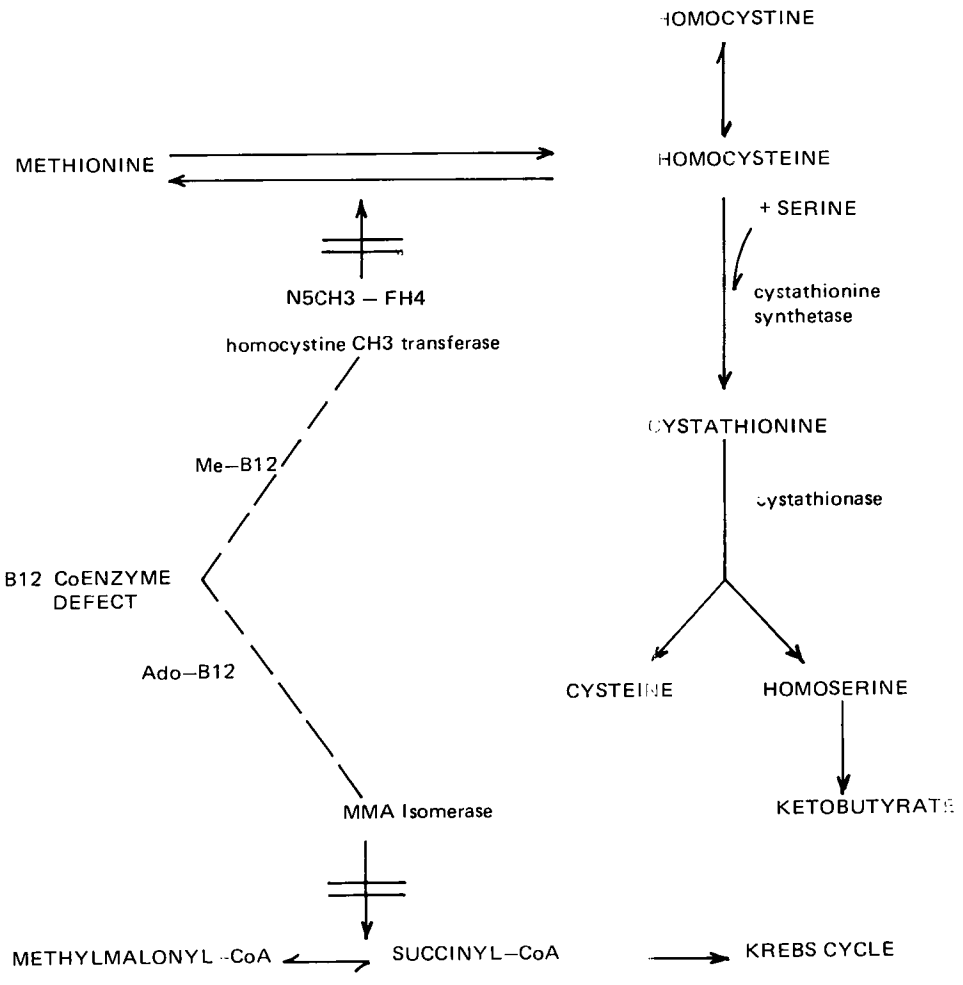

Fig. 1. B12 co-enzymes and aminoacid metabolism.

Family History

One brother, born in 1960, died aged 5 years of an undiagnosed progressive illness. The mother's pregnancy and labour were normal, but the boy had had feeding difficulties since birth. At 9 months of age had had unexplained high fever, repeated on several occasions subsequently. He sat up at the age of 12 months, crawled at 18 months, walked at 2½ years, but never walked properly and never developed normal speech. At about 3½ years of age he began to deteriorate with alternating episodes of drowsiness, irritability, ataxia, disturbed behaviour and increasing feeding difficulties. He eventually became comatose and finally died 4 months later. No autopsy was performed. Investigations, which included blood count, search for urinary metachromatic granules and examination of cerebrospinal fluid, gave normal results except that the pneumoencephalogram showed dilatation of the lateral ventricles.

A first cousin of the patient, now aged 10 years, tired easily and slept excessively, but both these symptoms were controlled by large daily doses of a combination of vitamin and mineral tablets, obtained by the mother from the local health food store. On examination, in April 1974, he was found to have subnormal intelligence, some reading difficulties, mild cerebellar dysarthria and limb inco-ordination. Serum vitamin B12 and folate levels and plasma and urine aminoacid chromatogram patterns were normal.

Examination

The patient was first seen in September 1972 at the age of 3 years and 3 months. Examination revealed a child with blonde hair, blue eyes and a vacant stare, running aimlessly around the room, with frequent fluttering of the eyelids and some degree of upward rotation of the eyeballs—as though in a petit mal episode. Height and weight were in the 90th percentile and head circumference was in the 75th percentile. A mild degree of clumsiness in the upper limbs and ataxia in the lower limbs could be observed intermittently and all four limbs were hypotonic. The tendon jerks were brisk in the lower limbs and the plantar responses were bilaterally equivocal. The remainder of the physical examination was normal.

Investigations

(A) Blood:—

Serum vitamin B12	–	1505 pg/ml	(normal range 190-900)
Serum folate	–	19.6 ng/ml	(normal range 3.5-16)

Plasma aminoacid chromatogram—

Methionine	–	0.005 μmole/ml	(normal range 0.015-0.025)
Homocystine	–	0.011 μmole/ml	(normal range 0-0.001)

Also raised levels of alanine, glycine, proline and serine.

(B) Urine:—

Methylmalonic acid	–	233.6 mg%	(normal range 0-12 mg/24 hrs)
Chromatogram	–	Methionine	0 (children 0-5 mg/24 hrs)
	–	Homocystine	increased

(C) Normal results were obtained in relation to the following:—
full blood count, blood ammonia, serum electrolytes, blood urea, serum uric acid, serum calcium, CSF examination, microscopic examination of urine, urine and stool cultures, thyroid function tests, skull radiographs, radiological bone age, electroencephalography, pneumoencephalography, Schilling's test, and biopsies of nerve, muscle and rectum.

(D) Nerve conduction studies—velocities slightly slowed for age.

(E) Plasma and urine aminoacid chromatogram patterns of the mother and the patient's elder sister (5 years her senior) were normal.

Treatment

This consisted of hydroxycobalamin 1 mg IM daily, pyridoxine 50 mg daily, folic acid 15 mg daily, choline 5g daily and a low protein (30 G daily) diet. Reasons for this combination of treatment are given in the discussion.

Progress

There was a marked mental and physical response in the first 12 months of therapy. Speech, co-ordination and manipulative skills improved rapidly and the episodes of drowsiness and irritability subsided. The patient became more attentive, behaviour became more purposeful and it became possible for her to communicate with other children through speech and action for the first time. However, she remained moderately mentally retarded and at the age of 6 years she had a mental age of 4 years and 6 months. Speech remained abbreviated with a short span. She was intolerant of sunlight or bright lights and her eyelids would flutter and her eyeballs roll upwards, though temporarily. Anti-convulsants had no effect on this symptom, but dark glasses reduced its severity considerably. The patient had a peculiar stale smell of her body, which was noted from the beginning of treatment. Changes in plasma and urine aminoacid levels and urinary methylmalonic acid before and during treatment are shown in Table I.

TABLE I

	PLASMA		URINE	
Normal Range	METH 0.015–0.025 μmole/ml H.CYS 0–0.001 μmole/ml		METH 10 – 25 mg/G creatinine H.CYS trace, MMA 0–12 mg/24 hr.	
	Before Treatment	During Treatment	Before Treatment	During Treatment
Methionine	0.005	0.04	0	24
Homocystine	0.011 0.034	0	slight increase	0
Methylmalonic Acid			933.6 mg/24 hrs	2.64 mg/24 hrs

DISCUSSION

The main features of the case described are mental retardation, poor development of speech, mild cerebellar disturbance and biochemical abnormalities comprising

(a) in blood—high serum levels of vitamin B12 and folic acid, raised plasma levels of homocystine with subnormal levels of methionine. After the ingestion of an amino acid load, plasma clearance of certain acids was abnormally slow, suggesting the presence of metabolic difficulties in the handling of some of these acids.
(b) in urine—raised levels of homocystine, but no detectable amounts of methionine. The excretion of methylmalonic acid was grossly increased.

The unique combination of high levels of homocystine and low levels of methionine in blood and urine and methylmalonic aciduria, suggested the presence of a metabolic disturbance of both sulphur containing amino acids as well as methylmalonic acid. In the first instance homocysteine, from which homocystine is derived, could not be remethylated by betaine and in the second methylmalonate could not be converted to succinate, because in each case the respective enzyme could not operate in the absence of vitamin B12 coenzymes which catalyse both reactions.

The various substances given to our patient, which we considered would be of therapeutic value and the reasons for their administration are as follows

1. Hydroxycobalamin in large daily doses. Levy *et al.* (1970) have demonstrated that cultured fibroblasts from their case, which was very similar to ours, metabolised succinate at subnormal rates and that this was corrected following the addition of hydroxycobalamin to the culture medium. Further, Goodman *et al.* (1970) have demonstrated in one of their patients that administration of large doses of hydroxycobalamin reduced both the homocystinuria and methylmalonic aciduria.
2. Folate was administered on the assumption that the deficiency of N5 tetrahydrofolate homocysteine methyltransferase activity could be improved by increasing the amount of tetrahydrofolate, which forms the basis of the enzyme molecule. This would increase the rate of conversion of homocysteine and homocystine to methionine.
3. Pyridoxine has been shown to lower serum methionine and homocystine in patients with homocystinuria (Stanbury *et al.* 1972). At least this should reduce the possible toxic effects of homocystine on the various body tissues, including the nervous system.
4. Choline orally accelerates the methylation of homocysteine by acting as a methyl group donor, leading to the decrease of homocystine and increase of methionine content in body tissues.
   The fact that blood and urine levels of both amino acids returned to normal during treatment with the above four agents, confirmed that this form of theoretical approach was correct.
5. Finally, the purpose of the low protein diet was to prevent excessive ingestion of methionine and the subsequent enhancement of homocystinaemia and homocystinuria, with their possible tissue damaging effects. It must also be appreciated that high homocystine blood levels lead to increased formation of α-ketobutyric acid which can lead to metabolic acidosis.

In view of the unusual features of this case and those of the other four reported cases, it appears that the discovery of homocystinuria in a patient does not give a complete diagnosis until both folate and vitamin B12 metabolism have also been thoroughly studied. The usual type of homocystinuria due to cystathionine synthetase deficiency is treated with low methionine diet and large doses of pyridoxine, that due to tetrahydrofolate deficiency requires folate in addition, whereas that due to defects in vitamin B12 coenzymes can only be treated along lines similar to those used in our case.

As regards the genetics of the case, it would appear that inheritance is along autosomal recessive lines and that the patient is—and her dead brother was—heterozygotes. Sex linked inheritance is ruled out because of the apparent male-to-male transmission in the case of the dead brother. If the patient's cousin is affected by the same disorder, then this would suggest parental consanguinity, which was not the case, or that the two brothers (fathers of the patient and her first cousin) must have married unrelated women who were both carriers of the same rare gene—the odds against this being almost astronomical. The most likely probability is that the cousin does not suffer from the same disorder, as was shown by the normal plasma and urine amino acid chromatogram patterns, normal vitamin B12 and folate in blood and absence of methylmalonic aciduria.

We realize that the presentation of the case is incomplete, in that metabolic information is not available from the patient's father and her sibs (except her older sister), or the cousin's parents and his sibs. It would only be when this information became available that the extent of the metabolic defect and its mode of inheritance could be determined in this family.

SUMMARY

The case is described of a child, aged $6\frac{1}{2}$ years, with retarded mental development, mild neurological signs and abnormal metabolism of sulphur-containing amino acids and methylmalonate, due to an inborn error in the formation of vitamin B12 coenzymes. The patient was treated for almost three years with hydroxycobalamin, folic acid, pyridoxine and choline. Though physical growth was normal, she continued to demonstrate a moderate degree of mental retardation. A brother of the patient died at the age of 5 years, probably of a similar, but undiagnosed, disorder.

As far as we are aware there are only four other reported cases similar to the case described here. Two years, probably of a similar, but undiagnosed, disorder.

As far as we are aware there are only four other reported cases similar to the case described here. Two of these patients died and in the other two the defect was so mild that no treatment was necessary. It would appear that our patient was the only severe case who has been kept alive with treatment and who, in fact, showed appreciable improvement during the follow-up period, which to date amounts to 3 years and 3 months.

For reasons detailed in the discussion, it is suggested that the diagnosis of homocystinuria is not complete until studies of folate and vitamin B12 metabolism are undertaken at the same time, so as to identify the metabolic defect(s) responsible for the condition.

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EPILEPSY AND DRIVING

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INTRODUCTION

The question of the safety in driving motor vehicles of drivers, both actual and potential, who suffer from epilepsy has been a matter of controversy for many years. Regulations governing this have differed from one country to another and even within Australia from State to State. In this country recommendations have been made by the National Health and Medical Research Council (fifty eighth session) and the Australian Association of Neurologists. Tasmania was prominent in adopting an enlightened view on this question and as a result of certain submissions made by the Tasmanian State Department of Health, the N.H. and M.R.C. in 1966 passed the following resolution: "in view of the obvious need for factual information on the subject of epilepsy and licence to drive, the Tasmanian State Department of Health could make a very valuable contribution to traffic injury research by setting up an investigation to study this problem". Such a scheme came into effect from January 1st, 1967, whereby all applicants for a driving licence in whom epilepsy had been admitted, all drivers who sustained an accident as a result of suspected epilepsy and all drivers in whom there was a reasonable suspicion of epilepsy were examined by the author acting in an advisory capacity to the Administrator of Road Transport. In collaboration with the State Department of Health, the Transport Department and the Police Department, a survey of this scheme has been conducted in the Department of Medicine, University of Tasmania. The objectives were as follows:

1. Assessing the contribution made to the total number of road traffic accidents by drivers suffering from epilepsy, where epilepsy was considered to be the cause of the accident.
2. Estimating the number of accidents resulting from a group of actual and potential drivers suffering from epilepsy who were initially or subsequently approved to drive—in other words, an attempt to judge the efficacy of the adopted screening methods.
3. Assessing the proportion of the population with epilepsy who are actual or potential drivers, who admit to this disorder.
4. Examining the association between epilepsy and alcohol.

METHODS

Every applicant in Tasmania for a Learner's Licence, Driver's Licence, Licence to drive a Licensed Passenger Vehicle, Driver's Licence Extension and Renewal of Driving Licence, who admitted to any form of epilepsy, actual or suspected, was referred for a medical examination to their local medical practitioner. The applicant was then referred to the author for examination together with the medical report from the medical practitioner. (In the case of all applicants to drive a Licensed Passenger Vehicle, medical examination and report were obligatory). Every driver who had been involved in an accident in which epilepsy was the cause, actual or suspected, was referred for examination. Finally, referrals were obtained from any driver who, as a result of information received by the Police or Transport Department, was

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suspected of suffering from epilepsy, after they had first been examined by their local medical practitioner. The following specific information was obtained about each examinee: source and reason for referral, duration and description of epilepsy, type and dose of medication or date of cessation of medication, duration of driving experience, details of accidents due to epilepsy and other causes, traffic offences, approval or disapproval of driving licence with dates, details of any further epilepsy following examination, information as to alcohol consumption. The survey began on January 1st, 1967, and concluded December 31st, 1975. The following recommendations were adopted throughout the survey for approval to drive:—

A driving licence would not be issued to a person with a history of epilepsy after the age of 10 years unless the person (1) had had no manifestations of epilepsy during the preceding two years; (2) was under regular medical supervision if he or she had suffered an attack within the previous five years; and (3) abstained from alcohol.

In the case of a person having a further fit after having been well controlled on treatment for more than three years and whose treatment was then ceased on medical advice, provided he returned to his former dose of anticonvulsants and fulfilled the other criteria, he was then permitted to drive after a further six months' probation period. Those who terminated their own therapy or who were irregular with their medication had again to achieve a two year period of freedom from fits. An isolated single seizure required full investigation and in general a six month waiting period, except in the case of a seizure resulting from alcoholism or if it followed a head injury known to be associated with a high incidence of epilepsy (Jennett 1962) when in both cases a two year fit free period was required.

No licence to drive a licensed passenger vehicle was issued to any person who had epilepsy at any time after the age of three.

RESULTS

220 persons were examined of whom 15 were discarded from the series due to doubt about the diagnosis, leaving 205 persons upon whom this survey is based (Table I).

TABLE I

Epilepsy and Driving Survey 1967–1975

Total Persons Examined with History of Epilepsy	205
Total Persons Examined Admitting Epilepsy	142

The total number of accidents due to epilepsy was 43, actual bodily injury occurring in the minority. The Australian Bureau of Statistics (Tasmanian Statistics 1975) supplies information about road traffic accidents but to be included in these statistics actual bodily injury (or death) must also occur. The mean population for 1975 was partially estimated and the number of accidents for 1975 averaged from the previous 8 years. The contribution made to the total number of road traffic accidents by drivers suffering from epilepsy in which epilepsy was the cause of the accident was 0.3%.

Of the 43 accidents due to epilepsy, the driver had not disclosed epilepsy previously in 33. Thus approximately 16% of the total number examined had an accident due to epilepsy which they had not disclosed on the original application nor on the renewals. In eight instances, the accident occurred as the result of a first attack of epilepsy (Table II).

TABLE II

Accident Rate

Total Accidents due to Epilepsy	43
Accidents due to Epilepsy where Epilepsy was not admitted	33
Accidents due to a first attack of Epilepsy	8
Accident rate for Epilepsy	0.3%

Twenty-two applicants were referred for examination following information supplied to the Police or Road Transport Department (excluding all those in whom an accident had occurred as the result of epilepsy). When these were added to the 33 drivers who had an accident due to epilepsy which had not previously been admitted, it was seen that 55 actual or potential drivers failed to disclose epilepsy, approximately 27% of those examined (Table III).

TABLE III

Non-Disclosure of Epilepsy

Persons referred following information from police or R.T.D. (ecluding accidents)	22	(10.75%)
Total Persons Examined who failed to admit to Epilepsy	55	(27%)

122 applicants were initially approved to drive, 83 were initially unacceptable. Not one of those initially approved to drive subsequently had a fit. Of the 83 unacceptable initially, 50 were ultimately licensed to drive, five of these subsequently had a fit and in two cases resulted in an accident, and in both these cases the drivers had previously sustained an accident due to epilepsy. Thus 10% of those ultimately licensed had a subsequent fit and the number of accidents resulting from those initially and ultimately licensed to drive was two out of 172 (Tables IV & V).

TABLE IV

Analysis of Initial Assessment

Persons initially approved to drive	122
Persons initially unacceptable	83

TABLE V

Analysis of Screening Methods

Persons Ultimately approved	50
Persons intially approved who later had a fit	0
Persons ultimately approved who later had a fit*	5 (10%)

* in two cases resulting in an accident

The incidence of epilepsy in the population is stated to be 0.63 new cases annually per thousand (Research Committee of the Australian College of General Practitioners, 1960). In Tasmania, the population 16 years and over is calculated to be approximately 270,000. It is variously stated that 20-40% of adult epileptics hold driving licences (Phemister 1961; Maxwell and Leyshon, 1971). Thus 57 new cases should be presenting themselves for examination each year. In actual fact the number who disclosed epilepsy over the nine year period was sixteen per year.

The prevalence of epilepsy in adult life is accepted to be about 4 per 1,000 population. In Tasmania, there are therefore about 1,080 epileptics of driving age and, accepting that about 30% hold a driving licence, then there are approximately 328 drivers suffering from epilepsy in Tasmania at any one time. It will be seen that the number examined over the nine year period falls far short of this (Table VI).

TABLE VI

Incidence and prevalence of Epileptic Drivers in Tasmania

Estimated incidence of Epileptic Drivers	57
Actual number who disclosed Epilepsy each year	16
Estimated prevalence of Epileptic Drivers	328
Actual number of Epileptic Drivers ascertained by survey	205

There was a known association between epilepsy and alcoholism in 17 (8.3%), determined as the result of self-admission or Police reports (Table VII).

TABLE VII

Association with Alcoholism	17 (8.3%)
Number with sleep epilepsy	8*

* one eventually had an attack whilst awake.

There were eight persons in the survey suffering from sleep epilepsy, of whom only one had an attack whilst awake which followed two years of exclusively sleep epilepsy. In all instances, the initial attack occurred during sleep and they had a minimum of three fits over a minimum period of two years.

DISCUSSION

Even though large numbers of drivers with epilepsy fail to disclose their disability when applying for or renewing driving licences, the accident rate is acceptable low (0.3%). Even lower rates have been reported from Scandinavia (Lund 1966).

Moreover, eight out of the 43 accidents due to epilepsy occurred as the result of the first manifestation of this complaint and no legislation can affect this group. The accidents resulting from epilepsy caused negligible bodily injury. It seems unnecessary therefore to enact more restrictive legislation which would only have the effect of encouraging epileptic drivers still further to conceal their condition. It is realistic to see the problem of epilepsy and driving in perspective with other causes of road traffic accidents, notably alcohol. To quote but one set of statistics: in Tasmania in 1974, of 121 drivers involved in fatal traffic crashes, 50% of them had raised blood alcohol levels. 80% of these drunk drivers were 25 years of age or under and were responsible for killing 55 persons, 50% of the total killed in 1974. Their average blood alcohol was 0.129, their average age was 19½ and their average driving experience was 2½ years (Jacobson and Kelly, 1975). It is against this background we should ask ourselves whether our time, resources and energy are being properly directed.

The duration of anticonvulsant therapy after a person has had two fit-free years remains a contentious problem. In this series, one has insisted on a minimum of three years and as a general rule encouraged at least a five year period. Juul-Jensen (1964) showed that when anticonvulsant therapy was withdrawn from 200 patients who had been fit free for at least two years that about one third had a further seizure in the following four years, and of these patients half had their recurrence during the first two or three months; most of the remainder occurred within the first year. In the present series, of the five patients who subsequently had a fit after having been ultimately licensed to drive, in no case had the fit recurred after cessation of anticonvulsants on medical advice. One patient was still receiving medication, having previously been difficult to control and it would have been better to insist on three years freedom from fits (instead of two years) before licensing this patient. One who had had an accident previously and who had a subsequent accident as the result of a fit was found to be unreliable with his medication. One who had sustained a previous accident due to a fit, probably associated with alcohol, had ceased medication after only a few months and then some two years later had another fit resulting in an accident. One had a fit one year after ceasing medication, which had been taken for only two years. The fifth patient who had had a previous accident had ceased medication for three days ("run out of tablets") before the fit recurred. Thus if four out of five of these drivers had followed instructions concerning their medication it is unlikely that a further fit would have occurred. Ritter and Ritzel (1972) similarly found that the therapeutic discipline of traffic offenders was very bad compared to that of epileptics free of conviction. If three years are accepted as being the minimum period for continuing medication after the last fit, then the two year fit-free period before granting a license to drive, as recommended in the U.S.A. (Medical Guide for Physicians), the Netherlands, Denmark and by the Australian Association of Neurologists may be more ap-

propriate than the three year period adopted in Britain (Statutory Instrument, 1971), and Germany, as with this requirement the patient would be allowed to drive as soon as his medication was ceased. Indeed, in Denmark, Kiφrboe *et al.* (1973) believed that, as a result of a prospective survey, it was possible in the majority of cases to establish the prognosis three months after treatment has been initiated, and he would grant approval as a general rule after a period of observation of one or two years.

Although the number (4%) who had exclusively sleep epilepsy for a minimum of two years was too small for any conclusions, Gibberd and Bateson (1974) were able to study a much greater number of patients, admittedly in a retrospective survey. They found that in the first two years after an initial attack, 13 out of 76 had waking attacks but by the end of three years only another three had waking attacks, and thereafter over the next 12 years only another seven began to have waking epilepsy. In my view, therefore, providing the initial fit was during sleep and providing all subsequent fits were exclusively during sleep for a period of at least two years from the date the licence is to have effect, then approval to drive may be given until the first waking seizure occurs. In Britain, the Regulations insist on a period of three years (Statutory Instrument, 1971).

CONCLUSIONS

It is concluded that the following regulations approving the issue of driving licences to patients with epilepsy result in an acceptable low accident rate, are not unnecessarily restrictive and should therefore result in a higher proportion of drivers and potential drivers disclosing their disorder:

1. The applicant has had no manifestations of epilepsy whilst awake for at least two years before the date when the licence is to have effect.
2. In the case of an applicant who has had such attacks exclusively whilst asleep during that period, that no attacks have occurred whilst awake since before the beginning of that period of two years.
3. Anticonvulsant medication is continued for a minimum period of three years (and preferable for at least five years).
4. The applicant is under regular medical supervision if an attack has occurred in the previous five years.
5. The applicant abstains from alcohol.

SUMMARY

205 actual and potential drivers suffering from epilepsy were examined over a period of nine years in Tasmania under a State scheme whereby all such persons are referred to one neurologist. In Tasmania 0.3% of all road traffic accidents were due to epilepsy. 16% of the total who had had an accident had failed to disclose their disability and another 10% who were non-accident cases had similarly concealed their epilepsy. Only about 28% of the expected number (per year) of new cases of epilepsy in drivers disclose their complaint. Alcohol was a significant association with epilepsy in just over 8%. Medication should continue for at least three consecutive fit-free years and preferable five years. Only two out of 170 drivers approved to drive had a subsequent accident due to epilepsy.

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SOME ASPECTS OF TUBERCULOUS MENINGITIS IN SURABAYA

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With the eradication of poliomyelitis, smallpox and cholera, tuberculosis remains one of the major health problems in Indonesia. It is not only frequent in the low income group, but is infiltrating the middle income group. It is therefore not surprising that tuberculous meningitis is one of the commonest diseases seen in neurological wards in Surabaya.

Before the use of ethambutol and rifampicin in the early 1970's, treatment failures were frequent because of the following circumstances:

(i) patients arrived in hospital in a far advanced stage of the disease (the only hospital in the eastern part of Indonesia with a fully equipped Department of Neurology is in Surabaya, and often patients travelled a long distance to reach Surabaya).

(ii) mycobacterial resistance to streptomycin is very high because of the indiscriminate use of streptomycin (Sujudi, Chatim and Pratanto, 1969).

(iii) para-aminosalicylic acid (PAS) is not effective in tuberculous meningitis, since the drug does not pass the blood-brain barrier in either healthy or sick individuals (Oliveira, 1972).

When rifampicin and ethambutol became available in Surabaya, the author planned a double blind clinical trial, to study the effects of both drugs. As there were conflicting reports regarding the penetration of both drugs into the CSF, the author combined the use of isoniazid, ethambutol and rifampicin with protease to improve the absorption and anti-inflammatory effects of the combination (Kenitu Okita, 1969).

MATERIALS AND METHODS

All patients with tuberculous meningitis who were seen by the author in Neurological Clinics in Surabaya (at the University hospital or in private) between the 1st January, 1971 and 1st January, 1975 were asked to cooperate in this study. Originally this group comprised 83 patients but 3 patients did not continue long enough in the study to allow proper evaluation.

The diagnosis of tuberculous meningitis was based on:

(i) clinical findings of meningeal irritation e.g. neck stiffness and a positive Kernig or Brudzinski sign, and

(ii) evidence of tuberculosis in the CSF (by direct smear, culture or animal occulation)

On arrival all patients were seen by the author and one of his assistants. The severity of illness on the day of admission was assessed on a scale, which was a modification of those described by Thrupp (1964) and by the British Medical Research Council (Gilroy and Meyer, 1969). The patients' progress was followed with daily clinical examination by the author or one of his assistants, and by lumbar puncture at weekly intervals. The CSF was examined in an independant clinical pathological laboratory. All of the patients had already been treated with antibiotics (mostly penicillin), but had derived no benefit from this

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treatment. The day the controlled study began, all previous medication was withdrawn. None of the patients included in the study had any associated illness, e.g. malaria or typhoid fever.

The patients were allocated at random to two subgroups. One group received conventional treatment with isoniazid, PAS and streptomycin, with vitamin B complex and vitamin C tablets. The other group received isoniazid, ethambutol, rifampicin and serratio peptidase orally, with vitamin B complex injections.

All the antibacterial agents except streptomycin were prepared in identical capsules and coded in such a way that neither the investigator nor the patient knew who received INH/PAS and who received INH, rifampicin and ethambutol. The dosages were as follows: isoniazid 400 mg/day; PAS 300 mg/kg/day; streptomycin 1 gram/day; rifampicin 600 mg/day; ethambutol 750 mg/day. Dexamethasone was given to all patients who were in Stages 2, 3 or 4 of the disease.

The following initial laboratory examinations were carried out on each patient before administration of therapy: complete blood count and differential white cell count, platelet count, urinalysis and liver function tests, e.g. serum glutamic-oxaloacetic transaminase and serum alkaline phosphatase estimations and bromosulphthalein retention measurement. These tests were repeated at monthly intervals. As mentioned above the CSF was examined weekly in a laboratory independent of the Department of Neurology.

In all patients an EEG was taken initially and was repeated at monthly intervals. An echoencephalographic examination was done when there was a suspicion of developing hydrocephalus. Radiographs of chest, paranasal sinuses and mastoids were taken routinely.

RESULTS

Clinical Details

Breaking the trial code showed that 42 patients had received isoniazid, rifampicin and ethambutol and 38 patients had been given isoniazid, PAS and stremptomycin. The sex, race and age distributions of the patients included in the two treatment groups are shown in Table I and Table II. There was no significant difference between the two treatment groups regarding age.

TABLE I

Sex and radical distribution of the two treatment groups

Criteria	INH/S/P	INH/R/E
Male	20 (52.6%)	22 (52.4%)
Female	18 (47.4%)	20 (47.6%)
Indonesian	27 (71.1%)	31 (73.8%)
Chinese	11 (28.9%)	11 (26.2%)

TABLE II

Age distribution in the two treatment groups

Age in years	INH/S/P	INH/R/E
1–20	6 (15.8%)	7 (16.7%)
21–40	12 (31.6%)	13 (31.0%)
41–60	7 (18.4%)	8 (19.0%)
61–80	13 (34.2%)	14 (33.3%)

The severity of illness on the day of admission was assessed on a scale which was a modification of the scales described by Thrupp (1964) and by the Medical Research Council of Great Britain (Gilroy and Meyer, 1969) as follows:

Grade 1. fully conscious and rational, with signs of meningeal irritation but no focal neurological signs or signs of hydrocephalus.
Grade 2. mentally confused and/or with focal neurological signs e.g. external ocular muscle paresis or hemiparesis.
Grade 3. convulsions without coma or shock
Grade 4. coma and shock.

As can be seen from Table III, the distribution of patients with severe illness (groups 3 and 4) was nearly identical in the two treatment groups. A history of household contact with tuberculosis was present in 78 patients (97.5%).

TABLE III

Severity of illness of patients in the two treatment groups

Criteria of severity of illness	INH/S/P	INH/R/E
Grade 1	7 (18.4%)	8 (19.0%)
Grade 2	13 (34.2%)	13 (31.0%)
Grade 3	11 (29.0%)	13 (31.0%)
Grade 4	7 (18.4%)	8 (19.0%)

In the present series, the incidence of meningitis in relation to income is indicated in Table IV. The symptoms of tuberculous meningitis for the present series and for the series of Tahernia (1967) and Smith (1975) are shown in Table V. The findings on admission to hospital are set out in Table VI. The 63 patients with a depressed conscious state showed levels of awareness on admission to hospital as shown in Table VII. The state of awareness has been classified to correspond with the groupings used by Gilroy and Meyer (1969). The 49 patients with cranial nerve palsies showed abnormalities as set out in Table VIII.

TABLE IV

Distribution of income groups in 80 tuberculous meningitis patients

Income group		Number	Percentage
Low	(< Rp.60,000)	47	58.7
Middle	(Rp.60,000–200,000)	24	30.0
High	(> Rp. 200,000)	9	11.3

TABLE V

Symptoms in 80 tuberculous meningitis patients, and in the cases of Tahernia (1967) and Smith (1975)

Symptoms	Chandra (80)	Tahernia (38)	Smith (43)
fever	76 (95%)	84.2%	68%
headache	76 (95%)	55.2%	52%
vomiting	62 (77.5%)	76.3%	76%
anorexia	62 (77.5%)	–	66%
constipation	45 (56.3%)	42.1%	–
convulsions	24 (30%)	39.4%	7%

TABLE VI

Findings on admission to hospital in 80 tuberculous meningitis patients in Surabaya. For comparison, the date of Tahernia (1967) and (Smith (1975) are shown.

Findings	Chandra	Tahernia	Smith
fever	95%	84.2%	81.4%
neck stiffness	92.5%	50%	74.4%
positive Kernig sign	88.7%	–	–
depressed consciousness	78.7%	–	30.2%
cranial nerve palsies (3,4,6,7 nerves)	61.3%	31.5%	11.6%
choroid tubercles	13.7%	–	11.6%
papilloedema	21.2%		9.3%
hemiparesis	20%		

TABLE VII

Level of awareness in 63 patients with depressed consciousness

Level of awareness	Number of patients	Percentage
coma	15	18.7
semi-coma	19	23.7
stupor	5	6.3
obtundity	24	30.0
TOTAL	63	78.7

TABLE VIII

Cranial nerve palsies in 80 tuberculous meningitis patients

Cranial nerve	Number of patients	Percentage
oculomotor (only)	5	6.3
trochlear	2	2.5
abducens (only)	22	27.5
oculomotor plus abducens	16	20.0
facial	4	5.0
TOTAL	49	61.3

Laboratory Investigations

The blood sedimentation rate was abnormal in 34 patients (42.5%). The abnormal haematological findings are compared with those of Muller (1972) in Table IX. The CSF findings are set out in Table X. It should be mentioned that the sugar concentration in the CSF was examined in the fasting individual and that it was compared with a simultaneously measured blood sugar level. The CSF protein level was considered abnormal if it exceeded 45 mg per 100 ml.

EEG findings: The EEG which was done in all patients on their first days of admission, showed abnormalities in 63 patients (78.7%). The nature of the abnormal findings may be seen from Table XI. By way of comparison, it may be noted that Muller (1972) found EEG abnormalities in all his 6 patients with tuberculous meningitis.

Echo-encephalography: In 63 patients echo-encephalography was done. Abnormalities were present in 43 patients (Table XII).

TABLE IX

Blood sedimentation rate and leucocyte count in 80 tuberculous meningitis patients in Surabaya, compared with findings of Muller (1972)

Blood finding	Chandra (80)	Muller (32)
Increased sedimentation rate (> 20 min in first hour)	80%	60%
Leucocytosis (more than 9000/mm^3)	42.5%	40%

TABLE X

CSF findings in 80 tuberculous meningitis patients in Surabaya, and in the cases of Tahernia (1967) and Smith (1975)

Findings	Chandra (80)	Tahernia (38)	Smith (43)
increased pressure (higher than 180mm)	23.7%	frequent	–
increased leucocytes	100%	90%	90.7%
less than 100/mm^3	26.2%	26%	
100–300/mm^3	51.3%	50%	
greater than 300/mm^3	22.5	14	
decreased glucose concentration (compared with blood sugar level)	98.7%	84%	76.7%
increased protein level	92.5%	76.8	88.4%
colloidal gold curve abnormal	92.5	–	–
positive acid fast smear	45%		41.8%
positive acid fast culture	55%	–	–

TABLE XI

EEG findings in 80 tuberculous meningitis patients

EEG findings	Chandra (80)
slight diffuse disturbances	30%
slight diffuse disturbances with focal disturbances	25%
severe diffuse and focal abnormalities	23.7%
Total with abnormalities	78.7%

TABLE XII

Abnormal echo-encephalographic findings in 43 tuberculous meningitis patients in Surabaya, compared with the series of Kunst (45 patients)

Echo-encephalographic findings	Chandra (43)	Kunst (45)
deviation of the midline echo	0	0
enlargement of the III ventricle	43 (100%)	
smaller than 12mm	35 (81.4%)	82%
normal 7mm)		
larger than 12mm	8 (18.6%)	18%

Radiographic abnormalities: In 68 patients chest radiographic abnormality compatible with tuberculosis was found (see Table XIII).

TABLE XIII

Chest radiographic abnormalities in tuberculous meningitis patients

Chest X-ray	Chandra	Tahernia (1967)	Smith (1975)
abnormality compatible with tuberculosis	72.5%	26.3%	69.7%
miliary pattern	23.7%	10%	23.2%

Pneumoencephalography was done in only eight patients. In one patient arrest of air in the pontine cistern was noted. In the other patients only diffuse ventricular dilatation was seen. Arteriography was done on all patients showing a hemiparesis and in these revealed the picture of an arteritis.

Results of treatment: The result of treatment are set out in Table XIV. The results of treatment with conventional INH/Streptomycin and PAS therapy are comparable with results obtained in other Asian centres (Table XV). To compare further the results of treatment, the durations of fever (a temperature higher than 37°C) after initiation of conventional and of rifampicin/ethambutol therapy were compared (Table XVI). As CSF changes could usually indicate response to therapy in tuberculous meningitis, the times needed in the two treatment groups for the CSF sugar and cell counts to return to normal were compared. (Table XVII). (The normal values for the CSF cells were 5 per mm^3 and for the sugar content, 20 mg% less than the blood sugar content).

TABLE XIV

Outcome after conventional therapy and after INH, rifampicin and ethambutol treatment in 80 tuberculous meningitis patients

Outcome	INH/S/P(38)	INH/R/E(42)	x^2	P
death	13 (34.2%)	4 (9.5%)	5.26	<0.05
neurologic sequelae	15 (39.5%)	6 (14.3%)	6.95	<0.01
full recovery	10 (26.3%)	32 (76.1%)	17.72	<0.01

TABLE XV

Outcome of treatment with INH, streptomycin and PAS in Surabaya and in Iran

Outcome	Chandra (38)	Tahernia (38)
death	34.2%	42.1%
neurologic sequelae	39.5%	13.1%
full recovery	26.3%	44.8%

TABLE XVI

Duration of fever (37°C) after initiation of therapy

Treatment group	Mean duration of fever (days)
INH/S/P (37)	3
INH/R/E (39)	1

TABLE XVII

Time for CSF sugar level and cell counts to return to normal values after initiation of therpay

Treatment group	Mean duration in days	x^2	P
INH/S/P	80 days		
INH/R/E	28 days	16.736	<0.001

Side effects of therapy: Side effects occurred in both the INH/S/P treated group and in the INH/R/E treated group (Table XVIII).

TABLE XVIII

Frequency of side effects in 80 tuberculous meningitis patients treated with INH/S/P or INH/R/E

Side effects	INH/S/P (38)	INH/R/E (42)
dizziness	3 (7.8%)	0
optic nerve atrophy	3 (7.8%)	1 (2.4%)
nausea	6 (15.7%)	1 (2.4%)
liver function disturbance	0	1 (2.4%)
urticaria	5 (13.1%)	2 (4.7%)

DISCUSSION

Tables I, II and III show that there were no significant differences between the two treatment groups in relation to age, sex, race and severity of illness. It was remarkable that a history of household contact with tuberculosis was obtained in 97.5% of cases. This is especially important as tuberculous meningitis appeared not only in the lower income group, but also occurred in the higher income group (Table IV). Table V shows that fever was one of the frequent symptoms, a finding also obtained by Tahernia (1967) and Smith (1975). Headache was much more frequent in the present series than in Tahernia's and Smith's patients, probably because both of these latter authors reported cases of tuberculous meningitis in children.

Table VI shows the findings on admission in hospital in 80 tuberculous meningitis patients. The lower incidence of depression of consciousness in Smith's patients might be explained by the fact that the detection of slight disturbances of consciousness in children is difficult. Table VIII shows that the sixth was the cranial nerve and was most often affected, followed by the oculomotor nerve. There were 4 patients in whom only the facial nerve was affected. This emphasizes the need to examine every patient with a facial nerve disturbance carefully and to perform a lumbar puncture if in doubt as to the aetiology.

Table IX shows that a decreased glucose concentration in the CSF was one of the most frequent findings in our patients. It should be emphasized that the CSF glucose concentration should always be compared to the blood sugar concentration. In adult patients with diabetes mellitus and tuberculous meningitis the decreased glucose concentration in the CSF became apparent only if the glucose level was compared with the blood sugar concentration. Although Smith (1975) offered a countrary opinion, the author is convinced that one of the most constant findings in the CSF in tuberculous meningitis is a decreased glucose concentration. An increased pressure in the CSF was a grave prognostic sign as most patients showing this fell into Grades 3 or 4.

All the patients in the severely ill group (coma and shock) and some Group 3 patients exhibited a severely abnormal EEG with gross diffuse and focal disturbances. When their clinical condition improved, these EEG records became more normal. Most of the patients in Grade 1 (fully conscious without focal neurological signs) did not show any abnormalities in their EEG records.

An enlarged IIIrd ventricle was a frequent abnormal echo-encephalographic finding, but deviation of the midline echo was not found. When the clinical condition improved the echo-encephalographic picture returned to normal. An enlargement of more than 12 mm seemed a bad prognostic sign, as all the patients showing this degree of enlargement died. The enlargement probably was caused by obstructive hydrocephalus due to adhesions.

An abnormal chest radiograph was found in 72.3% of the patients (23% showed a miliary tuberculous pattern). The Mantoux test was positive in most of the patients, which is not surprising considering the extensive spread of the tuberculosis. The value of the Mantoux test as a sensitive screening investigation is doubtful in Indonesia, since most of the adult population show a positive Mantoux test. Choroid tubercules are indicative of a tuberculous infection and every general practitioner working in the tropics should be familiar with their appearance.

The results shown in Table XIV are not surprising as resistance to streptomycin shows an increasing trend from year to year. The dose of streptomycin given in the present study was 1 gram daily by intramuscular injection for two weeks and then thrice weekly for the remainder of the duration of therapy. No intrathecal therapy of any nature was given. Corticosteroids (dexamethasone) were given to all patients with Grade 2, 3 or 4 disease. The patient was considered recovered when the cell and the sugar content in his CSF had returned to normal. A control lumbal puncture was then made every month to ensure that no relapse occurred. When three successive lumbal puncture were normal, the patient was returned for examination every two months.

Tables XIV, XVI and XVII show the superiority of the INH/rifampicin/ethambutol combination over conventional antituberculous therapy. There were few side effects in the INH/R/E group. We were not sure if the optic atrophy in one patient was caused by the inflammatory process or by the drug ethambutol.

Pharmacology and mechanism of action: Rifampicin is a derivate of the rifamycin group and is remarkably effective against tuberculosis. It penetrates the blood brain barrier only slowly if the dura is inflamed. In normal individuals the rate of penetration is minimal (Oliveira, 1972). Ethambutol is another effective drug against tuberculosis. Like rifampicin it penetrates into the CSF in very few normal individuals, but in tuberculous meningitis patients the penetration is much better (Pilheu, 1971). Even though CSF concentrations of both drugs falls during prolonged therapy, therapeutic levels can be sustained for several months. In this context it should be mentioned that streptomycin only enters the CSF when the meninges are inflamed. PAS fails to enter the CSF in both normal and meningitic patients.

To improve the levels of absorption of rifampicin and ethambutol, both of which are given orally, and to decrease the inflammatory effects of tuberculous meningitis a protease (serratio peptidase) was given. As it is a digestive agent, protease should improve absorption of the antibiotics, and as it breaks down bradykinin it should exert an anti-inflammatory effect (Kenitu Okita, 1969).

Prognosis: In both treatment groups the mortality was highest in Grade 4 cases in whom coma and shock were present on admission. We agree with Freiman and Geelhuisen (1970) that the most important prognostic factor in the outcome of tuberculosis remains the level of consciousness.

Another bad prognostic sign was a severely abnormal EEG with both diffuse and focal disturbances. Most of the patients who died showed this pattern. Other grave prognostic signs were an increased pressure of the CSF and an enlargement of the IIIrd ventricle of more than 12 mm on echo-encephalography (95% of the patients who died showed both these findings).

SUMMARY

Eighty tuberculous meningitis patients who were seen in the neurological clinics in Surabaya between the January 1971 and January 1975 were asked to cooperate in a double blind clinical trial.

One group was given isoniazid, streptomycin and p-aminosalicylic acid, the other group was given isioniazid, rifampicin, ethambutol and a protease. The outcome after the treatment with isoniazid, rifampicin and ethambutol was significantly better than that with isoniazid, streptomycin and p-aminosalicylic acid. The clinical and laboratory symptoms and signs are reviewed in detail.

Acknowledgment: We are grateful to Ciba Geigy, who donated the rifampicin ("Rimactane"), to Takeda Ltd. who supplied the serratio peptidase ("Danzen"), and to Lederle, who supplied the ethambutol ("Myambutol").

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AN ANIMAL MODEL FOR THE STUDY OF DRUGS IN THE CENTRAL NERVOUS SYSTEM

G. J. G. PARRY*

The passage of drugs into the central nervous system and their effect on nervous system metabolism can be studied by examination of CSF. A detailed systematic study of CSF in humans is not ethically justifiable and a laboratory animal must provide the alternative. Most studies of CSF in animals have relied on sporadic sampling by cisternal puncture. Only a small number of workers have used models which enable repeated sampling of CSF. The present paper describes such a model which is cheap, simple and effective and offers definite advantages over the models previously described.

In New Zealand the sheep is an animal which is in plentiful supply and is relatively cheap to buy, costing about as much as a medium weight rat. The sheep is simple to maintain and work with and can be kept with equal facility indoors or out of doors for long periods. Most breeds are docile to handle. However, because the sheep is a ruminant it is unsatisfactory for studying drugs following oral administration, since absorption is slow and variable.

METHODS

The animal model

To obtain CSF a cisternal puncture is performed under aseptic conditions in an anaesthetised sheep. The equipment required is very simple: a 14 gauge needle and syringe, a flexible catheter with end and side holes and a stopper for the free end. The needle is introduced in the midline, 3-4 cm behind the external occipital protruberance. The neck is flexed and the needle advanced towards the tip of the animal's nose until CSF is obtained. The catheter is passed through the needle which is then withdrawn. The free end of the catheter is then plugged and sutured in position (Figure 1). CSF may then be sampled as required for as long as the catheter remains in place and patent. We have found that 10-20 ml of CSF can be withdrawn over a 12 hour period. No ill effects have been observed. A larger volume could not be withdrawn in one day, presumably due to low CSF pressure. Thus the volume available for each sample will depend on the frequency of sampling. A catheter may remain patent for at least 2 weeks and would probably remain so for longer, but we have generally removed catheters after a few days. Catheters may be reinserted on a number of occasions so that the animal need not run the risk of complications when not used in experiments.

Problems with this procedure are few. The cisternal puncture is simple. The large needle may produce slight bleeding but this is unusual once expertise is attained. The introduction of the catheter may also produce bleeding but a soft catheter and a gentle technique minimize this. Superficial infection occurred on one occasion but meningitis was not seen. Occasionally CSF flow was slow, probably due to malposition of the catheter. This could be overcome by rotating or slightly withdrawing the catheter.

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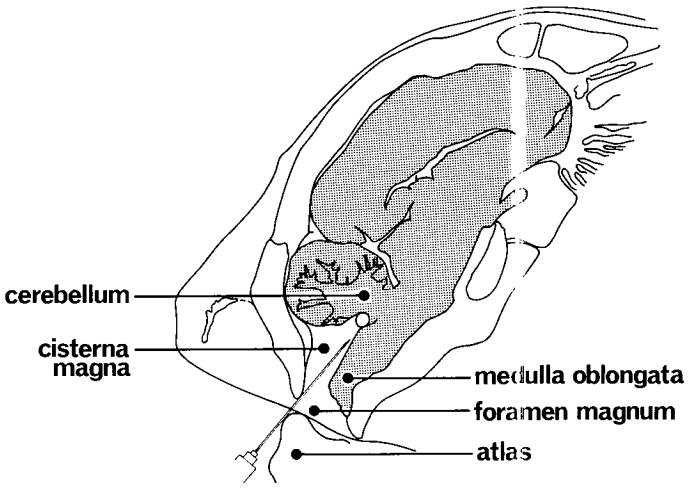

Fig. 1. Needle in cisterna magna for positioning catheter.

In the previously described animal models a guide was attached to the skull directing a needle into either the lateral cerebral ventricle or the cisterna magna. We found this method to be technically more difficult and more expensive in time and materials. Furthermore it was possible to withdraw only a small volume of CSF from the ventricular system, which limited the usefulness of these methods.

There are many potential applications for the present model. The passage of drugs such as antibiotics and cytotoxics into the central nervous system can be systematically studied. The effect of drugs such as socium valproate on gamma aminobutyric acid (GABA) metabolism, *l*-DOPA and bromocryptine on dopamine metabolism and of the anti-migraine drugs on serotonin and histamine metabolism, can also be studied. The model has the advantages of simplicity and economy to recommend it.

Clonazepam studies

The model has been used to study certain aspects of the pharmacokinetics of clonazepam. After placement of the catheter the animal was allowed to recover fully from the anaesthetic. A dose of 4 mg of clonazepam was given intravenously and blood and CSF were taken at 1, 5, 15, 30, 60, 120 and 240 minutes. In earlier studies samples were taken over a 24 hour period to determine serum half-life of clonazepam. CSF samples were immediately centrifuged and all samples were deep frozen for subsequent chromatographic analysis.

A highly sensitive and specific assay using gas liquid chromatography and an electron capture detector has been developed which allows measurement of clonazepam in body fluids in concentrations as low as 0.5 ng/ml. The details of the extraction are shown in Figure 2. The previously described methods are complex (de Silva *et al.*, 1974), and time consuming (de Silva *et al.*, 1974; Naestoft *et al.*, 1974) or plagued with problems of marked contamination (de Silva and Bekersky, 1974). The essence of our method is the introduction of a clean-up step as described by Naestoft *et al.* (1974) followed by the formation of an ethyl derivative (Figure 3). The retention times of 62 and 78 seconds for the internal standard and clonazepam respectively are considerably shorter than those reported previously for the benzophenones (de Silva *et al.*, 1974) or methyl derivative (de Silva and Bekersky, 1974). The chromatographic conditions were as follows: a Pye series 104 chromatograph with ^{63}Ni electron capture detector was used. It was fitted with a 2m x 2mm (internal diameter) glass column packed with 80-100 mesh Chromosorb W. The liquid phase was 4% OV 101. The carrier gas was oxygen free nitrogen at a flow of 25 ml/minute through the column and a 20 ml/minute detector purge. The detector temperature was 300°C and the column temperature 275°C. A typical example of the chromatogram under these conditions is shown in Figure 4.

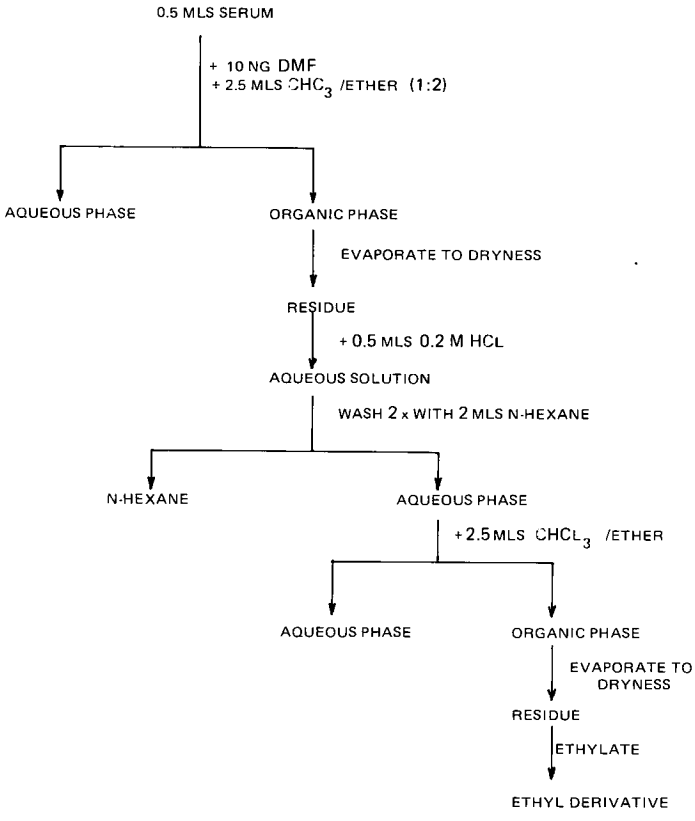

Fig. 2. Clonazepam extraction procedure.

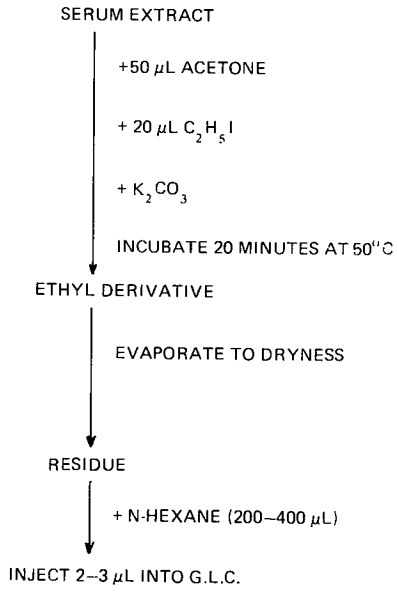

Fig. 3. Ethylation of clonazepam.

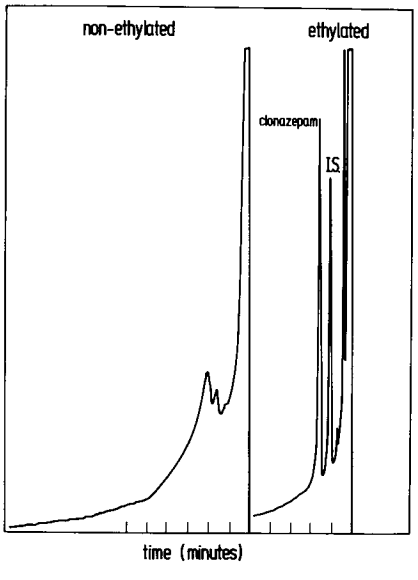

Fig. 4. Chromatograph of clonazepam and internal standard (I.S.).

RESULTS AND DISCUSSION

There was considerable individual variation in serum clonazepam concentration following a 4 mg intravenous dose. The peak concentration occurred at one minute and varied from 110 to 190 ng/ml. The concentration fell rapidly, levelling off between one and 2 hours and falling to 15-20 ng/ml by 4 hours. The concentration of unbound clonazepam was between 8 and 12% of the total (Figure 5). The CSF concentration of clonazepam closely approximated to the unbound serum concentration in all specimens, with a maximum value at one minute and a progressive fall thereafter (Figure 6).

Following intravenous administration of clonazepam the decline in serum concentration could be fitted by a curve representing the sum of 2 exponential functions (Figure 7). The first exponent corresponded to the rapid distribution phase and the second to metabolism and excretion. The drug had a half-time of elimination of 6-12 hours in the sheep. The biexponential decline in serum concentration following a single intravenous dose suggested that the kinetics of clonazepam could be described by a 2 compartment model.

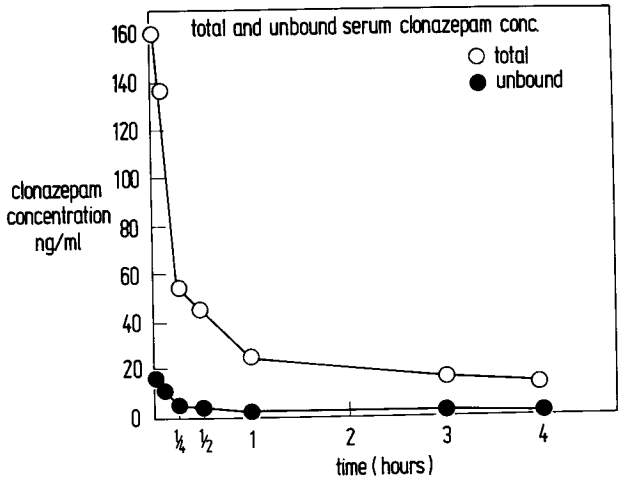

Fig. 5. Total and unbound serum clonazepam concentration.

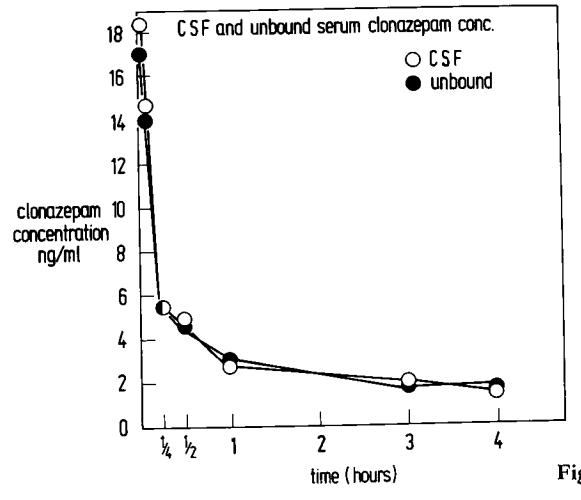

Fig. 6. CSF and unbound serum clonazepam concentration.

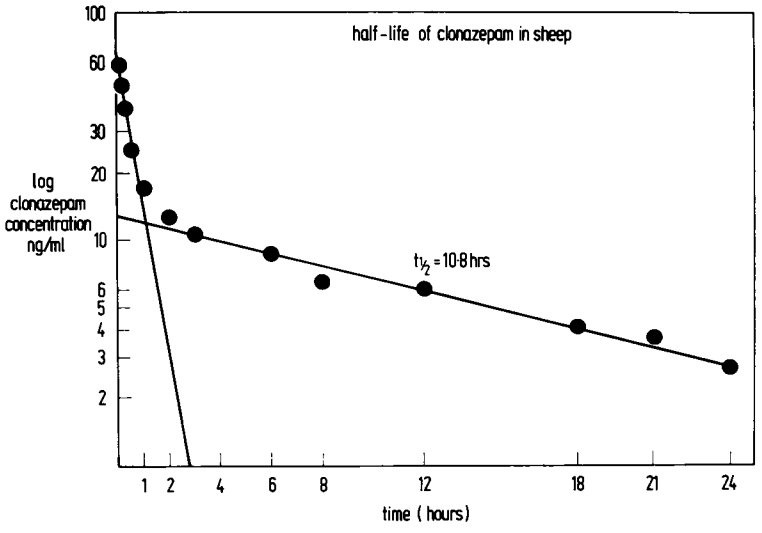

Fig. 7. Biexponential decline of plasma level of clonazepam following a single dose.

A smaller fraction of clonazepam was bound to serum proteins than was anticipated, so that measurement of CSF and unbound serum levels was easier than anticipated. However protein binding of this drug in different species may vary and this matter will be studied later in man. The very close approximation between CSF and unbound serum concentration in all samples suggests a free passive diffusion of unbound clonazepam into the central nervous system. The demonstration of rapid entry of clonazepam into the CSF provides a biochemical basis for the clinical effect of the drug in status epilepticus where Gastaut *et al.* (1971) observed cessation of convulsive activity and suppression of abnormal EEG activity within one minute of intravenous injection in the majority of cases.

Further work in the sheep will entail measurement of brain tissue concentrations of drug so that the distribution of clonazepam within the brain can be mapped out. Studies of protein binding, pharmacokinetics and metabolism of clonazepam in man are also planned.

SUMMARY

An animal model which allowed repetitive sampling of CSF is described. It had a wide potential application and was used to study the passage of clonazepam into the central nervous system. A highly sensitive clonazepam assay is described which allowed measurement of CSF and free serum concentrations as low as 0.5 ng/ml. Clonazepam passed rapidly into the central nervous system and its CSF concentration closely approximated to the concentration of unbound clonazepam in serum. Protein binding of clonazepam in the sheep was 90-95%.

ACKNOWLEDGEMENTS

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THE EFFECTS OF PHENOBARBITONE DOSE ON PLASMA PHENOBARBITONE LEVELS IN EPILEPTIC PATIENTS

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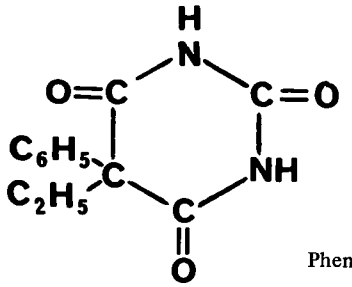
Phenobarbitone has been widely used as an anticonvulsant since it was introduced into therapeutics over 60 years ago (Hauptmann, 1912). However, compared with other anticonvulsants, phenobarbitone has been subject to relatively little study by modern clinical pharmacological methods. Because of this, it seemed worth exploring the relation between plasma phenobarbitone levels and dosage of the drug in a group of epileptic patients.



Phenobarbitone (5-ethyl-5 phenyl-barbituric acid).

MATERIAL AND METHODS

The study was based on steady state plasma phenobarbitone levels measured during the course of therapy in a group of epileptic patients treated with the drug. Data were not included unless the patient's age, sex, body weight, phenobarbitone dose and the dose of any drugs used concurrently were known, and unless the patient had received a constant daily phenobarbitone dose for more than 3 weeks. This period was long enough for the patient to be in a steady state as regards intake and elimination of the drug. A total of 121 persons (58 males, 63 females) were studied. The distribution of their ages (except for two adult subjects whose exact ages were not recorded) was as follows:

0-4 years	5-14 years	15-39 years	40 years and over
36	22	47	14

Pharmacokinetic observations were made on one additional adult male patient whose epilepsy was subsequently treated with N-methyl phenobarbitone.

Prior to 1974 plasma phenobarbitone levels were measured by a spectrophotometric assay (Wallace, 1969). Subsequently, a personally developed gas-liquid chromatographic assay was used to measure phenobarbitone as a butylated derivative (Hooper, Dubetz, Eadie and Tyrer, 1975).

Statistical analyses were carried out with the aid of a Hewlett Packard programmable desk calculator.

RESULTS AND DISCUSSION

Pharmacokinetics

Figure 1 shows the time-course of the plasma phenobarbitone level in a patient who was given the drug for the first time (as an oral dose of 240 mg). The data were analysed for absorption and elimination kinetic parameters in terms of a one-compartment open model (Wagner, 1971), as they fitted this model

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adequately. The result of the analysis is set out in Table I. The elimination half-life (48.7 hours) was shorter than the usually quoted values of 3 to 4 days (Mark, 1963), or 4 days (Buchthal and Lennox-Buchthal, 1972). It would imply that, with constant daily drug dosage, the drug would take 10 days to achieve steady state plasma levels in the patient studied. The drug's apparent volume of distribution (33.5 litres) was less than the expected volume of total body water, and is below the volume of distribution that Maynert (1972) thought likely for phenobarbitone (over 60% of body weight, which in this subject was 80kg). The absorption half-time (1.4 hours) suggested that virtually total absorption of the dose should have occurred within 8 hours of administration.

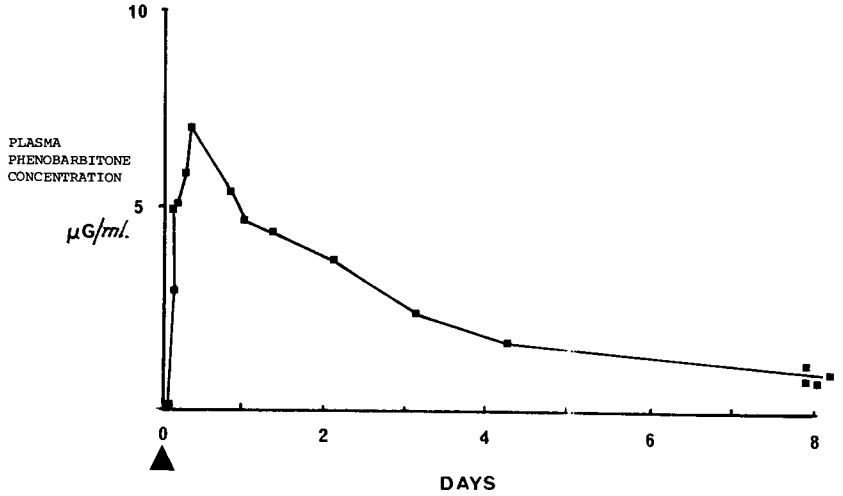

Fig. 1. Time-course of plasma phenobarbitone level in a patient after a 240 mg oral dose of the drug.

TABLE I

Pharmacokinetic parameters in one patient who received 240 mg phenobarbitone

Absorption rate constant	.505 hour^{-1}
Absorption half-time	1.37 hours
Elimination rate constant	−.014 hour^{-1}
Elimination half-time	48.67 hours
Apparent volume distribution	33.5 litres
Whole body clearance	0.48 litres per hour

If the subject studied is reasonably representative of persons with epilepsy, it appears likely that phenobarbitone would be well absorbed from the alimentary tract except in states of gastro-intestinal hurry. However, with the relatively slow elimination of the drug there would be an appreciable risk that drug plasma levels might not be in the steady state if these levels were measured less than two or three weeks after a dosage change. Because the elimination of the drug is relatively slow, plasma phenobarbitone levels would be expected to show little change over a dosage interval of, say, 12 hours. Therefore timing of the measurement in relation to the timing of drug intake in patients on regular phenobarbitone dosage would be of little importance.

Relation of Plasma Phenobarbitone level to Drug Dose

(i) The Whole Population. Plasma phenobarbitone levels were plotted against drug dose for all persons

studied in Figure 2. When a patient had plasma levels measured at different doses, these points are shown separately, but where there were multiple measurements on the one patient at the one dose, only the first measurement has been used.

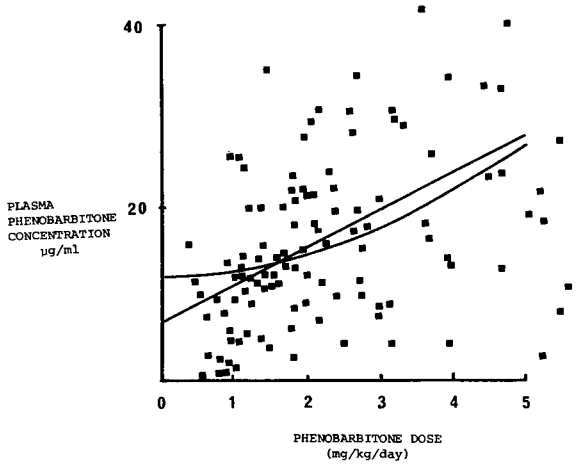

Fig. 2. Relation between plasma phenobarbitone level and drug dose.

There was a relatively wide scatter of points, even when considered in relation to the "therapeutic" range of plasma drug concentration of 15-25 µg/ml (Eadie and Tyrer, 1974). A statistically significant linear regression could be fitted to the data ($r^2 = .312$; $N = 133$), though a parabolic regression fitted slightly better ($r^2 = .331$). However the relatively wide scatter of values, and the fact that the regression lines intercepted the "y" axis at a plasma drug level of approximately 6 µg/ml, raised the possibility that the data could be analysed further to see if there were discrete subgroups within the total population studied.

(ii) Effects of age. In 1960, Plaa and Hine showed that the same phenobarbitone dose, on a body weight basis, produced lower plasma phenobarbitone levels in children than in adults. The plasma half-life of the drug was shorter in children than in adults (Garrettson and Dayton, 1970), though neonates eliminated phenobarbitone more slowly than adults (Melchior, Svensmark and Trolle, 1967). These observations suggested that the effects of age on the relation between plasma phenobarbitone level and dose should be studied in the present series.

The population of treated patients under study was divided into 4 age groups, all containing approximately the same number of subjects. The linear regressions for phenobarbitone plasma levels on drug dosage for each adjacent pair of age groups were then compared by analyses of covariance. When there were statistically significant differences in the elevations and/or slopes of regression lines the age groups were further subdivided into two, and the new regressions compared for differences between the adjacent subgroups. When differences in elevation and slope of a pair of regression lines were not significant at the 5% level of confidence, the groups studied were fused into a common larger group. These procedures were continued till four population groups were defined, on an age basis, the regression for each group being statistically significantly different from that for its neighbours. The regressions for these four age groups (0-4 years, 5-14 years, 15-40 years and over 40 years) are shown in Figure 3. It should be appreciated that, in this analysis, no data were available for neonates. Beyond the neonatal age group there was an obvious tendency for phenobarbitone dosage requirement to diminish progressively with age.

Effect of sex. Travers, Reynolds and Gallagher (1972) stated that, in their studies, women consistently received larger phenobarbitone doses on a body weight basis than men, and yet obtained lower serum concentrations of the drug. They made this assertion despite being unable to demonstrate in their patients that the difference between the sexes was statistically significant.

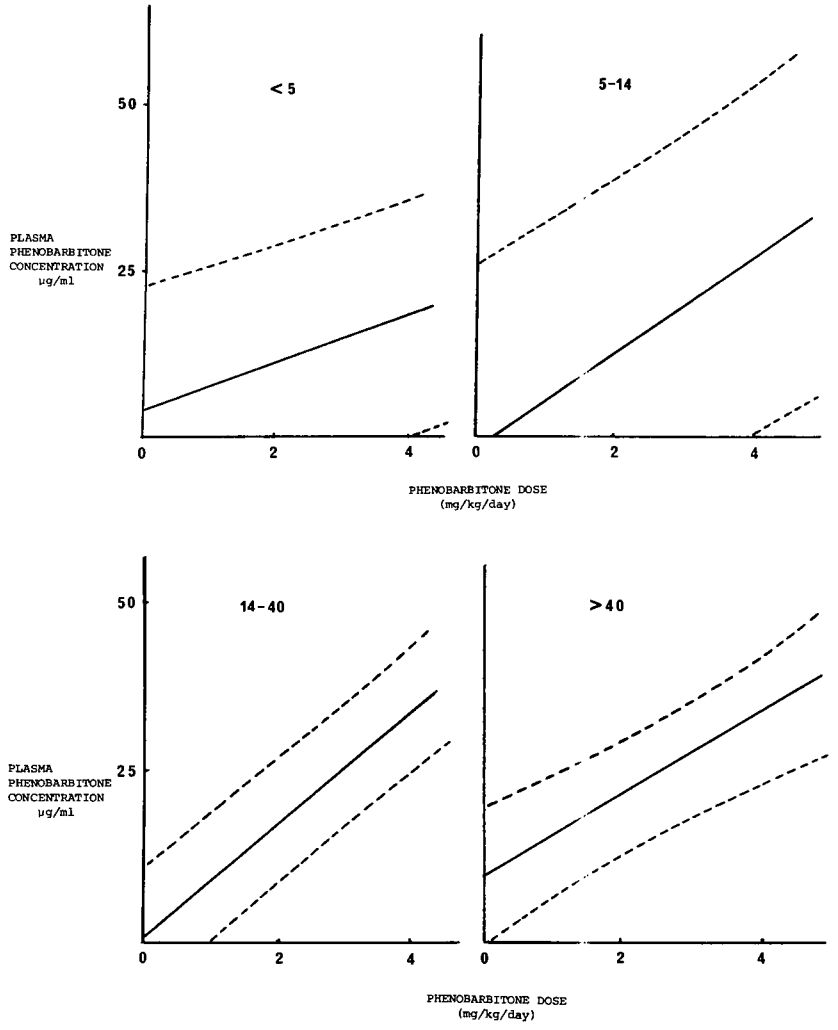

Fig. 3. Linear regression for plasma phenobarbitone level on drug dose in different yearly age groups (90% confidence limits for predicting plasma drug levels from dose are shown).

The relation between plasma phenobarbitone level and drug dose was studied in the males and females in the present series. The linear regressions for plasma drug level on dose for the two sexes are shown in Figure 4. Analysis of covariance indicated that the regressions differed in elevation at the 1% level of confidence. Females tended to require a lower dose than males to achieve a given plasma phenobarbitone level. This finding is contrary to the assertion of Travers, Reynolds and Gallagher (1972).

The effect of sex on the relation between plasma phenobarbitone level and drug dose was explored in the four age groups between which differences in regression for plasma level on dose had previously been demonstrated (see above). The regressions are shown in Figure 5. Analysis of covariance showed that sex had no statistically significant effect on the regressions for plasma level on dose in the age groups 5-14 years, 15-40 years, and over 40 years. However, in persons under 5 years the elevation of the regression line for females was significantly greater than that for males ($P<.01$). There was no significant difference in mean phenobarbitone dose being taken by males and by females in this age group ("t" = 0.529; df = 34; $P > 0.5$).

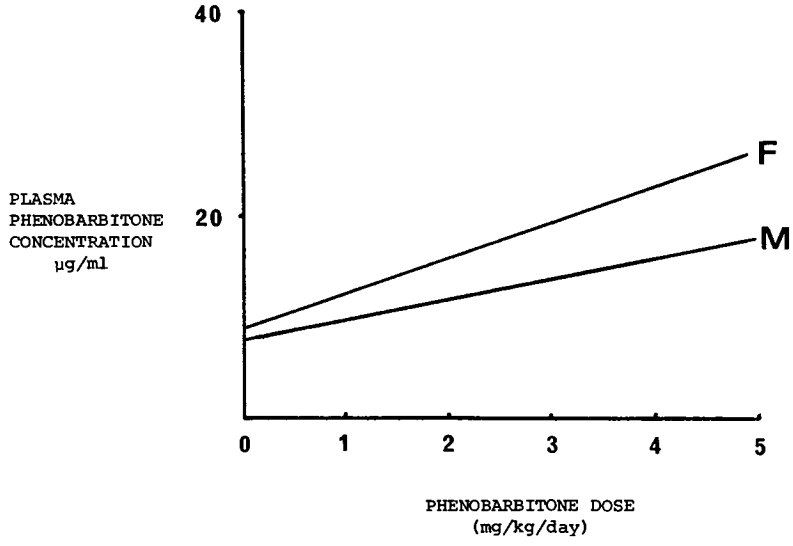

Fig. 4. Linear regression for plasma phenobarbitone level on drug dose in males and females.

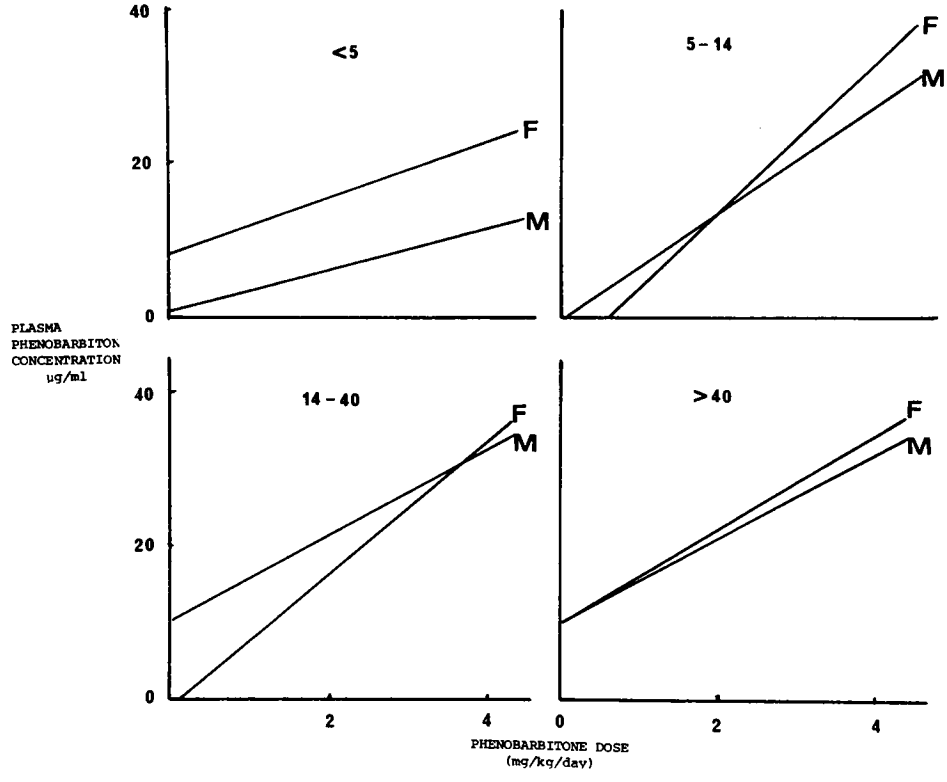

Fig. 5. Linear regression for plasma phenobarbitone level on drug dose in males and females of different ages.

Effect of concurrent therapy. The majority of the patients were taking drugs apart from phenobarbitone. The technique of multiple variable linear regression analysis was used to determine if the intake of other anticonvulsants in common use affected the relation between plasma phenobarbitone level and phenobarbitone dose. The regression for the relation between plasma phenobarbitone level (y) and dose of phenobarbitone(x_1), phenytoin (x_2), carbamazepine (x_3) and sulthiame (x_4), all in mg/kg/day, was as follows

$$y = 10.766 + 6.408x_1 - 1.396x_2 - 0.128x_3 + 0.138x_4$$

Except for the relation between phenobarbitone level and phenobarbitone dose, none of the partial correlation coefficients for the relation between phenobarbitone level and drug dose achieved statistical significance. Thus, intake of phenytoin, carbamazepine or sulthiame, anticonvulsants commonly used in association with phenobarbitone, did not disturb the relation between plasma phenobarbitone concentration, and phenobarbitone dose. This is not to say that therapy with one or other of these drugs may not alter plasma phenobarbitone concentrations in individual patients. If in some patients such an interaction raised plasma phenobarbitone levels, and in others caused the levels to fall, there might be no change in average levels of plasma phenobarbitone in the treated population. Therefore the multivariate regression technique would not detect the interaction. Nevertheless the failure to detect interactions indicates that the conclusions already drawn about the relation between plasma phenobarbitone level and phenobarbitone dose, and the effects of age and sex on this relation, do not have to be modified to take into account the effects of some other commonly used anticonvulsants administered concurrently.

Effect of Dose Increments in the Individual on Plasma Phenobarbitone Level. It has been said that steady state plasma phenobarbitone level increases in proportion to drug dose in individual patients (Richens, 1974). Studies of patients such as that illustrated in Figure 6 suggests that this may not be so. When plasma phenobarbitone level was plotted against drug dose for all patients in the present series who had levels measured at more than one dose and regression lines were drawn through the points for each patient, and extrapolated back to zero (Figure 7), a statistically significant majority of the extrapolations intersected the y (dosage) axis. The findings of Figures 6 and 7 suggest that the relation between plasma phenobarbitone level and drug dose in the individual is not linear. This finding is open to several interpretations e.g. increasing drug absorption with increasing oral dose, decreasing volume of distribution as dose increases, or partial Michaelis-Menten rather than simple first order elimination kinetics.

Determining Phenobarbitone Dosage

The findings described above can provide a basis for determining phenobarbitone dosage in patients not previously treated with the drug. Clearly the dosage requirement varies with age, and with sex in persons under 5 years, but the concurrent administration of other anticonvulsants is not likely to be important. If one were to aim to achieve a steady state plasma phenobarbitone level of 15 μg/ml, the minimum level which protects against febrile convulsions (Faero, Kastrup, Lykkegaard Nielsen, Melchior and Thorn, 1972), the average patient would require the following phenobarbitone doses:

0-4 years —male	5.1	mg/kg/day of phenobarbitone
—female	1.90	
5-14 years	2.30	
15-40 years	1.75	
over 40 years	0.90	

The data of Figure 3, showing the 90% confidence limits for predicting plasma phenobarbitone level from dose, indicate that such doses will tend to have more variable effects in children than in adults. This may suggest a more cautious approach to prescribing the initial dose in children. In the young, 2 mg/kg/day would probably be a safe commencing dose, while 1 mg/kg/day would be a safe dose for beginning therapy in most adults. Often such doses will have to be increased later if plasma phenobarbitone levels above 15 μg/ml are regarded as therapeutically desirable. In incrementing the initial dose the values cited above can serve as a guide to the likely definitive dose. However it should be remembered that the dose increment is likely to raise the plasma phenobarbitone level more than would be suggested by the relation between the initial plasma phenobarbitone level and the initial drug dose.

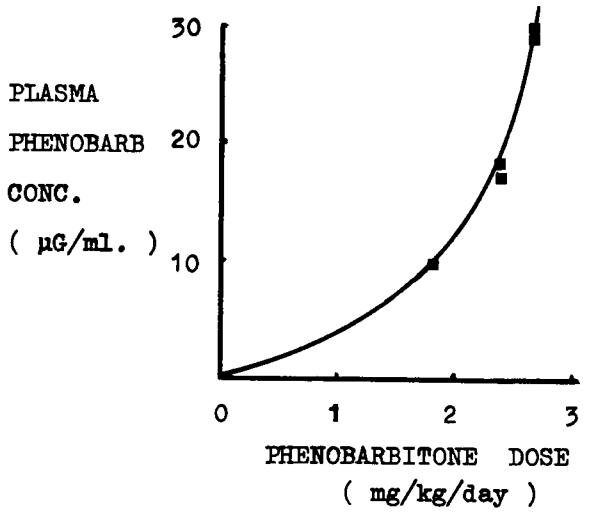

Fig. 6. Effect of dose increase on steady state plasma pheobarbitone level in one patient.

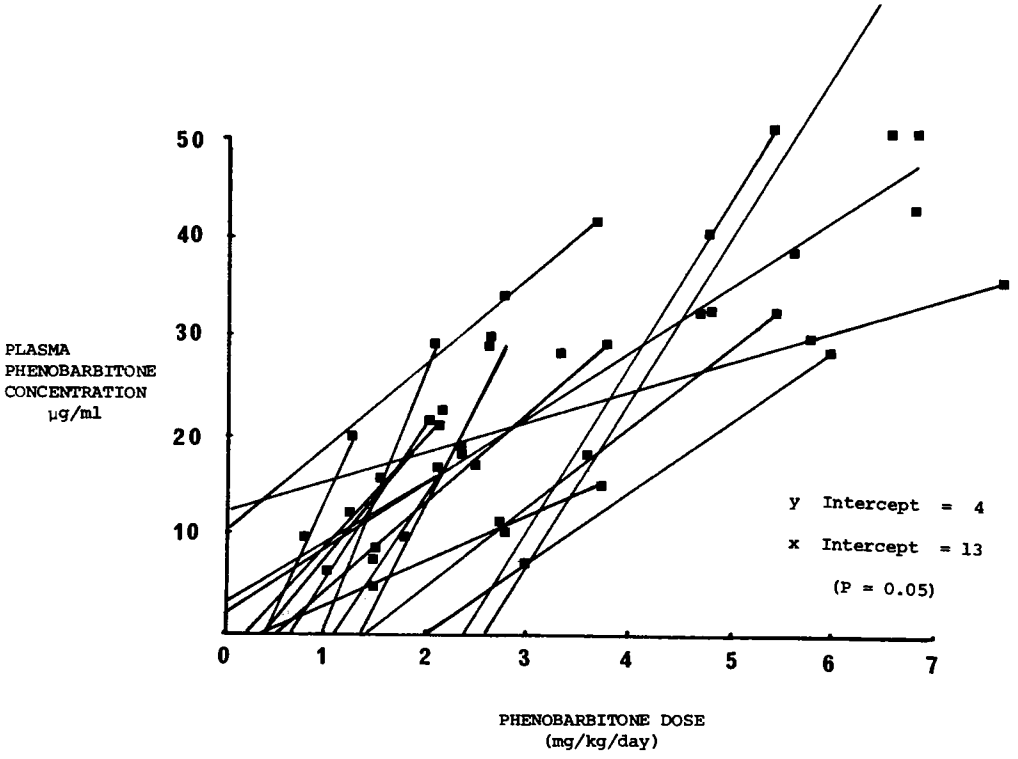

Fig. 7. Regression lines for plasma phenobarbitone level on drug dose in 17 individual patients extrapolated back towards zero.

SUMMARY

The relation between plasma phenobarbitone level and phenobarbitone dose was studied in 121 patients. The relation changed with age, the dosage requirement (on a body weight basis) tending to fall as patients grew older. Males under 5 years had a higher dosage requirement than females of the same age, but otherwise sex did not affect the relationship, nor did the concurrent intake of the anticonvulsants phenytoin, carbamazepine or sulthiame. In the individual, plasma phenobarbitone levels tended to increase out of proportion to dosage increases.

These findings can provide a basis for prescribing appropriate phenobarbitone doses in epileptics.

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ON THE VISUAL DISTURBANCES ASSOCIATED WITH MASSIVE BASAL ANEURYSMS.

ANTHONY FISHER and RICHARD L. COOPER*

INTRODUCTION

It is established that the pressure exerted by a basal aneurysm may cause paralysis of cranial nerves, among others the optic nerve and optic pathways. Jefferson (1937) could find only sixty-six reported cases with amblyopia and field defects in the literature, but he felt that the relationship was more common than the figures indicated.

The context of our title refers to aneurysms of the circle of Willis lying within the subarachnoid space, and arbitrarily greater than one centimetre in diameter. Massive basal aneurysm is an uncommon condition. In only nine of the twenty-two patients reported by Bull (1969) was there suggestion of, or proof of, implication of the visual pathways. It was therefore decided to analyse carefully the visual defects of the patients in the present series.

METHODS.

Five patients seen during the past fourteen years form the basis of our observations.

Visual acuity was estimated in the usual fashion using full correction after refraction. Central visual fields were studied on 1 metre and 2 metre Bjerrum screens using full and reduced illumination, where applicable. Peripheral fields were analysed with the arc perimeter. Autoplot campimetry (1 metre) was used on occasions.

CASE REPORTS

CASE 1. (M.B., S.C.G.H., No. 60429)

Progressive failure of distant vision was the complaint of an alert 72 years old woman. This was chiefly manifested by a difficulty in seeing the object ball when playing bowls.

For some years, systemic arterial hypertension had been treated with diuretic drugs. Examination showed controlled hypertension and incongruous bitemporal field loss with a central scotoma in the right eye (Figure 1).

Direct puncture carotid angiography performed under general anaesthesia was without incident or sequela and revealed a large, partly clotted aneurysm in the pre-sellar region, arising from the left anterior cerebral artery, (Figures 4 and 5). The patient declined proffered surgical treatment. Serial ophthalmic study in the past 2 years has shown minor change in acuity and the disappearance of the central scotoma, but the appearance of a binasal field defect (Figures 2 and 3).

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CASE 2. (I.B., R.P.H., No. 14926)

Seven years before presenting, this 55 years old woman had had an abrupt decline in vision in the right eye, with gradual improvement to near normal vision during the next 3 years.

Diplopia with horizontal separation of images was noted for distant objects eight months before presenting and, with this symptom, the vision declined in the left eye and was accompanied by throbbing left frontal and occipital headache. Examination revealed that the visual acuity was 6/18 in the right eye, coupled with a right temporal field defect (Figure 6). The left visual field could not be charted. Bilateral primary optic atrophy, more advanced on the left side, was the only other neurological sign recorded. Mild systemic arterial hypertension was found. Sellar and left sphenoid wing erosion was seen in the plain radiograms. Left carotid angiography showed elevation of the first part of the anterior cerebral artery, and elevation and slight lateral displacement of the terminal portion of the left carotid artery. No contrast appeared on the right side with cross compression of the carotid artery in the neck. Right frontal craniotomy disclosed a large aneurysm above and in front of the sella turcica. Operative haemorrhage prevented treatment of the aneurysm. The patient did not respond to treatment of post-operative collapse and died 48 hours later.

At necropsy the aneurysm, measuring 4.5 × 3.5 × 2 cm, arose from the terminal portion of the right internal carotid artery and carried the optic chiasm on its superior surface with the widely splayed optic nerves adherent to its lateral surface (Figure 7). The lumen of the aneurysm was almost completely filled with laminated adherent thrombus undergoing organization.

CASE 3. (R.C., R.P.H., No. 7083)

This 48 years old boiler maker presented initially with a subarachnoid haemorrhage which was shown to have arisen from a very large aneurysm of the left anterior cerebral artery, measuring 3cm by 2cm. No record of the visual fields was available at that time. The aneurysm was ligated intracranially.

Ten months later the patient presented with recurrent frontal headaches and failing vision in the right eye. The visual acuity was reduced to counting fingers at one metre from the right eye and was 6/18 in the left eye. The right visual field showed an inferior nasal defect to a 2 degree white target at 330mm, while the left field was full to a 1 degree white target at the same distance (Figure 8). Further angiography revealed stretching and upward displacement of right anterior cerebral artery and crenellation of the wall of the aneurysm, with variable contrast density in the lumen and lateral displacement of the terminal portion of left internal carotid artery and upward and lateral displacement of initial segment of left anterior cerebral artery. Re-exploration revealed that the aneurysm was still patent and had expanded to the right of the midline. There were dense arachnoid adhesions completely surrounding the lesion.

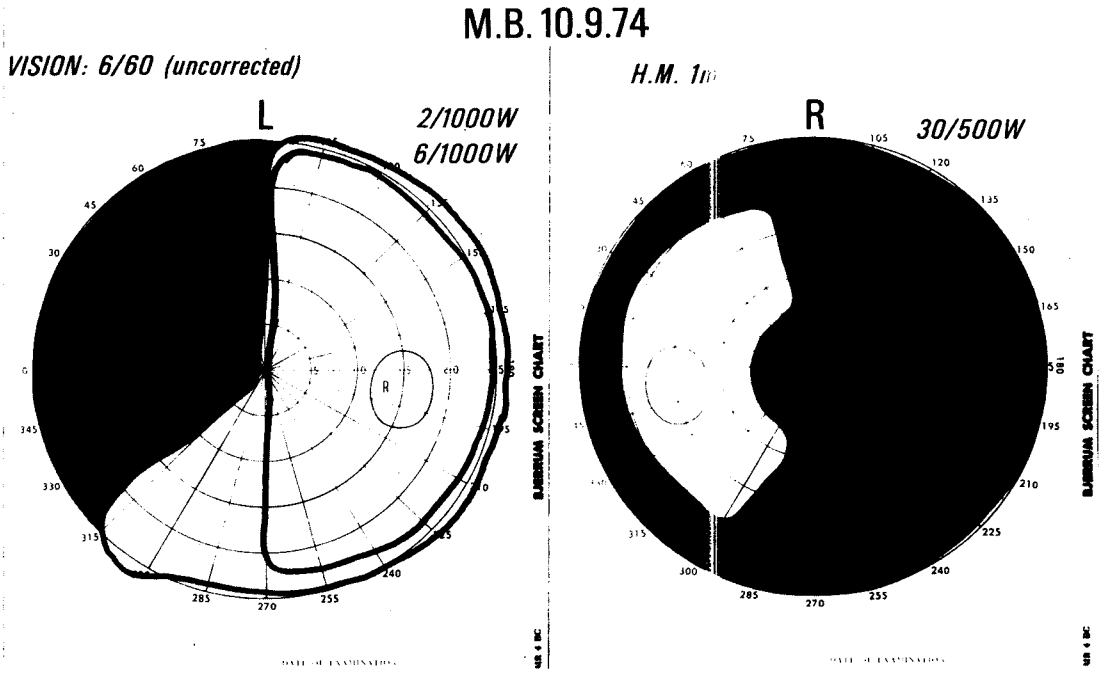
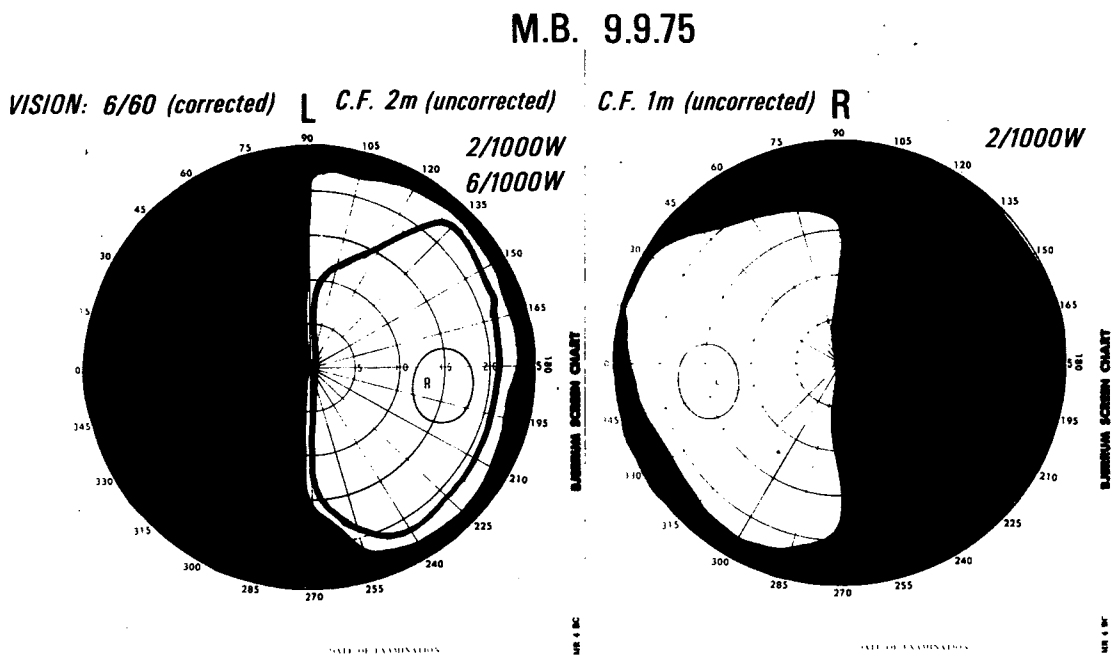
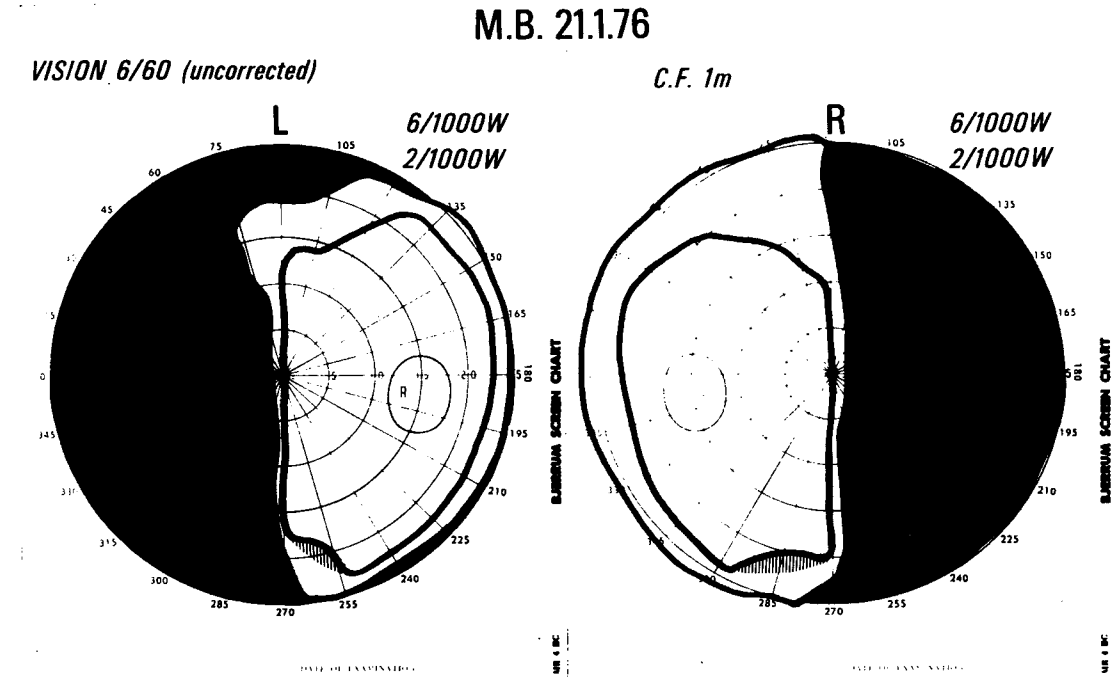


Fig. 1. Initial field defect in Case 1. Note the right central scotoma.





Figs. 2 and 3. Visual fields in Case 1, twelve months and sixteen months after presentation. Note the disappearance of the scotoma, and an early inferior binasal defect.

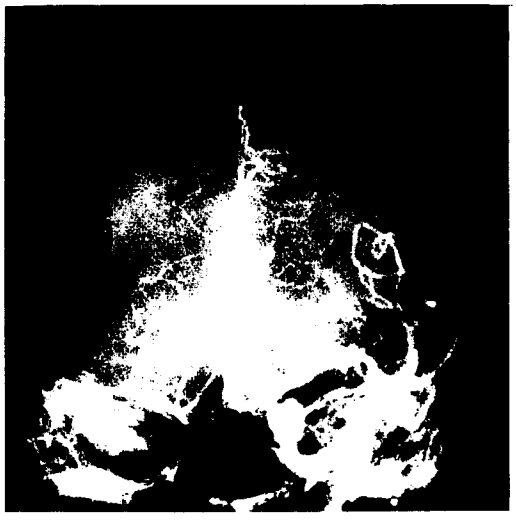


Fig. 4

Fig. 5

Figs. 4 and 5. Left carotid angiogram in Case 1, showing a massive anterior cerebral artery aneurysm and also a persistent trigeminal artery.

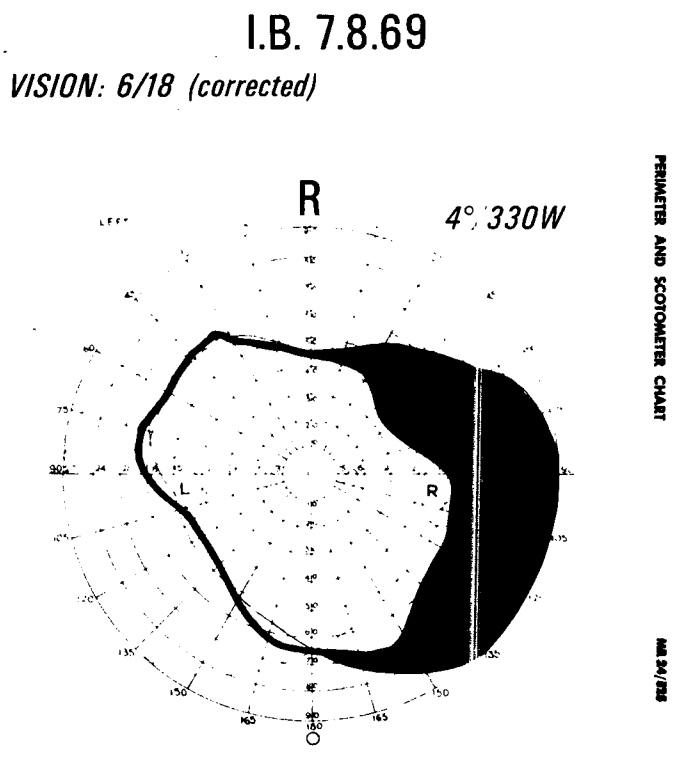


Fig. 6. Visual fields in Case 2.

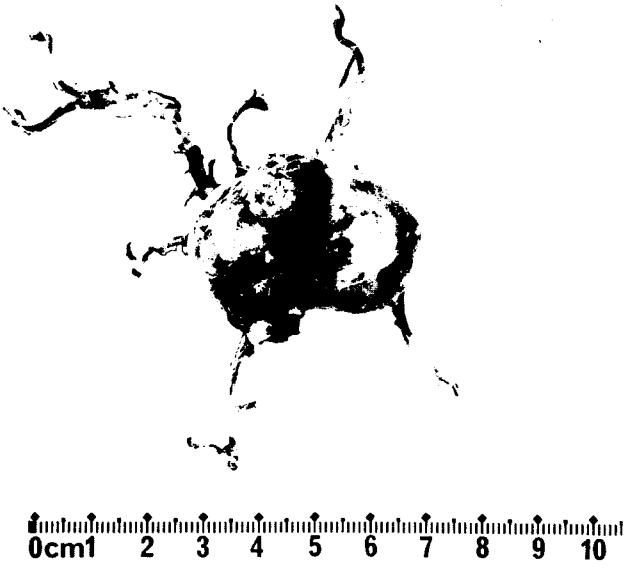


Fig. 7. The aneurysm seen at necropsy in Case 2.

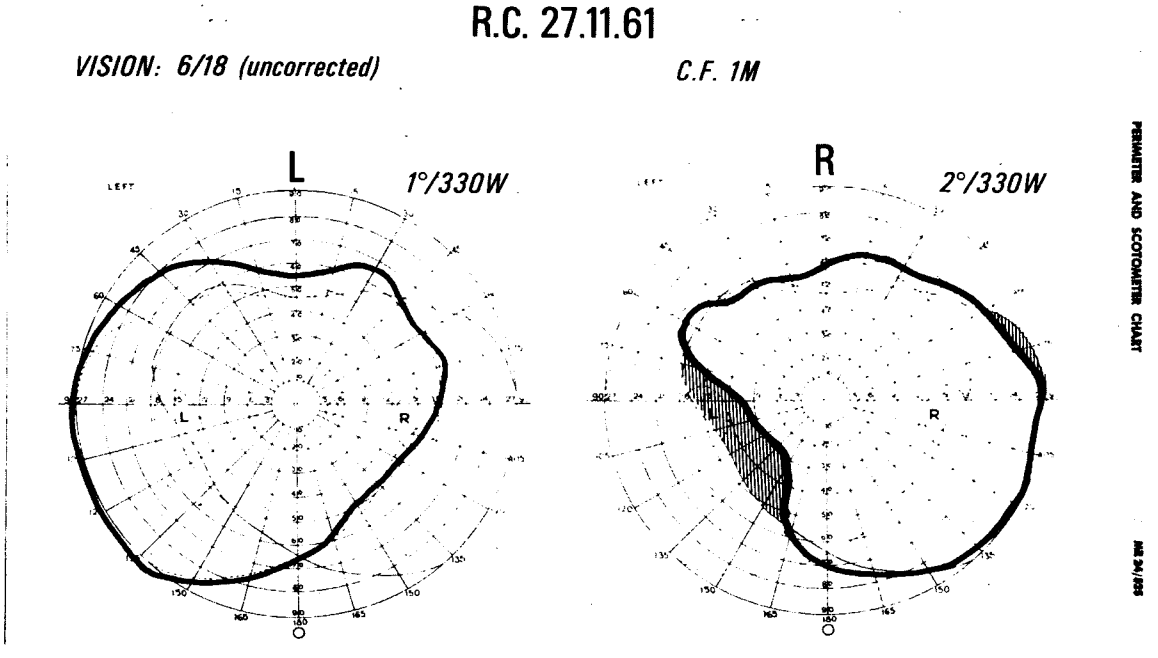


Fig. 8. Visual fields in Case 3, ten months after the initial operation. Note the right inferior nasal defect.

CASE 4. (J.F.B., R.P.H., No. 113356)

A motor mechanic aged 25 years was referred because of a 12 month history of a constant sensation of "a film" over the right eye. He had had meningitis at the age of 13 years and was an established migraineur. More or less constant discomfort above the right eyebrow had been present for a year.

Visual acuity was reduced to perception of hand movements in the right eye and could be corrected to 6/5 in the left. The right optic disc showed early atrophy. There was a dense central scotoma in the right visual field and a minor depressional defect in the left upper temporal quadrant (Figure 9). Skull radiographs revealed that the right optic foramen was enlarged. Right carotid angiography displayed a fusiform infra-clinoid, partly intra-cavernous aneurysm (Figures 12 and 13). Partial clotting within the aneurysm was noted. The terminal right internal carotid artery and both anterior cerebral arteries in their first part were displaced. No action was taken until eight months later when a dense left hemianopia was found. The right eye was blind (Figure 10). Further angiography confirmed the enlargement of the aneurysm. Ligation of the right carotid in the neck was followed rapidly by expansion of the left visual field and recovery in the temporal half of the right field. The nasal defect remained.

Eight months later, the visual acuity was 6/9 in the right eye, and 6/5 left with correction. The right field showed a concentric constriction worse on the nasal than temporal side, while the left was full (Figure 11).

CASE 5. (G.M.)

A moulder, aged 57 years, had noted transfrontal headaches for seven years. These headaches had been worse following a minor head injury. Defective vision had been present for nine months, and compressed difficulty in reading the beginning and the ends of words in large type.

Examination showed left sided anosmia, early bilateral primary optic atrophy, a visual acuity of 6/12 in the right eye, 6/18 in the left eye, and a bi-temporal hemianopia (Figure 14). A soft systolic bruit was audible on auscultation of the left orbit.

Left carotid angiography revealed an aneurysm measuring 3cm by 2cm, arising proximal to the carotid bifurcation and overlying the pituitary fossa (Figures 16 and 17). The aneurysm was clipped intracranially. Three days postoperatively, the visual acuity was 6/6 in the right eye and 6/12 in the left. Six months later, the right visual field had recovered partially (Figure 15).

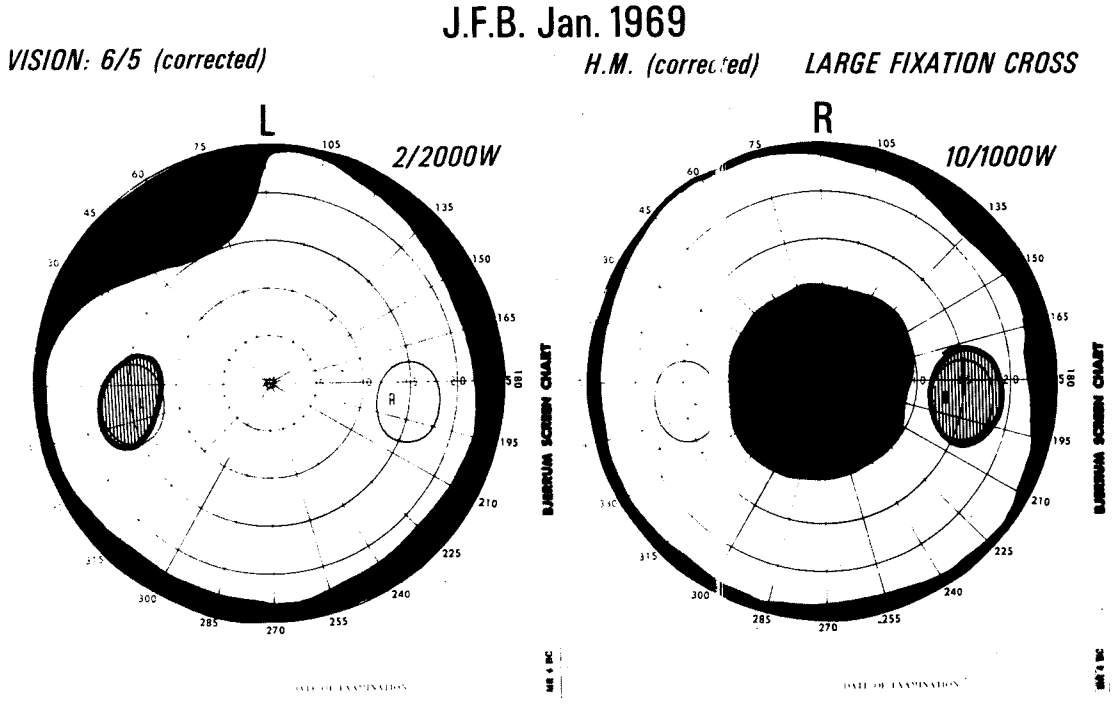


Fig. 9. Visual fields in Case 4.

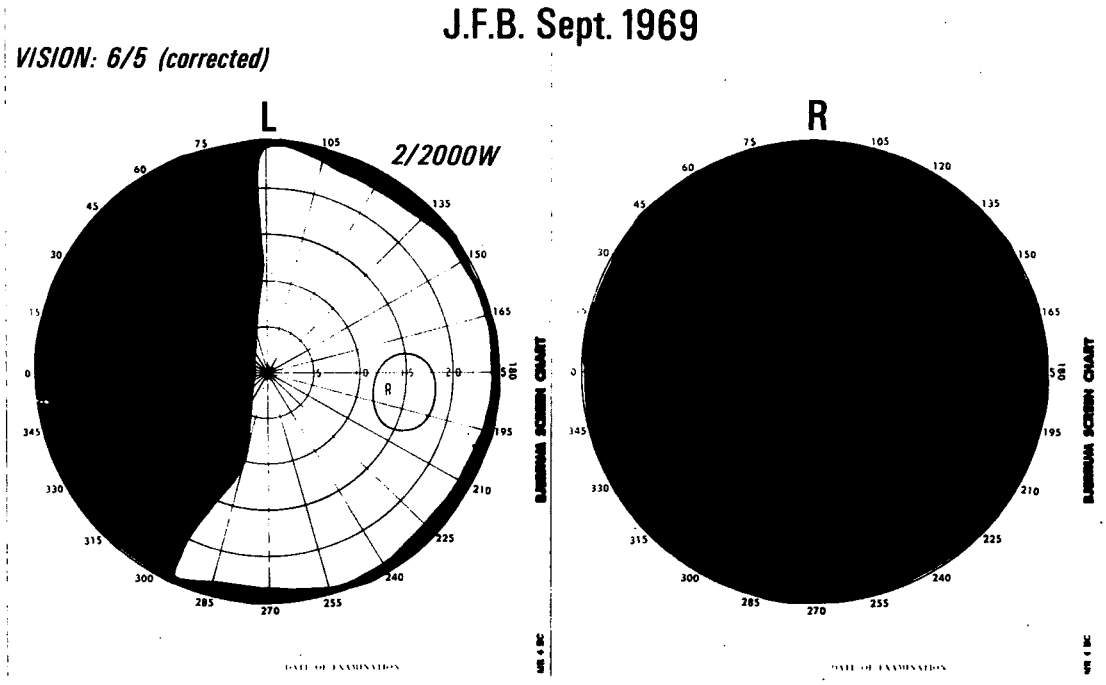


Fig. 10. Visual fields in Case 4, pre-operatively, ten months after presenting.

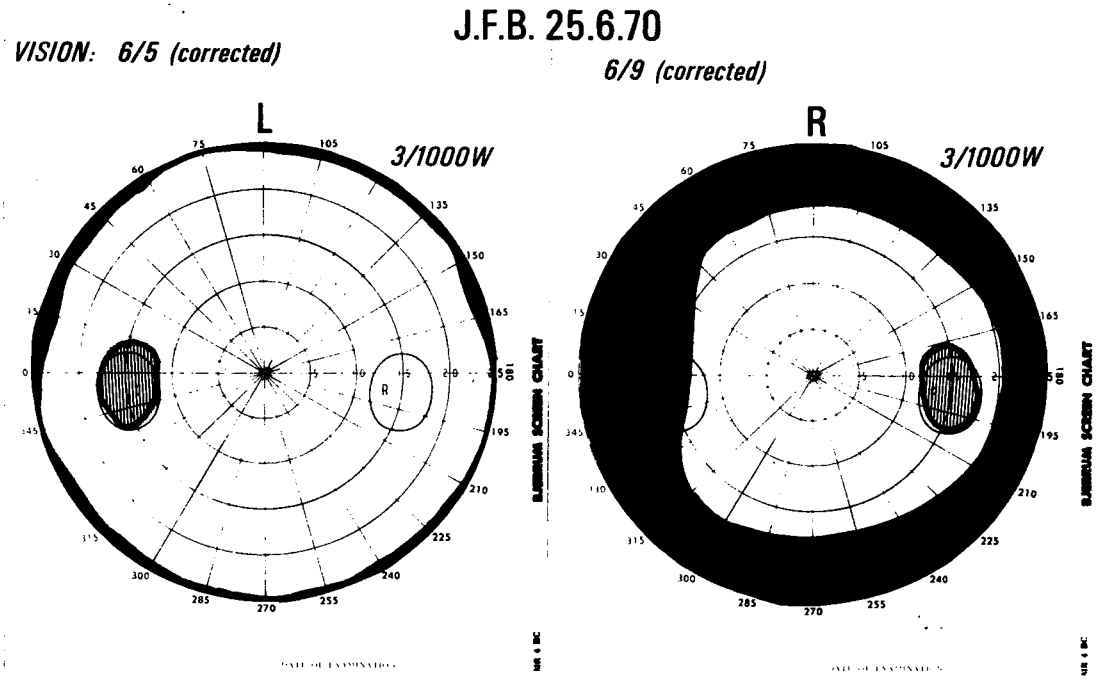
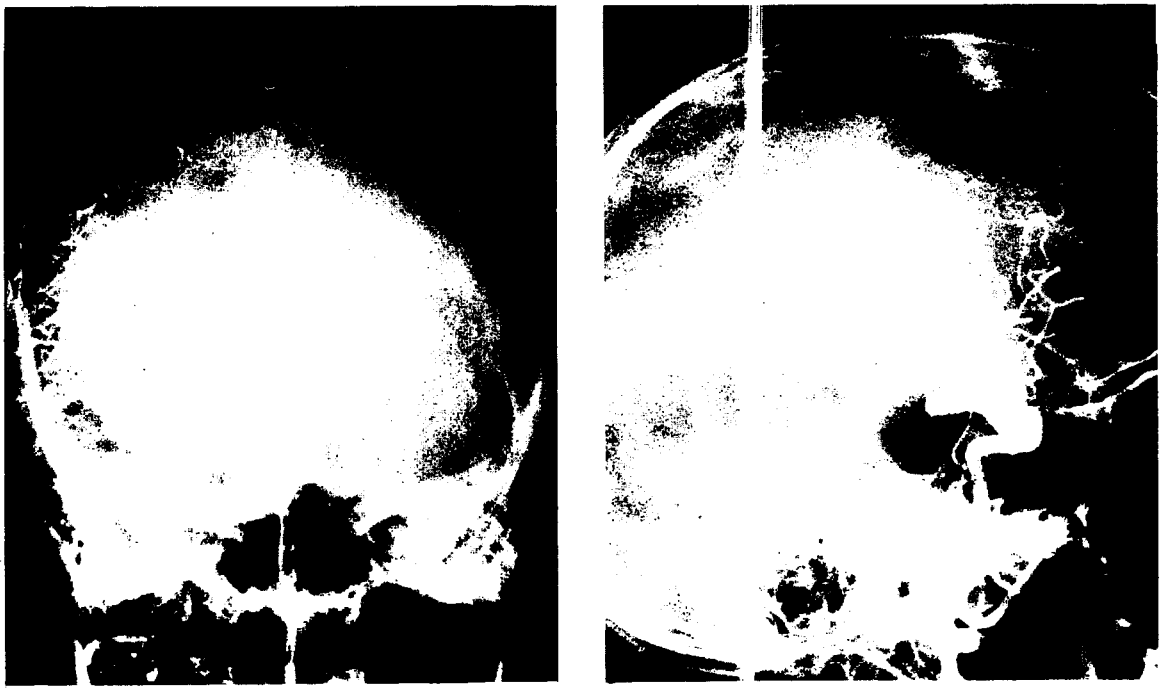


Fig. 11. Visual fields in Case 4, six months post-operatively. Note persisting nasal constriction on right side.



Figs. 12 and 13. Right carotid angiogram in Case 4, showing aneurysm.

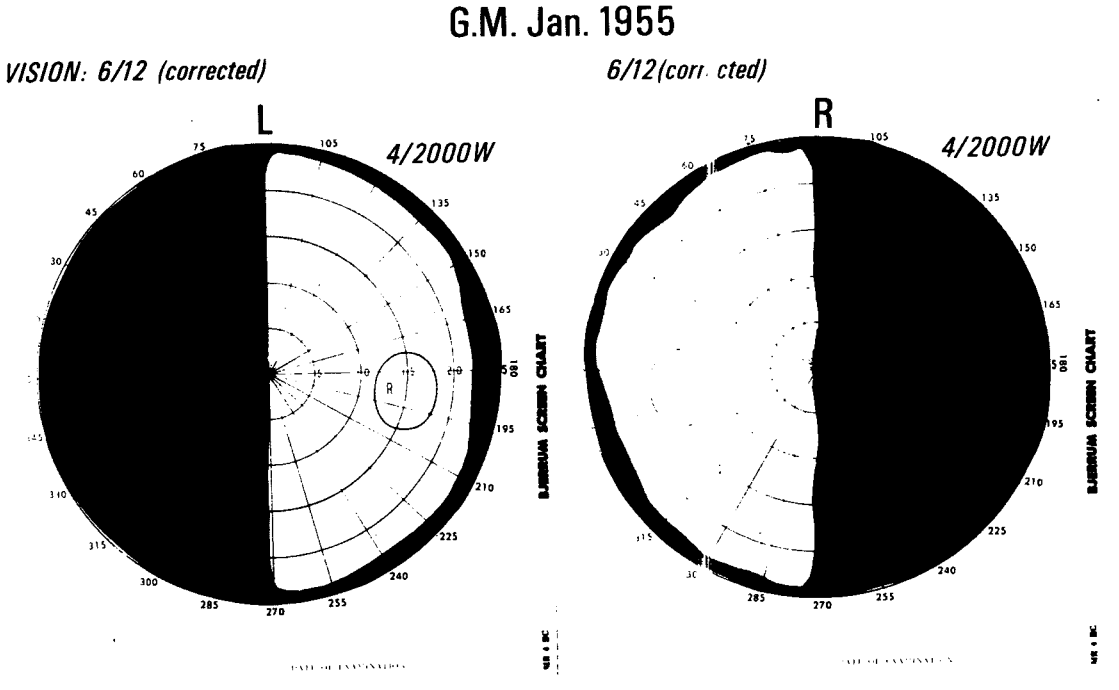


Fig. 14. Visual fields in Case 5 (pre-operative).

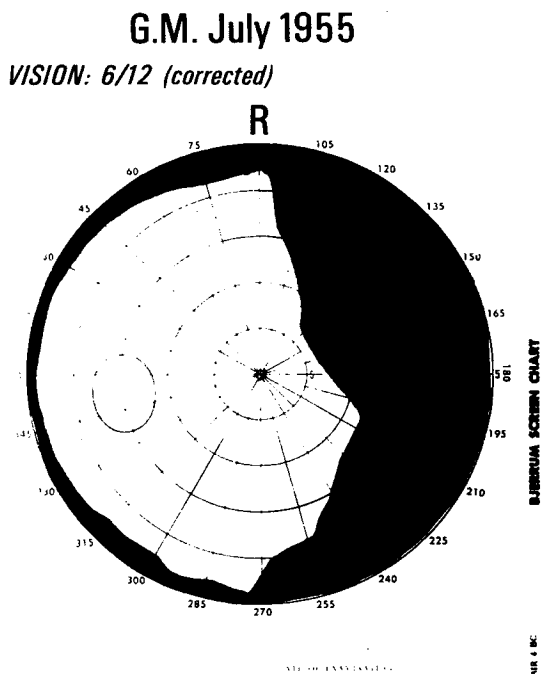
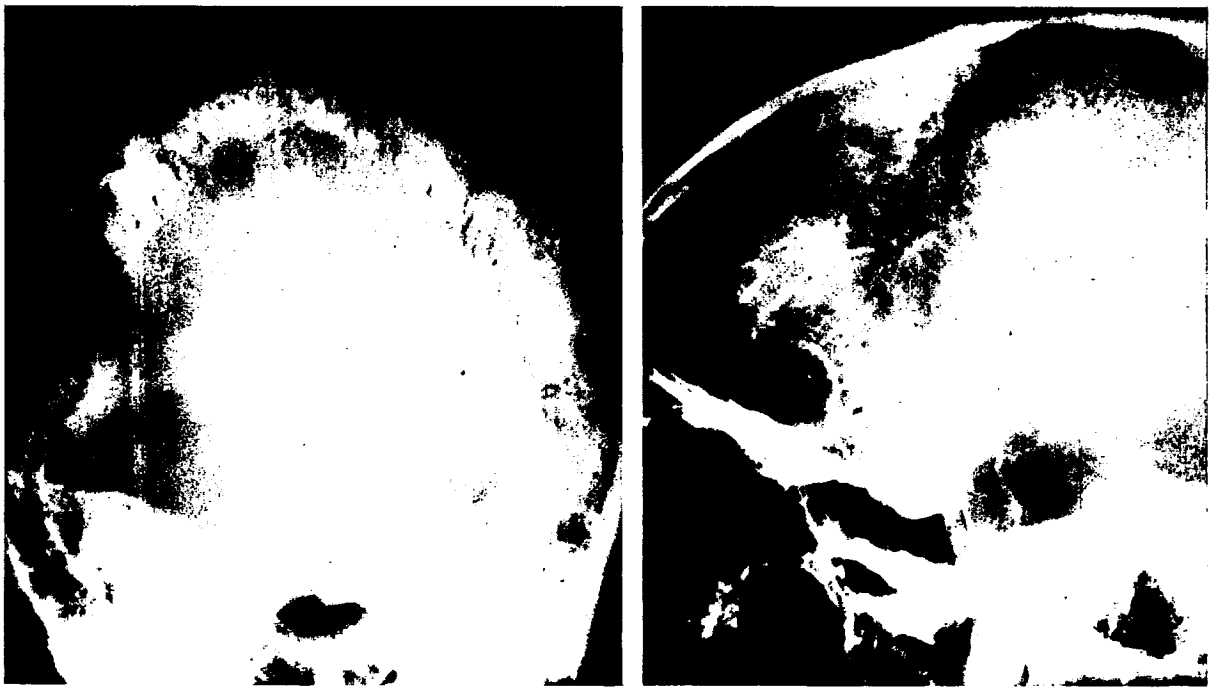


Fig. 15. Right visual field in Case 5 (six month post-operatively).



Figs. 16 and 17. Left carotid angiogram in Case 5.

DISCUSSION

Because of the anatomical relation of the visual pathways, it is not surprising that an aneurysm of almost any artery of the circle of Willis can produce direct and remote compression of the pathways and therefore progressive changes in the visual fields. These signs are significant features of the aneurysmal syndrome affecting the circle of Willis, but the pattern of the visual defect is so far from uniform that it is difficult to establish general rules.

While the type of visual field defect seen initially in Case 4 is reminescent of a "junction effect", namely scotoma on the side of the lesion and contralateral peripheral sector depressional defect, we do not believe that the uniocular central defect can be accepted as a junction scotoma. Harrington (1964) asserted that this defect is strictly limited by the vertical meridian. Traquair (1923) was less dogmatic in this context as he recalled that pathological lesions exist in longitudinal as well as transverse planes and may affect different parts of the nerve at different levels.

The binasal defect illustrated in Case 1 (Figure 3) and the unilateral nasal defect in Cases 3 and 4 are features recognized as more typical of basal aneurysms that of other expanding lesions in the chiasmatic region. Traquair (1924) did not accept that this defect should be termed a hemianopia, reserving this name for bilateral field defects, produced by a single chiasmatic or supra-chiasmatic lesion. It is quite conceivable that the field defects shown here could be the result of compression of the lateral aspect of the optic nerves against the internal carotid arteries or bony margins of the optic canals (O'Connell, 1973; O'Connell and du Boulay, 1973), or against the anterior cerebral arteries (Ricker and Kernohan, 1954).

When a basal aneurysm compresses the subchiasmatic pathway, Jefferson (1937) and Meadows (1949) commented on the relatively rapid fluctuations in the visual acuity and variations in the extent of the field defect. These features were demonstrated in two of our patients pre-operatively. The recovery of visual acuity and expansion of the visual fields following successful treatment of the aneurysms mirrored the recovery seen in patients after the removal of a pituitary adenoma.

Many observers believe that in optic nerve or chiasmatic compression, the severity of the impaired visual acuity and the extent of the visual field defect are dependent on a combination of direct pressure on, and ischaemia of, the neural elements. The rapid recovery following decompression has been attributed to relief of ischaemia. Kayan and Earl (1975) have challenged this view, noting the disparity between the duration of the compression and the rapidity of recovery, the latter being neither comparable with the return of function following ischaemia elsewhere in the nervous system, nor sufficiently delayed to be due to remyelination.

Fluctuation in visual acuity with environmental temperature change is an accepted feature in established multiple sclerosis affecting the optic nerve. It has been suggested (Davis and Jacobson, 1971; Davis, 1972) that this lability stems from a reduction in the "safety factor" for nerve conduction. Thereby, a small additional impairment results in reversible conduction block. It is possible that a similar reduction in "safety factor" for nerve conduction obtains in anterior visual pathway compression by an aneurysm. Increase in the "safety factor" for nerve conduction following successful decompression may account for the early phase of improvement in vision.

Massive basal aneurysms are of "extreme rarity" as Gull (1859) put it, and "all care however will often fail to enable us to form a correct opinion; even should we, as some have suggested, auscultate the cranium for an aneurysmal murmur!". Nevertheless critical study of the visual fields will certainly help.

SUMMARY

When massive basal aneurysms compromise the anterior visual pathways the resulting disturbances of vision are diverse and a firm clinical diagnosis is difficult.

Because of the rarity of the condition, a critical analysis of the visual defects was made in five personally studied patients with large anterior basal aneurysms in an effort to clarify the clinical features of the disorder. These observations were related to those reported in larger series of patients by Jefferson and Bull.

This study gives support to the opinion that the commonest visual defect seen with massive basal aneurysms is impairment of visual acuity, followed next in frequency by bitemporal hemianopia, and then by junction scotoma.

ACKNOWLEDGEMENTS

The authors are grateful to Associate Professor F. Mastaglia and Dr. M. Sadka for details of the clinical and pathological findings in Case 2, and to Mr. Ross Robinson F.R.A.C.S. for the clinical and operative details in Case 3. The photography was performed by Mr. R. Van Raalte, Department of Medical Illustration, Royal Perth Hospital.

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PROGRESSIVE FACIAL HEMIATROPHY (PARRY-ROMBERG SYNDROME).

R.H.C. RISCHBIETH*

First described by Parry in 1825 and later in more detail by Romberg in 1846, Eulenberg in 1871 first named the disorder, "Progressive Facial Hemiatrophy". There have been numerous subsequent descriptions of the disease and of its associated features, with surmises as to its aetiology. Archambault and Fromm (1932) reviewed 400 cases, commenting on the possible relationship of the onset to trauma, and to localized and generalized infections, including pulmonary tuberculosis, whilst Dawson (1966) described a case associated with pulmonary sarcoid. After reviewing theories of endocrine, trigeminal, parasympathetic, and generalized autonomic dysfunction as bases for the syndrome, Archambault and Fromm (1933) concluded that the lesions involved the sympathetic division of the autonomic nervous system at some point in either its central or peripheral course. Blair Rogers (1965) reviewed 772 cases. Rees and his colleagues in 1973 reported 40 patients coming to their two plastic surgery units for reconstructive surgery in the previous ten years. They reported good results from the use of repeated small injections of a silicone fluid (dimethoxyl polysiloxane) where all previous methods had met with indifferent success. This material is still not available for general use in the U.S.A. or in Australia. Suggestions have been made for the alternative use of "Silastic".

Characteristically progressive facial hemiatrophy begins in the first or second decade with progressive wasting of fat and subcutaneous tissue, and to a lesser extent of skin and muscle, and in cases with onset early in life, of cartilage and bone as well. The disease slowly progresses over two to ten years before usually arresting. Usually an area of increased or decreased pigmentation appears on one side, either just above the eyebrow or in the mid infra-orbital region below the lower lid and shortly afterwards this area enlarges in size and becomes atrophic, if it was not so at the onset. Eyebrow, eyelashes and scalp hair may become locally depigmented also at this stage, or even earlier. Progressive atrophy spreads from this site, often seemingly within the distribution of the branches of a trigeminal nerve and often leaving a deep groove in the paramedian area of the forehead adjacent to (but not at) the midline, sharply demarcating the atrophic area from the spared area of the other side of the face, the spared area of the other side of the face, the "en coup de sabre" effect. In about 4% of reported cases progressive atrophy of both sides of the face occurs.

There is a progressive loss of subcutaneous tissue with later atrophy of the overlying skin which may become thin, taut and dry, with a brownish grey discolouration and loss of skin adnexae and dermal vessels. Microscopically it is difficult to distinguish the histological changes from those seen in localised scleroderma or morphea, although the elastic tissue is better preserved in "primary Parry-Romberg syndrome" according to some observers. Palatal hemiatrophy, hemiatrophy of the tongue, atrophy of the salivary glands and various ocular abnormalities such as heterochromia iridis, iridocyclitis, anisocoria,

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with unilateral mydriasis, meiosis, enophthalmos, lens opacities, corneal ulceration, Horner's syndrome and various other sympathetic disorders may occur, as well as trigeminal neuralgia or anaesthesia and facial palsy and/or spasm. On occasion various disorders of the central nervous system are seen, migraine and epilepsy being the commonest. Both grand mal and minor epilepsy have been described, along with focal sensory and motor attacks. Electroencephalographic abnormalities on the relevant side and cerebral calcification may occur, while dilatation of the ipsilateral lateral ventricle and unilateral cerebral atrophy have been noted. At times the upper cervical area is also involved, at times the upper limb and at times there is a hemiatrophy of the whole body. There may be linear areas of atrophy of the trunk, with atrophy of one breast, while on at least one occasion hemiatrophy of the face has been associated with hemiatrophy of the ipsilateral lower limb. Haematological and biochemical studies have shown no relevant abnormality.

The aetiology of the condition remains obscure and no single aetiological factor has been demonstrated. Clearly it is not wholly a hereditary disorder. Familial cases are rare though not unknown. Although the cases described in the present paper are all females, in larger series there is in fact no increased incidence in females. Moss (1959) found in month old rats that unilateral cervical sympathectory produced a constant local decrease of fatty tissue with changes similar to progressive facial hemiatrophy, but autopsy material is still lacking. Some form of primary degeneration of the sympathetic nervous system has been postulated, but this does not seem to explain satisfactorily the involvement of other structures, notably those of the central nervous system. Presumably the basic disorder disturbing the sympathetic nervous system lies within the central nervous system itself, as suggested by Wartenberg (1945) and by Archambault and Fromm (1933) in the peri-ependymal zone of aqueduct and fourth ventricle, or as high as the posterior hypothalamus.

Certainly many of the cases are clearly associated with the localized form of scleroderma or morphea, although Singh and Bajpai (1969) go to great pains to delineate hemiatrophy of the face associated with morphea from primary facial hemiatrophy of Romberg (1846). Brain, in "Disease of the Nervous System" (1962), accepted that many cases were associated with scleroderma, whilst Walton in editing a later edition (1969) omitted this association. Rook, Wilkinson and Ebling (1966) in their discussion of morphea—the localised form of scleroderma—described facial hemiatrophy with the "en coup de sabre" deformity, sometimes with bleaching of the hair and eyebrow, hyperpigmentation at the edge of the lesion and pallor towards its centre, with or without deformity of the facial bone structure, hemiatrophy of the tongue, and involvement of lids, iris, fundus oculi and oculomotor muscles. Plaques of smooth shiny depigmented skin with a purplish border, hairless and analgesic, may be seen on the trunk and limbs, along with linear lesions.

Unilateral atrophy of one or more limbs may occur. Contractures may limit joint movement. Radiological evidence of spinal deformities, most often spina bifida, is frequent, lumbar pain being a common complaint.

Three cases of facial hemiatrophy have been seen at The Queen Elizabeth Hospital, Adelaide, by the Neurology Service in the last five years. These cases illustrate certain facets of the disorder.

CASE 1

Miss M.A.B. 40 years. Para-median crease in forehead noted aged 3. Fairly rapid wasting right side of the face over next year with little subsequent progression.

Infected thumb aged 14 followed by weakness of left arm, with evident weakness of left leg a year later. Poor circulation of left hand without classical Raynaud's symptoms. Some shortening of left tendo Achilles (corrected aged 34). Temporal lobe epileptic episodes with automatisms about twelve times yearly since aged 14, and rarely focal motor seizures involving left side of face and left arm. No grand mal seizures. Bilateral retro-orbital headaches. Corneal ulcer right eye aged 27, with severe visual impairment, No complaints of arthropathy.

On examination: Intellectual tests normal. Severe right hemifacial atrophy with "en coup de sabre" in right paramedian area of forehead and sunken area right zygoma, devoid of hair. Irregular area of brownish pigmentation and atrophy over right angle of jaw and upper neck 2½ diameter. Very ill defined area of brownish pigmentation in the perianal region bilaterally. Opaque right cornea, optic disc not visible. Pale left optic disc, visual acuity 6/6 on left, nil on right. No facial numbness nor weakness. Right sided deafness. Left hand and fingers smaller than right. Left leg shorter than right. Mild weakness of left trapezius, deltoid, triceps, finger extensors and abductors with milder weakness of flexors of left lower limb and left sided hypertonia and hyper-

reflexia with left extensor plantar response. Left sided inco-ordination. Minimal sensory impairment for two point discrimination and joint position sense in left upper limb. No evidence arthropathy. Electro-encephalograph (1974) showed alpha rhythms well developed on the left, absent on right, otherwise no abnormality. Airencephalogram (1960) showed dilatation of right lateral ventricle with some dilatation of cortical sulci. CSF normal.

CASE 2

Miss B.R.S. 50 years. Poliomyelitis aged 8 with fever and weak right leg. Hysterical aphasia aged 10. Poliomyelitis recurrence aged 11 with fever. Right sided facial hemiatrophy first apparent aged 15 associated with pigmentation of the atrophic area and atrophy of the right leg and thigh, accompanied by right sided headaches and 'blackouts' not classical of grand mal. Facial hemiatrophy really became noticeable aged 20 but probably has progressed little since. Intermittent lumbar backaches and right lumbosacral discomfort since aged 11. Severe Raynaud's phenomena aged 41. Bilateral cervical and lumbar sympathectomies aged 43. Subsequent right phrenic paralysis.

On Examination (1970): Reddish-brown depressed area in right paramedian region of forehead 'en coup de sabre'. Right enophthalmos, right superior oblique palsy, wasted atrophic right leg. Depressed atrophic discolored plaques right mid-dorsal region (D5), thoraco-lumbar regions bilaterally, right sacrum, right thigh, compound cellular naevus left axilla. Radiographs of chest: normal. Radiographs of skull: right hemicranial atrophy, small right mandibular ramus. Radiographs of spine: partial lumbarization of S1. EEG: normal. Air Encephalogram: slight dilatation right lateral ventricle. Electromyogram and nerve stimulation: slowed right posterior tibial nerve conduction velocity and fibrillations in right extensor digitorum brevis. Nerve biopsy: normal sympathetic ganglia and nerves in cervical and lumbar regions. Haematological and bio-chemical parameters: normal. Anti-nuclear factor absent.

Fig. 1.

Fig. 2.

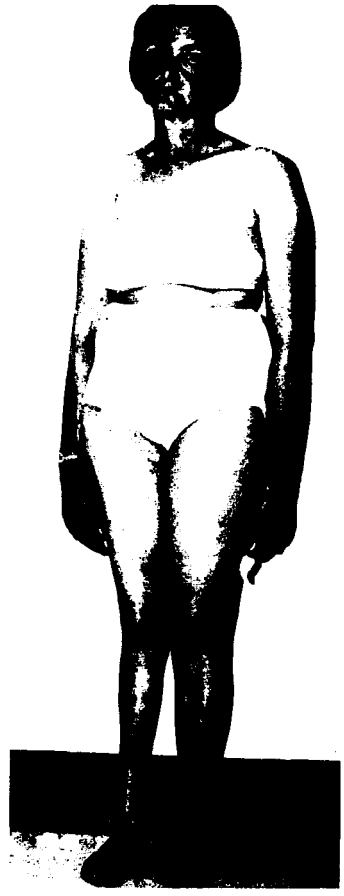

Fig. 3.

Gradual development of other patches over right temple, coccyx, sacrum, back of right thigh, right calf anteriorly and posteriorly. Continuing complaint of Raynaud's phenomena in hands and feet which however felt warm and dry. In 1970 could scarcely walk without aid, but condition responded well to psychotherapy and physiotherapy and she remained ambulant.

CASE 3

Mrs. D.B. Aged 50 years. Thickening beneath left breast noted at age of 20 years: diagnosed as localized scleroderma. Gradually increasing number of patches of depigmentation progressing later to pigmentation on trunk, arms and thighs. Aged 37: gradual onset of wasting left side of face, commencing below left eye, progressive for a year, but since static. Aged 42: two month episode blurred vision in left eye, painless, with full recovery, but relapsed aged 47 when minimal signs of left macular degeneration were noted. Episodic irritating rash all over body. Raynaud's phenomena.

Aged 47: operation for membranous bursa behind left knee. *On examination*: left vision 6/6—J3, full visual fields, no evident iris lesion. Loss of subcutaneous tissues left cheek with inability to bury eyelashes fully. Some limitation of back flexion and extension. Oval patches of depigmentation and pigmentation arms and trunk, with paler areas on thighs and macular yellowish rain-drop spots on abdomen and trunk where patient had scratched. Radiographs of skull and spine: normal. Radiographs of chest: calcified lesions left mid zone. Brain scan: normal. E E G: focal sharp and slow wave disturbance left mid-temporal region. Haematology and biochemical screen: normal. E S R: 9. Immunoglobulin O and M elevated. Left carotid ungeogram: intracranial branches of small calibre. Dermatologist reported "most of her integument has been damaged by scleroderma".

Aged 50: left eye very light-sensitive. *On examination* visual acuity unchanged. Mild left facial atrophy with atrophic left half of tongue. Slight left ptosis. Minimal pyramidal type weakness, with increased left limb tone and reflexes. Despite patient's report that left leg and arm smaller than right, no convincing asymmetry of limb bulk.

SUMMARY

Three cases of progressive facial hemiatrophy are presented. In all three cases there is evidence of localised scleroderma or morphea in association with the facial hemiatrophy. This would seem to support the contention that the two disorders are closely related.

In two cases, ocular complications are prominent and in one Raynaud's phenomena provide clear evidence of sympathetic hyperactivity in support of Wartenberg's hypothesis. In two cases epilepsy and asymmetrical dilatation of the lateral ventricle suggest that there may be a central rather than a peripheral cause for the sympathetic overactivity.

ACKNOWLEDGEMENTS

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ELECTROPHYSIOLOGICAL AND PATHOLOGICAL STUDIES IN SPINOCEREBELLAR DEGENERATIONS

J.G. McLEOD and J.A. MORGAN*

INTRODUCTION

It is now well established that in Friedreich's ataxia there are electrophysiological abnormalities in peripheral nerves which consist of impaired sensory conduction and mild slowing of motor conduction. (Dyck and Lambert, 1968; Preswick, 1968; McLeod, 1971; Oh and Halsey, 1973; Salisachs *et al.*, 1975). The impairment of sensory conduction has been correlated pathologically with loss of large diameter fibres in the peripheral nerve which in turn is related to the loss of dorsal root ganglion cells (Dyck and Lambert, 1968; McLeod, 1971).

Nerve conduction studies and sural nerve biopsy are therefore helpful in the diagnosis of Friedreich's ataxia but the changes in the peripheral nerve in patients with other forms of spinocerebellar degeneration are less well established. The object of the present work has been to perform electrophysiological and pathological studies on patients with other forms of spinocerebellar degeneration.

METHODS

Two children with classical Friedreich's ataxia, nine patients with hereditary spastic paraparesis and eleven patients with other forms of hereditary spinocerebellar degeneration were studied.

Motor conduction was examined in the median, ulnar and lateral popliteal nerves and sensory action potentials were recorded in the median and ulnar nerves. Mixed nerve action potentials were recorded from the ulnar nerve and from the lateral popliteal nerves. Neurophysiological techniques have been described fully elsewhere. (Walsh and McLeod, 1970). Sural nerve biopsy was performed in selected patients and quantitative studies were carried out on the myelinated and unmyelinated fibres (McLeod, 1971)

RESULTS

Friedreich's Ataxia

It is known that electrophysiological and pathological studies are helpful in the diagnosis of adult cases of Friedreich's ataxia but in order to determine whether or not the typical changes are also present in the younger age group, two patients aged six were examined. In both cases sensory conduction was impaired and there was a reduction in the numbers of large diameter fibres in the sural nerve biopsy (Figure 1).

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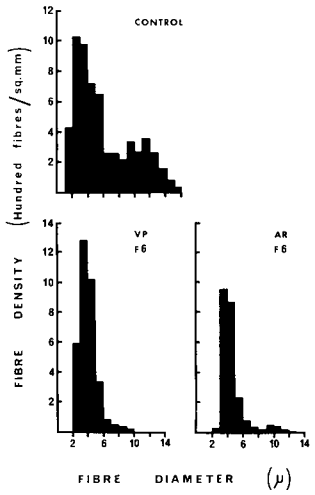

Fig. 1. Histograms of fibre diameter distribution of myelinated fibres in sural nerves of a control subject, and of two patients, aged six, with Friedreich's ataxia.

Hereditary Spastic Paraparesis

Hereditary spastic paraparesis is a hereditary disorder characterised by progressive weakness and spasticity affecting predominantly the lower limbs. There is no clinical evidence of involvement of cerebellar pathways or of the peripheral nervous system. Impairment of deep sensation has been described in some patients and is compatible with the finding of posterior column degeneration (Behan and Maia, 1974). The condition may be inherited as an autosomal dominant or as an autosomal recessive gene.

Nine patients in three families with the characteristic clinical features of the disorder have been studied, in two of whom the inheritance was dominant (Figure 2) and in one of whom the inheritance was recessive. In all patients studied motor and sensory conduction were entirely within the normal range (Figure 3). These findings are consistent with the pathological observations that the anterior and posterior roots and peripheral nerves are normal (Behan and Maia, 1974).

Sural nerve biopsy was performed on two sporadic cases of hereditary spastic paraparesis and in both cases the biopsy was normal.

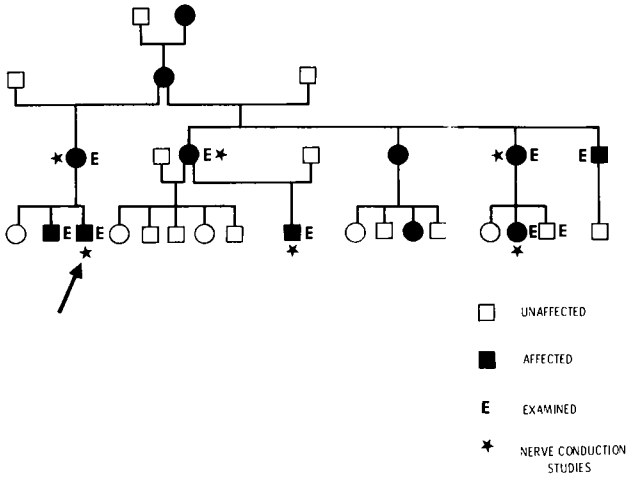

Fig. 2. Pedigree of one family studied with autosomal dominant form of hereditary spastic paraparesis.

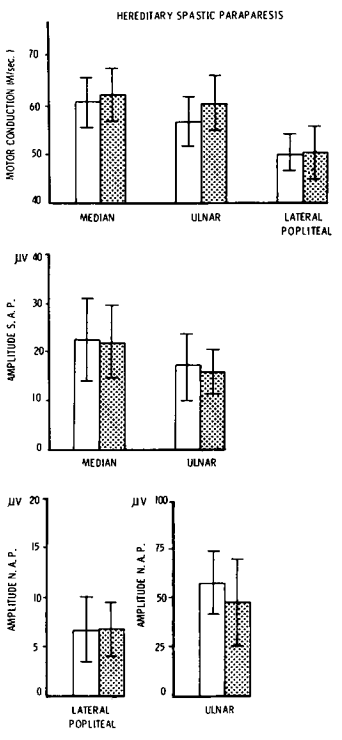

Fig. 3. Results of nerve conduction studies in patients with hereditary spastic paraparesis.

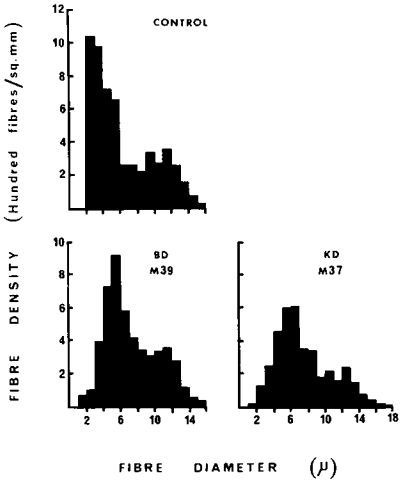

Fig. 4. Histograms of fibre diameter distribution of myelinated fibres in sural nerves of a control subject and two patients with olivo-ponto-cerebellar degeneration.

Other Spinocerebellar Degenerations

Serious difficulties arise in the clinical classification of the other hereditary spinocerebellar degenerations. As pointed out by Greenfield (1954) it is not possible to distinguish during life between the familial olivo-ponto-cerebellar degenerations and the pure cerebello-olivary or the late cortical cerebellar degenerations although it is recognised that pyramidal tract signs do not occur in the latter conditions.

Two members of the family with a dominantly inherited spinocerebellar degeneration have been studied and an autopsy was performed on one subject. In both cases the age of onset of ataxia and dysarthria was at the end of the second decade and there was a steady progression of disturbance of speech and gait. On examination there was marked dysarthria, nystagmus, gross inco-ordination of upper and lower limbs, brisk reflexes, extensor plantar responses and no sensory disturbance. There was no muscle wasting. Autopsy on the one patient revealed gross loss of Purkinje cells in the cerebellar cortex, degeneration of the inferior olives, degeneration of pontine nuclei and degeneration of spinocerebellar tracts, posterior columns and pyramidal tracts. The clinical and pathological features and mode of inheritance were similar to those of the Menzel type of olivo-ponto-cerebellar degeneration. Nerve conduction studies on both patients demonstrated mild impairment of sensory conduction and decrease in amplitude of mixed nerve action potentials.

Sural nerve biopsy was performed on both patients. There was mild reduction of the total density of myelinated fibres in one (3835 fibres per mm^2) but the other was within the normal range (5205 fibres per mm^2). Fibre diameter distributions were normal and in this respect the nerves differed from those of Friedreich's ataxia (Figure 4).

Nine other patients were also examined with similar clinical features, in whom there was clinical history of spinocerebellar degeneration. However it should be emphasized that there was no final pathological confirmation of the diagnosis in these patients. Electrophysiolog cal studies were performed. For the whole group of eleven patients it may be seen that although motor conduction velocity in most instances was within the normal range, there was a tendency for sensory conduction to be impaired (Figure 5).

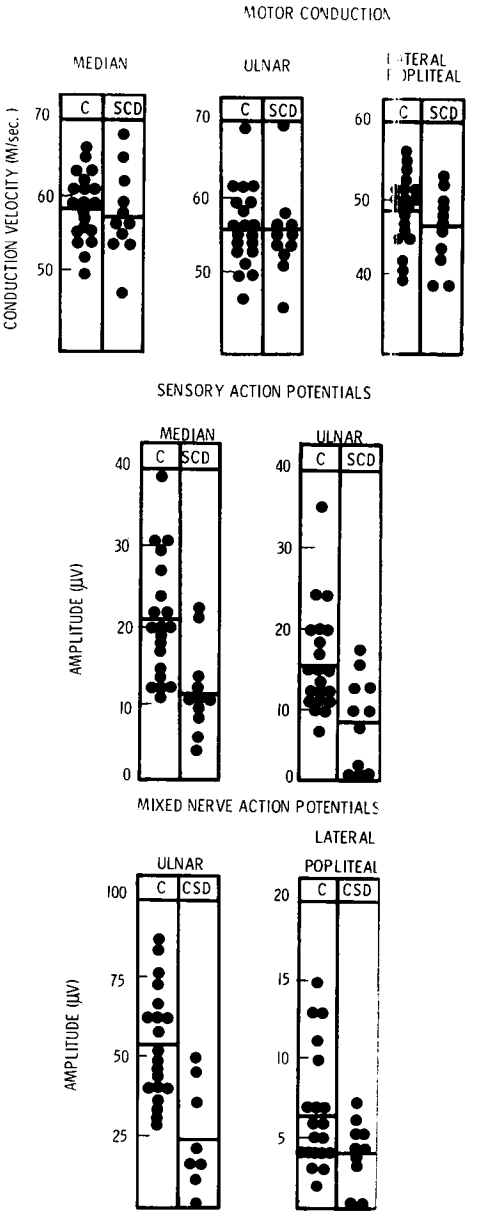

Fig. 5. Results of nerve conduction studies in patients with spinocerebellar degenerations other than Friedreich's ataxia and hereditary spastic paraparesis.

DISCUSSION

Impairment of sensory conduction and mild slowing of motor conduction are characteristic electrophysiological features of Friedreich's ataxia and are related to the loss of large diameter fibres in the peripheral nerves. The electrophysiological and pathological changes may be seen early, in the first decade. Dunn (1973) has shown that sensory action potentials may be absent as early as at two years of age in some patients.

In hereditary spastic paraparesis motor and sensory conduction are normal. These findings are consistent with the lack of clinical evidence of involvement of the peripheral nervous system in the condition. Impairment of deep sensation has been described in some patients but this is probably due to the degeneration of the posterior columns which sometimes occurs and does not imply involvement of the peripheral nervous system (Behan and Maia, 1974).

Electrophysiological studies are often mildly impaired in the other spinocerebellar degenerations so far studied in detail. In one family with familial olivo-ponto-cerebellar degeneration, although there was mild impairment of conduction, there was only slight reduction in fibre density in the sural nerve and there was no differential loss of the large diameter fibres such as may be seen in Friedreich's ataxia. It is concluded that electrophysiological studies and sural nerve biopsy are helpful in the differential diagnosis of the spinocerebellar degenerations.

SUMMARY

Electrophysiological and pathological studies have been performed on the peripheral nerves of patients with spinocerebellar degenerations. In Friedreich's ataxia there is impairment of sensory conduction and mild slowing of motor conduction which may be correlated with loss of large diameter fibres in the sural nerve. The abnormalities in Friedreich's ataxia are present early, in the first decade. In hereditary spastic paraparesis the nerve conduction studies and sural nerve biopsy are normal. In the other spinocerebellar degenerations including the Menzel type of olivo-ponto-cerebellar degeneration there is mild impairment of conduction and a mild loss of myelinated fibres in the sural nerve. However the abnormalities differ from those seen in Friedreich's ataxia.

ACKNOWLEDGEMENTS

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THE USE OF CLONAZEPAM IN THE TREATMENT OF TIC DOULOUREUX (A PRELIMINARY REPORT)

B. CHANDRA*

After carbamazepine came to be generally used in the treatment of trigeminal neuralgia, the therapeutic management of the condition was considered so easy that the general practitioner virtually lost interest in the disease (Blom, 1963; Rockliffe and Davis, 1966; Hassler and Walker, 1970). In recent years, however, reports have appeared to the effect that carbamazepine failed to meet the earlier expectations. Wepsic (1973) wrote that although the use of carbamazepine was initially successful in controlling the frequency of painful attacks of trigeminal neuralgia, the drug lost its effectiveness as time passed and the patient turned to surgical treatment. The present writer had the same experience with his patients. After initial favourable results with carbamazepine, some patients ceased to respond to the drug. Such patients usually were reluctant to undergo operations, and sought alternative drug therapy for relief of pain.

As some neurologists regarded trigeminal neuralgia as a form of sensory epilepsy (carbamazepine is an anticonvulsant) and as the anticonvulsant clonazepam was known to affect synaptic transmission at levels caudal to the mesencephalon, the author decided to try clonazepam in those patients with *tic douloureux* refractory to carbamazepine. Another consideration was that no serious side-effects from clonazepam had been reported (Chandra, 1972, 1973; Dunermuth and Kovacs, 1974).

MATERIAL AND METHODS

Between January 1st, 1967 and January 1st, 1974, 119 patients with trigeminal neuralgia were seen in the Outpatient Clinics of the Department of Neurology, Airlangga University School of Medicine, or in the private practice of the author in Surabaya. Diagnosis was made on the basis that the following criteria were present (Kerr, 1967; Finneson, 1969; Lance, 1969; Hassler and Walker, 1970):

1. intermittent sharp lancinating pain of short duration,
2. pain restricted to the distribution of the fifth cranial nerve,
3. no impairment of motor or sensory function of the fifth nerve or of any other motor or sensory nerve of the face, and
4. precipitation of the pain by stimulation of the face (trigger areas).

Initially all the 119 patients were given a trial with carbamazepine 400-600 mg per day in divided dose. Seventy-nine (66%) showed improvement while 40 patients (34%) did not respond well. From this latter group of patients, 20 were asked to co-operate in a trial of therapy with clonazepam. One patient did not continue long enough with this trial to allow proper evaluation. The remaining 19 patients ranged in age from 50 to 79 years (mean = 68 years). There were 12 female patients (63.2%) and seven male patients (36.8%). All the patients were initially seen by the author. Their progress was followed by means of personal interview. To rule out the possibility that spontaneous temporary subsidence of symptoms might be

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falsely attributed to medication, only those patients who had had the disease for more than one year were included.

The mandibular division of the trigeminal nerve was involved by pain in 11 patients (57.9%), and the maxillary division in ten patients (52.6%), while the ophthalmic division was involved only in two patients (10.5%). The right side of the face was affected in 12 patients (63.2%), the left side in seven patients (36.8%). None of the patients had any associated neurological illness. Ten days before the trial began, all previous medication was withdrawn. The dosage of clonazepam given to the patients was 0.1 mg/kg body weight/day. The duration of treatment was one year. The usual initial laboratory examinations e.g. complete blood count (including platelet count), urinalysis and liver function tests, were done on each patient before administration of the drug. These investigations were repeated at bi-monthly intervals after the trial was started.

This study began on January 1st, 1973 and concluded in July, 1974. For statistical purposes, the results of treatment were evaluated on the basis of the degree of remission obtained. The classification employed was as follows:

Poor: between 0 and 25 per cent decrease in painful attacks,
Fair: between 26 and 50 per cent decrease,
Sufficient: between 51 and 75 per cent decrease,
Good: between 76 and 99 per cent decrease,
Excellent: pain-free period of over four months.

RESULTS

The results of treatment are given in Table I.

Although side-effects were not rare, they were usually mild. They were present only in the initial stages of treatment and disappeared as treatment was continued. At no time was it necessary to interrupt treatment on account of these side-effects (Table II).

In all patients, EEGs were taken before and during administration of the drug. The use of clonazepam increased fast activity diffusely in the EEGs, as compared with the records before treatment.

TABLE I

Results of clonazepam treatment in 19 patients refractory to carbamazepine

Result	Excellent	Good	Sufficient	Fair	Poor
No. of patients	10	3	2	1	3

TABLE II

Frequency of side-effects with clonazepam treatment in 19 patients

Side-effect	Dizziness	Somnolence	Ataxia
No. of patients	2	1	1

DISCUSSION

Although the number of patients in this series is too small to arrive at a definite conclusion, the inference from the results (Table I) is that clonazepam shows some promise in the treatment of trigeminal

neuralgia. It appears justified to try clonazepam in cases of trigeminal neuralgia refractory to carbamazepine before considering surgical intervention.

Although side-effects were not rare (21%) they were mild and did not necessitate interruption of treatment. In the two patients who complained of dizziness, the ENT specialist who was consulted did not find any abnormalities in the vestibular apparatus. After a week the complaints disappeared spontaneously.

The influence of clonazepam on the EEG, which was reported earlier in studies on the use of clonazepam in *petit mal*, was seen also in this group of patients who were all in an older age group (Chandra, 1972; 1973).

Clonazepam is a benzodiazepine derivative which has been found 5 to 10 times more effective as an anticonvulsant than diazepam. Its formula is shown in Figure 1. Chemically clonazepam, hydantoins and barbiturates all contain the chemical grouping which Toman (1965) described as the classic anticonvulsant structure:

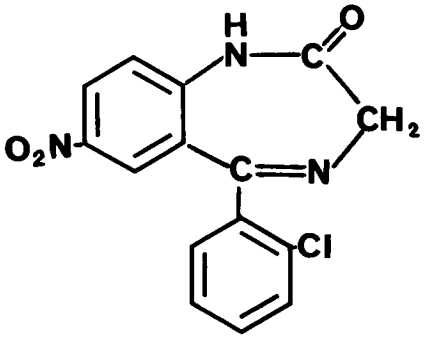

Fig. 1. Formula of clonazepam.

Carbamazepine has different structure, consisting of the tricyclic dibenzazepine ring. The only structural similarity between clonazepam and carbamazepine is than that both possess three rings in their molecules.

From animal experiments (on cats) it is known that clonazepam inhibits the spreading of seizure activity in the brain stem, thalamus and limbic system. If one considers trigeminal neuralgia as a form of sensory epilepsy with paroxysmal discharges, one might propose a hypothesis that clonazepam inhibits the spread of these abnormal discharges (Leung, 1972).

SUMMARY

Results are reported of a preliminary trial with clonazepam in 19 patients with trigeminal neuralgia refractory to carbamazepine treatment. In this series of patients, 13 (68.4%) showed excellent or good improvement. No serious side-effects were seen. The pharmacology and mechanism of action of clonazepam are discussed. It is suggested that patients with trigeminal neuralgia, who do not respond to carbamazepine, should be given clonazepam before surgery is considered.

ACKNOWLEDGEMENT

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SERIAL NERVE CONDUCTION STUDIES IN PATIENTS WITH MATURITY ONSET DIABETES MELLITUS

G. DANTA*

It is now widely accepted that functional and structural peripheral nerve abnormalities in diabetes mellitus are a consequence of metabolic disturbances. However, objective evidence of variation of peripheral nerve function and structure with changes in the metabolic state of diabetes is scanty. Nerves of rats with alloxan-induced diabetes have faster conduction velocities and their nerve fibres show lesser degrees of histological abnormality if hyperglycaemia is controlled than if it is left untreated (Preston, 1967). In humans, two published studies are available showing improvement of motor conduction velocity in peripheral nerves of patients with diabetes mellitus, during a period of treatment of hyperglycaemia of 35 days in one (Gregersen, 1968), and 6 months in the other (Ward et al, 1971). The present study extends these investigations by prolonging the period of observation, and also by studying conduction in sensory and mixed, as well as motor nerves.

MATERIAL AND METHODS

Eighteen patients and 10 control subjects were studied, the two groups being of similar sex and age composition. Control subjects were examined only once, while patients were re-examined at intervals of 6 months for up to $2\frac{1}{2}$ years. One patient died of myocardial infarction after the initial examination. The other 17 patients were examined 3 to 6 times. The mean period of observation was 1.4 years. In no patient was the hyperglycaemia severe, and good response to treatment with insulin, oral hypoglycaemic agents and diet, was maintained throughout the period of study in all patients.

Motor conduction was studied in both peroneal nerves and in the right median nerve between the axilla and elbow, and also between the elbow and wrist. Sensory conduction was studied in the right median nerve between the index finger and wrist. Mixed nerve conduction was studied in the right median nerve between the wrist and elbow, and also between the wrist and axilla. Surface electrodes were used throughout. For each evoked potential the latency, amplitude and duration were measured, and maximal conduction velocities were calculated. It was ascertained that neither room temperature nor skin temperature influenced the results.

Among the 18 patients 5 had a mild symmetrical peripheral neuropathy, one with a superimposed foot-drop. Eleven patients had some symptoms of peripheral nerve dysfunction, but apart from absent ankle jerks and impaired vibration sense in the feet found in some patients, no other signs of a generalized peripheral neuropathy were present. Two patients were asymptomatic and had no neurological signs.

RESULTS

During the period of study there was no extension of neurological signs, but improvement in signs was observed in only one patient, namely some recovery from foot-drop. A number of patients, however,

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reported improvement in peripheral neuropathic symptoms during the period of observation. Among 16 patients with symptoms, 2 reported disappearance of symptoms and 5 reported improvement.

Only 3 patients at the initial examination and one patient throughout the series of examinations were found to have entirely normal electro-physiological findings. In all other patients abnormalities in one or other of the parameters studied were present at some stage during the study.

Table I shows mean motor, sensory and mixed nerve conduction velocities in control subjects and in patients at 3 different periods, namely at the initial examination, then after treatment for 6 and 12 months, and finally after treatment for 18, 24 and 30 months. Results in patients at the initial examination were compared with values in control subjects, whereas results in patients during subsequent examinations were compared with their initial values. Statistically significant differences are indicated by asterisks. Systematic change during the period of study could only be shown for mixed nerve conduction velocities. There was a progressive increase in velocities (calculation of regression coefficients, $p<0.001$), and this is shown in Figure 1. Distal motor latencies did not differ significantly in patients and in control subjects at any period of the study.

Table II shows mean amplitudes of the sensory and mixed nerve action potentials. These were very variable and, although the means at the initial examination in patients were lower than in control subjects, only the mixed nerve action potential between the wrist and axilla was significantly so. When all subsequent examinations were compared with the initial one, it was found that the amplitudes of the sensory nerve action potentials decreased, whereas the amplitudes of the mixed nerve action potentials between wrist and axilla increased. In Figure 2 are plotted mean amplitudes of sensory and mixed nerve action potentials in patients during the period of study. There was a significant progressive decrease in sensory nerve action potential amplitudes (calculation of regression coefficient, $p<0.05$). No systematic change of compound motor action potential amplitudes was found.

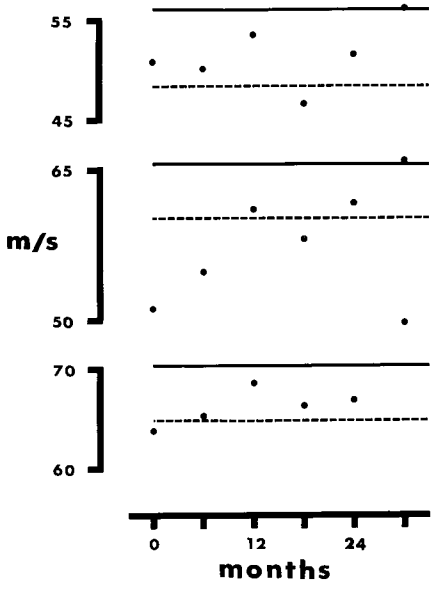

Fig. 1. Median nerve conduction velocities in patients at various stages of treatment. Mean sensory (top trace) and mixed nerve (wrist to elbow segment – middle trace; wrist to axilla segment – bottom trace). The solid line in each trace represents the mean values in control subjects, and the dotted line is 1 SD below the mean.

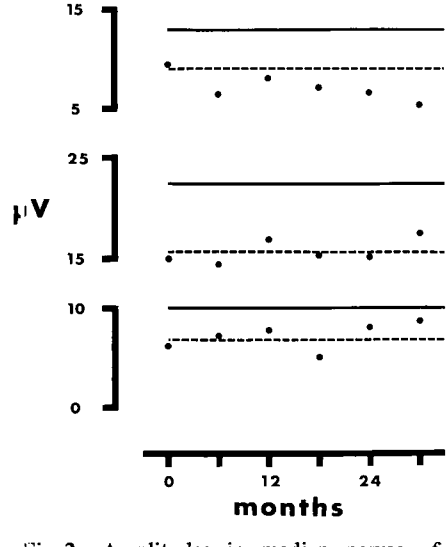

Fig. 2. Amplitudes in median nerves of patients at various stages of treatment. Mean sensory (top trace) and mixed nerve (wrist to elbow segment – middle trace; wrist to axilla segment – bottom trace). The solid line in each trace represents the mean value in control subjects, and the dotted line is 1 SD below the mean.

TABLE I

Mean maximal conduction velocities (m/s) in patients at initial examination, after 6–12, and after 18–30 months, and in control subjects. Number of examinations given in brackets. Probabilities for initial examination refer to differences from values in control subjects (Wilcoxon test). Probabilities for subsequent examinations refer to differences from initial values (sign test).

			Patients						Controls	
Nerve	Mode	Segment	Initial		6 – 12 mos		18 – 30 mos			
Peroneal	Motor	Knee to ankle	42.7**	(35)	43.6*	(66)	45.1***	(48)	47.1	(20)
Median	Motor	Axilla to elbow	60.8	(18)	63.3	(33)	63.3	(24)	65.0	(10)
Median	Motor	Elbow to wrist	55.8	(18)	54.0	(33)	53.7	(24)	58.3	(10)
Median	Sensory	Index finger to wrist	50.8	(15)	51.7	(24)	50.7	(22)	56.0	(10)
Median	Nerve	Wrist to elbow	52.9*	(16)	59.8	(32)	60.8*	(24)	65.6	(10)
Median	Nerve	Wrist to axilla	63.9*	(14)	67.0*	(28)	68.4*	(22)	70.3	(10)

* $p < 0.05$
** $p < 0.02$
*** $p < 0.01$

TABLE II

Mean amplitudes (μV) of median nerve sensory and mixed nerve action potentials in patients at initial examination, after 6–12, and after 18–30 months, and in control subjects. Number of examinations given in brackets. Probabilities for initial examination refer to differences from values in control subjects. (Wilcoxon test). Probabilities for subsequent examinations refer to differences from initial values (sign test).

	Stimulus	Recording	Patients						Controls	
Mode	Site	Site	Initial		6 – 12 mos		18 – 30 mos			
Sensory	Index finger	Wrist	9.4	(18)	7.2*	(33)*	6.6*	(24)*	12.9	(10)
Nerve	Wrist	Elbow	15.0	(18)	15.6	(33)	15.6	(24)	22.4	(10)
Nerve	Wrist	Axilla	6.2*	(18)	7.6**(33)**		6.7**(24)**		10.1	(10)

* $p < 0.05$
*** $p < 0.01$

DISCUSSION

Serial examination of nerve conduction in patients with maturity onset diabetes mellitus during a period of $2\frac{1}{2}$ years demonstrated two systematic changes. One was improvement in motor conduction velocity and progressive increase in mixed nerve conduction velocity. The other was progressive decrease in amplitude of sensory nerve action potentials but an overall increase in amplitudes of the mixed nerve action potentials in the same nerve.

Although one must exercise considerable reservation when extrapolating electrophysiological findings to structural changes, some inferences may reasonably be drawn. The reduction in conduction velocities in diabetics is best explained by paranodal and segmental demyelination of peripheral nerve fibres, a common finding in nerves of diabetic patients, both with and without neuropathy. Increase in conduction velocities then would likely be the result of remyelination in large nerve fibres.

Several explanations may be offered to account for the observation of a progressive fall of amplitude of the sensory nerve action potentials in the face of increase in motor and mixed nerve conduction velocity in the same nerve. Sensory nerve conduction in our study measured function in the most distal part of the peripheral nerve. It is possible, therefore, that while conduction improved in more proximal parts of the peripheral nerves as a result of repair of demyelination, a distal "dying-back" neuropathy progressed despite control of hyperglycaemia. One would then expect distal motor and sensory latencies to become prolonged, but this was not found.

Another explanation may be that sensory fibres, whose function is measured by sensory nerve action potential amplitudes, are affected in a manner different from other nerve fibres. Differential affection of motor and sensory nerve fibres in some diabetics has been observed histopathologically. For instance Dolman (1963) found much more severe demyelination within dorsal than ventral roots in some autopsy cases.

Whatever the explanation, it seems that two distinct processes impairing peripheral nerve function are operative in diabetes. As already mentioned, repair of demyelinated nerve fibres seems a likely explanation for the recovery of motor and mixed nerve conduction velocities. An independent process, possibly affecting the axons primarily and not responding to normalization of hyperglycaemia, would account for the finding of a progressive decline in sensory nerve action potential amplitudes. Bischoff (1973) has adduced evidence, based on electron microscopic studies of diabetic peripheral nerve fibres, of a primary affection of axons, distinct from any secondary axonal changes due to demyelination.

Our findings of a proressive fall in amplitude of the sensory nerve action potentials despite adequate treatment of hyperglycaemia is in keeping with the poor, protracted and inconsistent response to treatment of chronic established neuropathy in diabetes mellitus, and the fact that a predominantly sensory neuropathy is the commonest one seen in diabetic patients. Methods of treatment directed towards metabolic disturbances other than hyperglycaemia may be required to influence this process. At the same time our findings emphasize the importance of strictly controlling hyperglycaemia which was then associated with improvement in some aspects of peripheral nerve function.

SUMMARY

Serial study of peripheral nerve conduction in 18 patients with recently diagnosed maturity onset diabetes mellitus during a period of treatment of hyperglycaemia for 2½ years showed improvement in motor conduction velocity, progressive increase in mixed nerve conduction velocity, but at the same time progressive fall of amplitude of sensory nerve action potentials. It is argued that two independent metabolic processes may underlie peripheral nerve dysfunction in these patients, only one of which is beneficially affected by control of hyperglycaemia.

ACKNOWLEDGEMENT

I am grateful to Dr. L. Alexander for referring the patients from his diabetic clinic.

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MEASUREMENT OF CEREBROSPINAL FLUID IgG IN THE DIAGNOSIS OF MULTIPLE SCLEROSIS

E.W. WILLOUGHBY*

In the search for a diagnostic laboratory test for multiple sclerosis, interest has centred on the gammaglobulin fraction of the cerebrospinal fluid (CSF) proteins. Most patients with multiple sclerosis do have changes in the CSF gammaglobulins but the proportion found to have an abnormality depends to a large extent on the type of test used. An abnormality is most consistently seen when the CSF proteins are analysed by electrophoresis on agar or agarose gel. With this method, 79% to 94% of affected patients are reported to have an increased number of discrete bands in the gammaglobulin region, an appearance known as the "oligoclonal" pattern (Laterre, Callewaert, Heremans and Sfaello, 1970; Link and Muller, 1971; Stenuit and Delmotte, 1972). Similar changes have been reported as "false positives" in up to 5% of patients with other neurological disorders (excluding acute infections of the central nervous system).

Unfortunately electrophoresis has disadvantages which make it unsatisfactory for routine use. Preliminary concentration of 4 to 5 ml of CSF is necessary and assessment of the protein pattern requires experience and can be difficult. It is essentially a qualitative procedure. There have therefore been a number of methods described for quantitation of CSF gammaglobulin and, more recently, IgG specifically. The results are most reliably expressed by recording gammaglobulin or IgG as a percentage of total CSF protein or of CSF albumin. Abnormally high IgG levels are reported in from 55% to 87% of patients with multiple sclerosis and in up to 20% of patients with other neurological disorders, depending on the method used (Hartley Merrill and Claman, 1966; Schneck and Claman, 1969; Riddoch and Thompson, 1970; Tourtellotte, 1970; Fischer-Williams and Roberts, 1971; Link and Müller, 1971; Berner, Ciemins and Schroeder, 1972; Savory and Heintges, 1973; Ansari, Wells and Vatassery, 1975).

Many of the reports have come from laboratories engaged in active research on CSF proteins and it is difficult to determine the place of measurement of CSF IgG in day to day clinical practice in a centre such as Auckland with laboratories occupied largely with routine work. The present report outlines recent experience in Auckland Hospital with the measurement of CSF IgG, concentrating on its value as a diagnostic aid in patients with suspected multiple sclerosis. Most of the results have been obtained with the widely used technique of Single Radial Immunodiffusion but preliminary results of measurement of IgG and albumin in CSF and serum using the newer technique of Electroimmunodiffusion (Rocket Immunoelectrophoresis) will also be described.

LABORATORY METHODS

Quantitation of CSF and serum IgG by Radial Immunodiffusion was carried out on Partigen plates supplied by Behringwerke, using enclosed instructions and standard Behringwerke IgG solutions. A 20 μl sample of unconcentrated CSF or standard solution was put into each well in the agarose, the area enclosed by the ring of precipitate which forms around the well being proportional to the concentration of

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IgG in the sample. Precipitate diameters were measured after three days diffusion at room temperature. In the Auckland laboratory the error with this technique can be expressed as a coefficient of variation of 5%. Total CSF protein was measured by a standard turbidimetric method using sulphosalicylic acid (Ayer, Dailez and Fremont-Smith, 1931). Accuracy is said to be ±5 to 10% but unexpected variations and odd results occur in our laboratory at times. Electroimmunodiffusion or Rocket Immunoelectrophoresis was carried out on serum and CSF using the technique of Laurell (1972), and electrophoresis apparatus and IgG standards supplied by Behringwerke. Concentrated human serum albumin obtained from Commonwealth Serum Laboratories was dialysed, freeze-dried and weighed to produce a standard albumin solution. Samples of standard human serum (Behringwerke) were used as controls. Anti-IgG or anti-albumin antiserum (Dakopatts) was added to 1% agarose (Miles Laboratory) in 0.075 molar barbitone buffer (pH 8.6) so that the concentration of antiserum was 1% by volume. IgG and albumin were estimated on separate plates using unconcentrated CSF samples and serum diluted 1 : 100 with normal saline for IgG, and 1 : 400 for albumin. The voltage applied across the plates was 11 volts/cm for four hours for albumin and 11 volts/cm for sixteen hours for IgG. Albumin produced a sharp anodal rocket with its base at the well and the more heterogeneous IgG, which migrated largely towards the cathode but partly towards the anode, with this antiserum produced a more plump, cigar-shaped precipitate straddling the application well. In each case the length of the precipitate was proportional to the concentration of antigen in the sample in the well. The plates were dried by compression with filter paper and the precipitates stained with Coomassie Brilliant Blue.

PATIENTS

Cerebrospinal fluids from 206 patients were studied, 150 by Radial Immunodiffusion alone, 16 by Rocket Immunoelectrophoresis alone. In a further 40 both methods were used. All 16 patients studied by Rocket Immunoelectrophoresis alone had "other neurological diseases" (see below). The patients were divided into 4 groups.

Group 1.—Multiple Sclerosis. In 18 of the 22 patients in this group, a clinical diagnosis of definite or probable multiple sclerosis was made, without reference to the CSF IgG result, by the neurologist in charge of the patient. The ages of the patients ranged from 23 to 56 years. When the CSF sample was taken all but 2 patients had an exacerbation of their disease and except for 1 patient who had been taking prednisone, 60 mg. daily for 3 days, none were treated with corticosteroids. The other 4 patients in this group were middle-aged, with the syndrome of progressive spastic paraparesis of uncertain cause. In 3 of the 4, the latency of visual evoked cerebral potentials after stimulation by pattern reversal was measured, with abnormal results in all 3.

Group 2.—153 patients with other neurological disorders, excluding those disorders in Group 4 and patients with meningitis or subarachnoid haemorrhage. The disorders involved were as follows: epileptic seizures—29; cerebrovascular disease—23; peripheral neuropathy—17; presenile or senile dementia—18; tumours of brain or spinal cord—14; miscellaneous—52.

Group 3.—"Normals". 19 patients with no known structural neurological disease. All had been admitted to hospital for investigation, mostly because of headaches which proved to be either migrainous or associated with depression.

Group 4.—12 patients with neurological disorders (other than multiple sclerosis) in which the CSF IgG is often raised. Included were 8 persons with neurosyphilis, 3 with encephalitis (2 with viral encephalitis and 1 with encephalomyelitis of the post-infectious type) and 1 patient with subacute sclerosing panencephalitis.

RESULTS

a. Radial Immunodiffusion. CSF IgG values recorded as a percentage of total CSF protein are plotted in

Figure 1 for 190 patients. The dotted line at 14% represents the mean of the group of "normals" plus 2 standard deviations (6.2 + 7.6), and could be considered to be the upper limit of the normal range. However, because of the small number of patients in this group, values of 15% and 16% were considered to be borderline normal. All of the patients with values above 14% had normal serum IgG levels (also measured by Radial Imunodiffusion) and those in Groups 1 and 2 had negative serological tests for syphilis in the CSF.

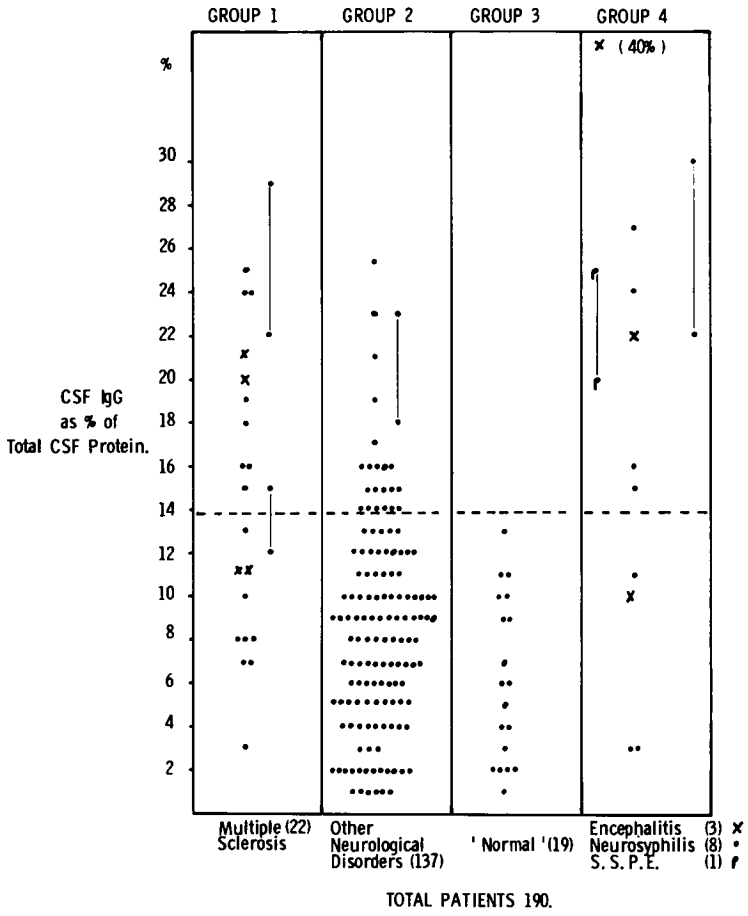

Fig. 1. CSF IgG measured by Radial Immunodiffusion and recorded as a percentage of total CSF protein in 190 patients. The numbers of patients in each group are in brackets. The four crosses in Group 1 indicate middle-aged patients with the syndrome of progressive spastic paraparesis of undetermined cause. The plots joined by a line indicate two CSF samples taken at different times from one patient. The dotted line at 14% represents the mean of the values for Group 3, plus 2 standard deviations (6.2 – 7.6).

In Group 1 only 6 of the 18 patients with typical multiple sclerosis had values convincingly above the normal range (i.e. 17% or above) and there were a further 4 in the borderline zone of 15% to 16%. The CSF IgG value did not correlate well with the clinical severity of the disease nor with the certainty of the clinical diagnosis. Four of the patients with values comfortably within the normal range had active typical disease and 2 patients each with the convincingly high value of 24% had only minor signs and were considered to be probable rather than definite cases of multiple sclerosis. Total CSF protein in the 18 patients ranged from 12 to 156 mg/100ml (normal up to 55 mg/100 ml). The 6 patients with total protein levels above normal had active disease of at least moderate severity but none had CSF IgG percentage values

above 16%. The 6 patients with values of 18% or above all had normal CSF total proteins. Two of the middle-aged patients with progressive paraparesis had high values and 2 were normal while all 4 had normal total CSF protein levels. Only 3 patients in Group 1 had increased numbers of white cells in the CSF (13, 19 and 28/cmm), their CSF IgG percentage values being 6, 15 and 25% respectively.

Of the 137 patients with other neurological disorders in Group 2, only 6 had CSF IgG percentage values above 16% but there were a further 10 in the borderline zone of 15% to 16%. The patients with significantly high values included a woman of 48 years with sensory symptoms attributed to a left cerebral hemisphere lesion of an uncertain nature (25%), a man of 70 years with lymphosarcoma not clinically affecting the nervous system (23%), a woman of 33 years with headaches and odd neurological symptoms classified as possible multiple sclerosis (21%), a woman of 63 years with motor neurone disease (19%), a man of 63 years with presenile dementia (17%) and a boy of 16 years with lymphocytic leukaemia affecting the central nervous system (23% and 18%—the lower value being obtained after treatment when the neurological signs had largely resolved and the white cells in the CSF had disappeared). Of the 10 patients in the borderline zone, 3 had cerebrovascular disease, 2 had subacute myelopathy of uncertain cause, 2 had epileptic seizures, 2 had the Guillain-Barré syndrome and 1 had a palsy of cranial nerve VI of uncertain cause. Only 4 of the 16 patients with high or borderline values had symptoms and signs which might have suggested a diagnosis of multiple sclerosis.

The mean value ± 1 standard deviation for Group 1 was 15.0 ± 7.0, and for Group 2 the mean was 8.7 ± 5.0. Although these values are significantly different ($p < .005$) there is clearly no sharp distinction between the Groups if one is considering the result for an individual patient. The results for the patients in Group 4 will not be discussed.

b. Rocket Immunoelectrophoresis. Results of measurement of IgG and albumin in CSF and serum were recorded by calculating the ratio IgG/albumin in the CSF and serum separately and by dividing the CSF ratio by the serum ratio to produce an Index. Results for this calculated Index in 56 patients are plotted in Figure 2. The dotted line at 0.85 represents the upper limit of the normal range defined by Delpech and

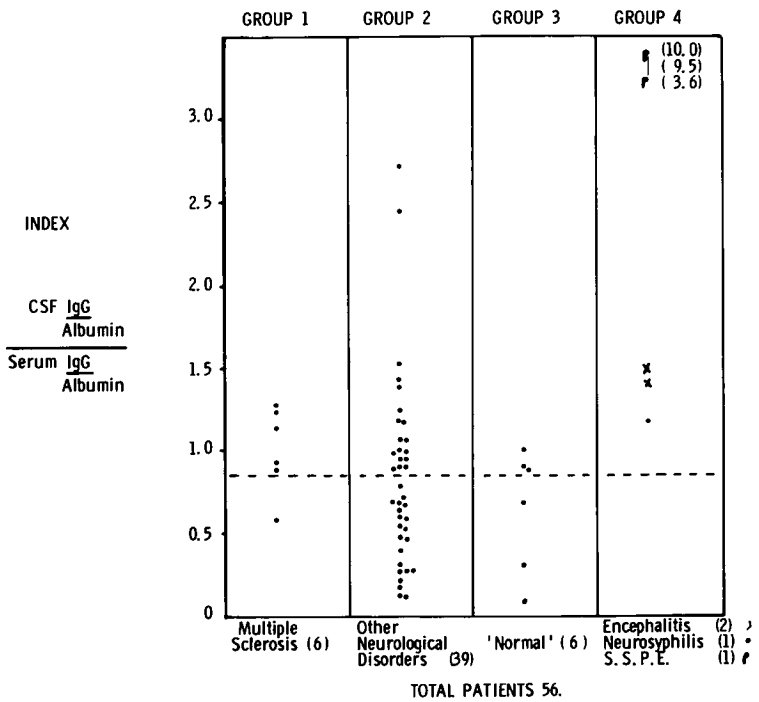

Fig. 2. Results for measurement of IgG and albumin in serum and CSF by Rocket Immunoelectrophoresis in 56 patients, the result for each patient being recorded as the calculated Index. The dotted line at 0.85 represents the upper limit of the normal range defined by Delpech and Lichtblau (1972).

Lichtblau (1972). The few normal results in this series indicate that our upper limit of normal will be higher than that of Delpech and Lichtblau (1972). Whatever the limits of the normal range, it is clear that the separation of patients with multiple sclerosis from those with other neurological disorders in this series is even less satisfactory than with the method of assessment illustrated in Figure 1. Patients in Group 2 with a high value for the Index included a woman of 33 years with myocarditis and patchy neurological lesions of an uncertain nature (Index of 2.73), a woman of 73 years with multiple cerebral secondary deposits (Index of 2.46), a woman of 69 years with encephalopathy and jaundice of uncertain cause (Index of 1.52), a man of 54 years with visual loss due to an unruptured anterior communicating artery aneurysm (Index of 1.43), a man of 29 years with subacute bacterial endocarditis and a cerebral infarct (Index of 1.24) and a man of 27 years with long-standing left sided and generalised epileptic seizures (Index of 1.23).

CSF IgG was measured by both methods in 40 patients. Rocket Immunoelectrophoresis gave absolute levels for CSF IgG in general 30% to 40% higher than those obtained by Radial Immunodiffusion. When the CSF IgG percentage value measured by Radial Immunodiffusion and the Index obtained by Rocket Immunoelectrophoresis were compared in individual patients the correlation was rather variable. For example, the 3 patients of Group 1 in Figure 2 with clearly raised values for the Index (1.27, 1.23 and 1.13) had IgG percentage values of 8, 15 and 25% respectively, and patients in Group 2 (Figure 2) with Index values of 2.46, 1.43 and 1.37 had IgG percentage values of 13%, 4% and 10% respectively.

DISCUSSION

The Radial Immunodiffusion results are similar to those described in previous reports (Riddoch and Thompson, 1970; Link and Müller, 1971; Ansari, Wells and Vatassery, 1975). In the present study a little over half of the patients with multiple sclerosis (12 of 22) had a CSF IgG percentage value either slightly or convincingly above normal and 16 of 137 (12%) of a group of patients with other neurological disorders also had a value above normal. It is clear that a normal CSF IgG level (recorded as a percentage of total CSF protein) in no way argues against a diagnosis of multiple sclerosis. On the other hand, a convincingly high level in a patient with a disorder suggestive of multiple sclerosis, with normal serum IgG levels and negative CSF serology, for syphilis, does provide reasonable support for the diagnosis.

Apart from the need to rely on the doubtfully accurate total CSF protein measurement, one of the main disadvantages of this method is the difficulty in evaluating the significance of a high CSF IgG in the presence of raised serum IgG levels. In this situation increased amounts of IgG leak from the serum into the CSF, even in the absence of neurological disease. As there is no consistent correlation between CSF and serum IgG levels in different patients (Hartley, Merrill and Claman, 1966), there is no satisfactory way of correcting for the raised serum level. Simultaneous measurement of IgG and albumin in CSF and serum which can be done simply by Rocket Immunoelectrophoresis, is one way of overcoming this problem. Relating IgG in both CSF and serum to albumin as a reference protein makes allowance for a rise in CSF IgG resulting from an isolated rise in serum IgG. Results can be recorded by plotting the ratio IgG/albumin in the CSF against the same ratio in the serum but can be illustrated more satisfactorily by dividing the CSF ratio by the serum ratio to produce an Index as was done in Figure 2. Delpech and Lichtblau (1972) and Ganrot and Laurell (1974) have shown that there is a significant correlation between these ratios in normal patients and that a normal range can be more clearly defined when these ratios are compared than when the ratio CSF IgG/albumin is considered in its own. Using this method Ganrot and Laurell (1974) were able to separate clearly patients with multiple sclerosis from normal subjects, although Delpech and Lichtblau (1972) were less successful. In the present study, separation of patients with multiple sclerosis from those with other neurological disorders was no better with this technique than by recording CSF IgG measured by Radial Immunodiffusion as a percentage of total CSF protein. However patients with high serum IgG levels could not be assessed by the latter method.

There are reasons for suspecting that, in this study, the rather unsatisfactory results obtained with Rocket Immunoelectrophoresis are at least partly due to technical difficulties with the method. Grubb (1970) and Ansari Wells and Vatassery (1975) obtained similar absolute CSF IgG values with Radial Immunodiffusion and Rocket Immunoelectrophoresis whereas our values were, in general, 30 to 40% higher

with the latter technique. Some of our earlier results when we had difficulty finding a satisfactory standard albumin solution are of uncertain reliability. A further source of error may be the prolonged storage at −20°C for several months of most of the CSF and serum specimens, some of which were thawed and refrozen twice, before the measurements by Rocket Immunoelectrophoresis were made.

Despite these discouraging results, we plan to continue to try and improve the technique of Rocket Immunoelectrophoresis as it offers some potential advantages over Radial Immunodiffusion for assessing IgG. An electrophoresis chamber with power source is necessary and although it takes a little more time to set up a batch of tests, it is cheaper to run. There are at least theoretical advantages in measuring all proteins by the same method and in not having to rely on the total CSF protein measurement. Recording CSF IgG as a percentage of total CSF protein is probably not reliable when the total protein is less than 10 mg/100 ml. (Schneck and Claman, 1969; Fischer-Williams and Roberts, 1971). It is also useful to be able to assess the significance of a high CSF IgG in a patient with a raised serum IgG level. This is particularly important in Auckland where there are a large number of Polynesians who tend to have serum IgG levels distinctly higher than those in Europeans. We proceed, however, with a certain amount of scepticism about the value of any of the quantitative methods for measuring CSF IgG as, even if the technique is reliable, the information obtained is of limited value to a clinician faced with a diagnostic problem in an individual patient.

SUMMARY

CSF IgG was measured in 190 patients by Single Radial Immunodiffusion. A high value for the ratio CSF IgG/total protein (normal values being up to 14%) was obtained in 12 of 22 patients (54%) with definite or probable multiple sclerosis and in 16 of 137 patients (12%) with other neurological disorders excluding acute infections, subarachnoid haemorrhage and neurosyphilis. In 56 patients IgG and albumin were measured in CSF and serum using Rocket Immunoelectrophoresis (Electroimmunodiffusion) and results assessed by dividing the radio IgG/albumin in the CSF by the same ratio in the serum to obtain an Index. Because of the small number of normal patients, it was not possible to define a normal range but separation of patients with multiple sclerosis from those with other neurological disorders was even less clear-cut than with the first method. Minor technical difficulties with the Rocket technique and prolonged storage of some of the specimens may at least partly explain the discouraging results with this method. It was concluded that the measurement of CSF IgG was of limited value to a clinician attempting to make a diagnosis in an individual patient with neurological disease.

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HISTAMINE$_2$–RECEPTOR BLOCKADE WITH CIMETIDINE IN THE MONKEY CRANIAL CIRCULATION

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INTRODUCTION

The pathogenesis of classical and common migraine and cluster headache is as yet unknown. Although histamine is one of the humoral agents which have been implicated in these conditions (Sicuteri, 1967; Anthony and Lance, 1971), a cogent argument against its involvement has been the apparent failure of conventional antihistamines such as mepyramine and diphenhydramine to provide worthwhile therapeutic benefit (Kallós and Kallós-Deffner, 1955; Ostfeld *et al.*, 1957; Rooke *et al.*, 1962).

For many years it has been known that some of the actions of histamine, such as provoking secretion of gastric acid, cannot be blocked by conventional antihistamines. This stimulated a search for drugs which could antagonize these refractory effects of histamine. The first report of an agent which possessed such activity was that of Black *et al.* (1972), who demonstrated that burimamide blocked the gastric acid secreting action of histamine in rats, cats, dogs and man. Ash and Schild (1966) had previously suggested that histamine receptors could be subdivided into different classes, following experiments using a variety of histamine analogues which possessed agonistic activity. On this basis, the conventional antihistamines were designated histamine$_1$-receptor antagonists, and burimamide was termed a histamine$_2$-receptor antagonist.

Since the introduction of burimamide, metiamide (Black *et al.*, 1973) and more recently cimetidine (Brimblecombe *et al.*, 1975a, b) have been shown to be histamine$_2$-receptor antagonists. Both of these compounds are much more potent than burimamide, and are well absorbed when administered orally. Unfortunately, metiamide, which has a thiourea group in the side chain, was associated with leucopenia in 3 of the 450 patients initially tested with the drug (Lancet editorial, 1975). Cimetidine has no thiourea group, and leucopenia has not been detected in animal toxicity studies (Brimblecombe *et al.*, 1975a, b) or in the clinical trials performed so far (Balmer, personal communication).

Since histamine receptors can be subdivided into two groups, it is possible that the cranial vascular actions of histamine may be mediated by either histamine$_1$-receptors, or histamine$_2$-receptors, or by both. The apparent lack of efficacy of histamine$_1$-receptor antagonists in cluster headache and migraine may therefore be related to the nature of the cranial vascular histamine receptors rathen than histamine not being involved in the pathogenesis of these conditions. To investigate the nature of the cranial vascular receptors for histamine in primates, and hence to determine whether cimetidine may be of potential benefit in cluster headache and migraine, we have compared the effects of cimetidine and mepyramine on cranial and systemic vasodilator responses to histamine in anaesthetized monkeys. Changes in internal and external carotid vascular resistance induced by intracarotid infusions of histamine were used to evaluate cranial vascular reactivity, and the vasodepressor effects of i.v. doses of histamine provided a measure of systemic vascular reactivity.

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METHODS

Eight *Macaca nemestrinas* monkeys (4.0 to 8.5 kg) were anaesthetized with pentobarbitone sodium (30 mg kg^{-1} i.v.), paralysed with gallamine triethiodide (4 mg kg^{-1} i.v.) and artificially ventilated with room air via an endotracheal tube. Expiratory CO_2 levels were monitored to ensure that ventilation was maintained at pre-paralysis levels. Arterial blood pressure was measured continuously with a pressure transducer connected to a polythene catheter passed into the aortic arch via a femoral artery. A polythene catheter in a femoral vein was used for i.v. administration of drugs and fluids. Anaesthesia was maintained during the course of the experiment by continuous i.v. infusion of pentobarbitone sodium (6 mg $kg^{-1}h^{-1}$) and gallamine triethiodide (8 mg $kg^{-1}h^{-1}$) in an i.v. drip solution (0.9% w/v sodium chloride or 5% w/v dextrose). Rectal temperature was maintained in the range 36 to 38° C.

The common and external carotid arteries on one side were exposed, and electromagnetic flow probes were placed on both vessels. Blood flows were monitored with two electromagnetic flowmeters, and recorded on a pen recorder. Zero flow references were obtained periodically by occluding the vessels distal to the appropriate probe. A fine vinyl catheter with an aperture in the wall was passed into and out of the common carotid artery, with the aperture dwelling in the lumen of the vessel. One end of this catheter was used for the intracarotid infusion of solutions of histamine or other vasoactive agents by a motor-driven syringe. The other end of the catheter was connected to a pressure transducer, so that perfusion pressure in the region of the carotid bifurcation, *i.e.* carotid bifurcation blood pressure (CBBP), could be recorded. Aortic arch blood pressure and expiratory CO_2 levels were also recorded.

The dissection, and the methods of measurement of blood flow and other parameters, have been described in detail by Welch *et al.* (1974) and Spira *et al.* (1976). However, in the present experiments, carotid bifurcation rather than aortic arch blood pressures were used to calculate all vascular resistances, since carotid bifurcation blood pressure is a more accurate indication of changes in the cranial circulation (Spira *et al.*, 1976). Venous pressures in the internal and external carotid circulations were assumed to be zero, and the pressure difference across the circulation concerned was considered to be equal to carotid bifurcation blood pressure. Internal carotid blood flow (ICF) was calculated by subtracting external carotid blood flow (ECF) from common carotid blood flow. Internal carotid vascular resistance (ICVR) and external carotid vascular resistance (ECVR)were calculated from the equations ICVR = CBBP/ICF and ECVR = CBBP/ECF. The changes in internal and external carotid vascular resistance induced by intracarotid infusions of histamine and other vasoactive agents were expressed as percentages of the steady-state values of resistance immediately preceding each infusion.

Cumulative dose-response curves for the effects of intracarotid infusions of histamine in the internal and the external carotid circulations were obtained by increasing the rate of infusion of the histamine solution each time the changes in bloof flow reached peak levels, until no further changes in blood flow could be elicited. The cranial vasoconstrictors noradrenaline and 5-hydroxytryptamine, and the cranial vasodilators bradykinin and prostaglandin E_1, were also infused into the carotid circulations in these experiments, to validate the responsiveness of the monkey and to assess the specificity of the antihistamines. Histamine was also given by i.v. injection in varying doses to obtain dose-response curves for the systemic vasodepressor effects of histamine.

In each monkey used in these experiments, reproducible control dose-response relationships were established for cumulative intracarotid infusions of histamine and at least one of the other vasoactive agents, and for the vasodepressor effects of i.v. injections of histamine. Cimetidine or mepyramine was then administered by i.v. injection over a 30 second period. After 10 minutes, cumulative intracarotid infusions of histamine and the other test agents and i.v. injections of histamine were repeated, separated by at least 10 minutes to allow recovery. This procedure was then repeated using a higher dose of antihistamine. In four of the monkeys used in these experiments, cimetidine was used first, in three successively increasing doses given at intervals of approximately 90 minutes. After completing the intracarotid and i.v. administration of the test agents, a subsequent dose of 2 mg kg^{-1} of mepyramine was then given, and the intracarotid and i.v. effects of histamine were again tested. In the other four monkeys, mepyramine was used at three successively increasing dose levels, and in one of these monkeys, cimetidine (1 mg kg^{-1}) was subsequently administered. In each experiment, cranial vascular responses to histamine and the other vasoactive agents (*i.e.* changes in internal and external carotid vascular resistance) were expressed as percentages of the

maximal effect (E_{max}) obtained in each circulation in their control infusions, and these values were used to construct cumulative dose-response curves. The ratio of the dose of histamine or other vasoactive agent producing a given effect in the presence of cimetidine or mepyramine to the dose producing an equivalent effect in the control curve, *i.e.* the dose ratio, was determined at 50% of the E_{max} in each curve. A dose ratio greater than 1 indicates a shift to the right of the dose-response curves. The extent of the shift, as indicated by the dose ration, is directly related to the degree of blockade. Modification of the cranial vascular responses to the test agents by cimetidine or mepyramine was assessed in terms of the mean values of dose ratio and E_{max}. Dose-response curves for the vasodepressor effects of histamine were also constructed, and dose ratios were evaluated at an arbitrary response level of a decrease of 15 mm Hg in diastolic blood pressure. The mean values of these dose ratios were used as a measure of blockade of vasodepressor responses to histamine.

The drugs used were histamine dichloride (Calbiochem), 5-hydroxytryptamine creatinine sulphate and mepyramine maleate (May & Baker), noradrenaline acid tartrate (Sterling), prostaglandin E_1 (Upjohn), bradykinin (Sandoz), and cimetidine (SK&F 92334) (Smith, Kline & French). Doses were expressed in terms of the active moieties, with the exceptions of histamine and mepyramine which were expressed in terms of the salts. Stable stock solutions of the drugs were diluted with 0.9% w/v sodium chloride solution immediately before use.

In the external carotid circulation, cimetidine in doses of 0.25, 1 and 5 mg kg^{-1} blocked the vasodilator response to intracarotid infusion of histamine. The blockade produced by 1 mg kg^{-1} of cimetidine is illustrated in Figure 1, which shows tracings from a typical experiment. Greater doses of histamine are re-

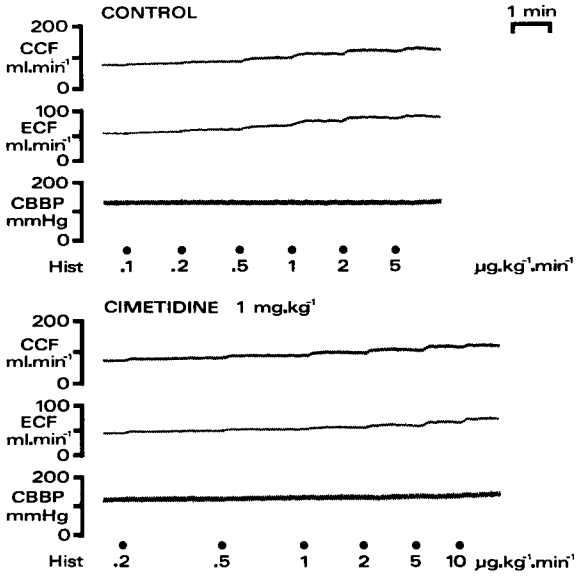

Fig. 1. Tracings from an experiment showing the effects of cumulative intracarotid infusions of histamine at the indicated dose levels on common carotid blood flow (CCF), external carotid blood flow (ECF) and carotid bifurcation blood pressure (CBBP), before (upper panel) and after i.v. administration of cimetidine (lower panel).

quired to produce blood flow changes equivalent to those produced during the control histamine infusion. Cumulative dose-response curves for histamine-induced decreases in external carotid vascular resistance were shifted to the right in a parallel fashion by cimetidine, and the mean dose ratios from all experiments are shown in Table 1. The two higher doses of cimetidine produced small decreases in the maximal response to histamine, as indicated by the E_{max} values quoted in Table 1. Cimetidine antagonized the internal carotid vasodilator response to intracarotid histamine to a lesser extent, appreciable blockade occurring only after the 5 mg kg^{-1} dose (Table 1). Maximal responses to histamine were slightly increased.

TABLE I

Effects of cimetidine on responses to histamine. Values shown are means (±S.E.) of the dose ratios and E_{max} values (% of control E_{max}) determined from cumulative dose-response curves. Dose ratios and E_{max} values are also shown for the subsequent administration of mepyramine in these experiments.

Response	Parameter	Cimetidine (mg kg^{-1})			Mepyramine (mg kg^{-1})
		0.25	1	5	2
External carotid dilation (n = 4)	Dose ratio	1.5 ± 0.2	2.0 ± 0.1	9.3 ± 4.3	14.0 ± 3.7
	E_{max}	104 ± 5	85 ± 10	72 ± 6	130 ± 8
Internal carotid dilation (n = 4)	Dose ratio	1.0 ± 0.3	1.1 ± 0.3	3.4 ± 1.2	25.6 ± 18.4
	E_{max}	100 ± 18	112 ± 34	12[illegible] ± 38	91 ± 5
Vasodepression (n = 4)	Dose ratio	0.6 ± 0.1	0.8 ± 0.2	0.[illegible] ± 0.4	15.8 ± 8.4

n = Number of experiments

In these experiments, the subsequent administration of 2 mg kg^{-1} of mepyramine appreciably increased the degree of blockade of histamine responses in the internal carotid vasculature, but only slightly enhanced the blockade in the external carotid circulation. Dose ratios and E_{max} values after the addition of mepyramine in these experiments are also shown in Table 1.

Vasodepressor responses to i.v. doses of histamine were unaffected by cimetidine at any of the dose levels used. Figure 2 shows aortic blood pressure tracings from a typical experiment, and the mean dose

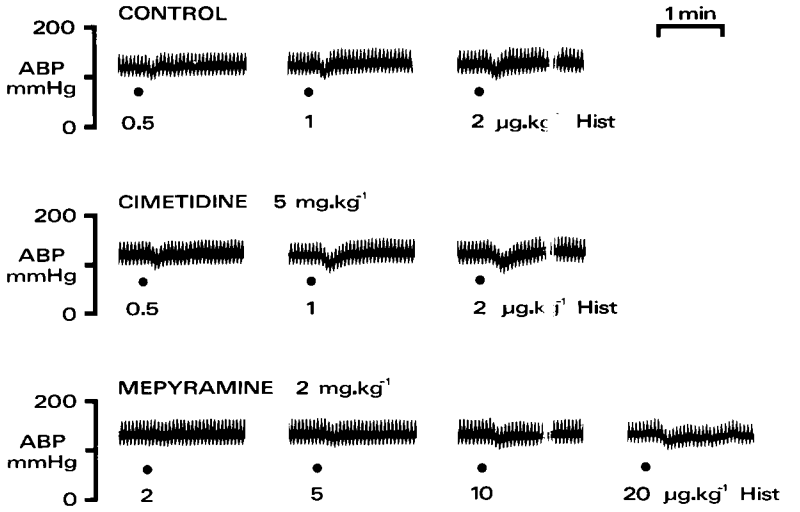

Fig. 2. Tracings from an experiment showing the effects of i.v. injections of histamine at the indicated dose levels on aortic blood pressure (ABP), before (upper panels) and after i.v. administration of cimetidine (middle panels) and mepyramine (lower panels.

ratios from these experiments are given in Table 1. After the subsequent addition of mepyramine (2 mg kg^{-1}), responses to i.v. histamine were markedly blocked (Figure 2 and Table 1). The i.v. administration of cimetidine itself had no appreciable effects on cranial vascular resistance and systemic blood pressure.

TABLE II

Effects of mepramine on responses to histamine. Values shown are means (±S.E.) of the dose ratios and E_{max} values (% of control E_{max}) determined from cumulative dose-response curves.

Response	Parameter	Mepyramine (mg kg^{-1})		
		0.5	2	10
External carotid dilation (n = 4)	Dose ratio	1.3 ± 0.2	1.4 ± 0.3	2.0 ± 0.6
	E_{max}	106 ± 14	117 ± 12	114 ± 5
Internal carotid dilation (n= 4)	Dose ratio	1.1 ± 0.5	2.0 ± 0.7	3.2 ± 2.0
	E_{max}	98 ± 23	89 ± 26	179 ± 34
Vasodepression (n = 3)	Dose ratio	3.5 ± 1.4	7.3 ± 2.3	8.5 ± 1.9

n = Number of experiments

Responses to noradrenaline, 5-hydroxytryptamine, bradykinin and prostaglandin E_1 were unaltered by cimetidine.

In other experiments, mepyramine was the initial antihistamine used, and was administered in successively increasing doses of 0.5, 2 and 10 mg kg^{-1}. In these experiments, histamine-induced external carotid vasodilatation was blocked only after the highest dose of mepyramine. In the internal carotid circulation, mepyramine antagonized responses to histamine to a greater extent that in the external carotid circulation. The mean dose ratios and E_{max} values are given in Table II. Comparisons of the dose ratios in Tables I and II indicate that in the external carotid circulation, a similar degree of blockade was produced by 1 mg kg^{-1} of cimetidine and 10 mg kg^{-1} of mepyramine, while in the internal carotid vasculature, a similar degree of blockade was produced by 5 mg kg^{-1} of cimetidine and 10 mg kg^{-1} of mepyramine. Vasodepressor responses to i.v. histamine were blocked by all doses of mepyramine (Table II). In one experiment, cimetidine (1 mg kg^{-1}) was subsequently administered after the highest dose of mepyramine. Blockade in the external carotid circulation was markedly increased. In contrast, antagonism in the internal carotid vasculature was only slightly increased, and blockade of vasodepressor responses was unchanged.

DISCUSSION

The spectrum of blockade obtained in the present experiments indicates that the dilator effects of histamine in the extracranial vasculature are mediated predominantly by histamine$_2$-receptors, whereas both histamine$_1$- and histamine$_2$-receptors are involved in its dilator effects in the internal carotid circulation. The systemic vasodepressor effects of histamine appear to be mediated largely by histamine$_1$-receptors. These conclusions are supported by comparisons of the dose levels producing blockade in the present experiments with those in other investigations. The doses of cimetidine which block the external carotid vascular effects of histamine are comparable to those that inhibit histamine$_2$-receptor mediated secretion of gastric acid in rats, cats and dogs (Brimble combe *et al.*, 1975a, b). Likewise, mepyramine blocks the vasodepressor responses to histamine in our experiments at doses similar to those which block histamine$_1$-receptor mediated vasodepression in dogs and cats (Parsons and Owen, 1973; Black *et al.*, 1975). Cimetidine appeared to have a competitive blocking action in the carotid territories, as the dose-response curves were shifted to the right in a parallel fashion, although some variability in the E_{max} values was observed, suggesting that non-competitive mechanisms could also be involved in the blockade. The antagonism of the effects of histamine by cimetidine appeared to be specific, since it did not alter responses to noradrenaline, 5-hydroxytryptamine, bradykinin or prostaglandin E_1.

While histamine is known to induce vasodilatation in the cranial circulation of monkeys and man (Sokoloff, 1959; Karlsberg *et al.*, 1963; Handa *et al.*, 1966; Glover *et al.*, 1973; Spira *et al.*, 1976), the only previous investigation into the nature of these cranial vascular histamine receptors is that of Glover *et al.* (1973). They found that histamine-induced dilatation of isolated perfused *post mortem* specimens of human superficial temporal artery was mediated by histamine$_2$-receptors. The findings in the present experiments are similar to those we have made using metiamide in the monkey cranial circulation (Mylecharane *et al.*, 1975). In keeping with our findings of both histamine$_1$- and histamine$_2$-receptors in the internal carotid circulation, it is of interest to note that histamine$_1$-receptor antagonists can prevent the development of the headache resulting from exogenous histamine-induced cerebral vasodilatation (Ostfeld *et al.*, 1957). Furthermore, one of the investigators who acted as a subject in the early human trials with burimamide noted that it greatly relieved the headache induced by exogenous histamine (Parsons and Owen, 1973).

Findings on the nature of the cranial vascular histamine receptors in other species differ to some extent from those in monkeys and man. In the rabbit isolated perfused ear artery (a branch of the external carotid artery), histamine produced both constriction mediated by histamine$_1$-receptors, and dilatation mediated by histamine$_2$-receptors (Glover *et al.*, 1973). Similar observations have been made in isolated segments of extracranial and intracranial arteries from cats (Edvinsson and Owman, 1975).

In proposing the use of histamine$_2$-receptor antagonists in the treatment of cluster headache and migraine, the role of histamine in these conditions must be considered.

As mentioned previously, administration of exogenous histamine intra-arterially or intravenously produces a "histamine headache" (which is due to vasodilatation in the cerebral circulation (Pickering and Hess, 1933; Northfield, 1938; Schumacher and Wolff, 1941). Histamine headache differs markedly from the characteristic headache of migraine and cluster headache (Schumacher and Wolff, 1941; Lance and Anthony, 1971). Although exogenous histamine fails to produce the typical features of migraine and cluster headache, there is evidence that endogenously liberated histamine is involved in the pathogenesis of these disorders.

In cluster headache patients, Anthony and Lance (1971) found significant increases in the levels of whole blood histamine during the attacks. Histaminuria during the attack in some subjects has also been found (Sjaastad and Sjaastad, 1970). Some of the clinical features observed in at least 70% of cluster headache patients, namely lacrimation and nasal congestion (Lance and Anthony, 1971), are characteristic effects of histamine. Horton (1943) drew attention to the high incidence of duodenal ulcer in cluster headache patients. While this may simply be due to the stress of severe recurrent headache, it is also possible that increased gastric acid secretion as a consequence of elevated histamine levels may be responsible.

In migraine, there is relatively less direct evidence for the involvement of histamine. Firstly, whole blood histamine levels are not raised during headache attacks, although post-headache levels are significantly increased (Anthony and Lance, 1971). Histaminuria during the attack was found in only one of eleven patients investigated by Sjaastad and Sjaastad (1970). Secondly, basophils, which contain more than half of the histamine present in blood, are degranulated and increased in number on the affected side during a migraine attack (Thonnard-Neumann and Taylor, 1968; Thonnard-Neumann, 1969). Histamine is directly implicated in allergic asthma and hay fever, and in both of these conditions blood basophil levels are similarly increased (Kimura *et al.*, 1973; Hirsch, 1975); unfortunately, these reports made no comment on whether the basophils were degranulated or not. Mast cells, which are rich in histamine, are distributed in relatively higher numbers in the connective tissue surrounding small blood vessels. During migraine attacks, mast cells in the temporal region of the scalp are degranulated (Sicuteri, 1963). The degranulation of mast cells and liberation of histamine can be achieved experimentally using drugs such as compound 48/80. When this agent is injected into the carotid artery in human subjects, it elicits vasodilatation and pain resembling that found in migraine headache (Sicuteri, 1963, 1967). Finally, it has been thought that in a proportion of migraine patients, an allergic mechanism is involved, in which case the histamine released by the antigen involved may contribute to the vascular changes and pain of migraine. Kallós and Kallós-Deffner (1955), in a study of a selected group of patients whose migraine was associated with specific allergens and was accompanied by other allergic manifestations such as rhinitis, asthma,

angioneurotic oedema and urticaria, found that challenge with the specific allergen always induced a migraine attack, whereas challenge with placebo or other allergen did not.

Thus, if histamine is indeed involved in the pathogenesis of migraine and cluster headache, antagonism of its cranial vascular effects may be of therapeutic benefit. Our findings on the nature of the cranial vascular histamine receptors suggest that a histamine$_2$-receptor antagonist alone may be effective when only the extracranial circulation is involved. However, if intracranial vascular effects are also involved, *e.g.* in cluster headache patients with an accompanying Horner's syndrome, both histamine$_1$- and histamine$_2$-receptor antagonists in conjunction may be necessary. Since other vasoactive agents are also implicated in these disorders, other antagonists such as methysergide may also be needed in conjunction with appropriate antihistaminic therapy. Although the effectiveness of histamine$_1$-receptor antagonists alone has been doubted, the investigations on which these conclusions have been based are insufficiently comprehensive or controlled. It is perhaps noteworthy that cyproheptadine and pizotifen are clinically effective in migraine (Lance *et al*, 1970), and both of these agents possess conventional histamine$_1$-receptor blocking activity.While they also block the effects of 5-hydroxytryptamine, we have found in the monkey cranial circulation that the antihistaminic activity of pizotifen is appreciably greater than its activity in blocking the effects of 5-hydroxytryptamine (Mylecharane *et al.*, 1976). It would seem that a thorough clinical trial of both histamine$_1$- and histamine$_2$-receptor antagonists in migraine and cluster headache is warranted.

SUMMARY

Histamine has been implicated in the pathogenesis of cluster headache and migraine. However, conventional antihistamines such as mepyramine have been of little therapeutic benefit in these conditions. The recent recognition that histamine receptors can be subdivided into two groups, histamine$_1$- and histamine$_2$-receptors, raises the possibility that the apparent lack of efficacy of histamine$_1$-receptor antagonists such as mepyramine is related to the nature of the cranial vascular histamine receptors rather than histamine not being involved.

To investigate the nature of these receptors, we have evaluated the actions of cimetidine, a recently developed histamine$_2$-receptor antagonist, and mepyramine, on cranial and systemic vasodilator responses to histamine in anaesthetized monkeys. In the cranial vasculature, changes in internal and external carotid vascular resistance induced by intracarotid infusions of histamine were calculated from measurement of blood flow and perfusion pressure. The vasodepressor effects of i.v. doses of histamine were used as a measure of systemic vascular reactivity.

Cimetidine (0.25, 1 and mg kg^{-1}) blocked the effects of histamine in the external carotid circulation, but had no effect on vasodepressor responses. The highest dose of cimetidine used also blocked the internal carotid vasodilator effects of histamine, but to a lesser extent than in the external carotid vasculature. In contrast, mepyramine, at doses which resulted in substantial blockade of vasodepressor responses to histamine, produced moderate blockade in the internal carotid circulation, and had little effect in the external carotid vasculature.

Thus the dilator effects of histamine in the external carotid vasculature are mediated predominantly by histamine$_2$-receptors, whereas both histamine$_1$- and histamine$_2$-receptors are involved in its dilator effects in the internal carotid circulation. A trial of cimetidine in migraine and cluster headache appears warranted.

ACKNOWLEDGEMENTS

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PERFORMANCE CHANGES DURING RECOVERY FROM CLOSED HEAD INJURY

D. GRONWALL*

INTRODUCTION

The immediate effects of concussion are evident even to the untrained observer. There may be respiratory arrest, the patient may lose consciousness for some time, and on regaining consciousness may be nauseated, vomit, have disturbances of vision, and be mildly ataxic. However once this acute period has passed, evidence of disturbed brain function may be less obvious. The patient may still complain of poor concentration, poor memory, fatigue, irritability or headache, but he may show no abnormality on standard neurological examination, and may gain normal scores on standard psychometric tests.

Consequently, many workers have suggested that post-concussional complaints are neurotic in origin (e.g. Miller, 1966; Lidvall, Linderoth and Norlin, 1974). However, it now appears that concussion does produce a generalised effect on brain function which may persist for some weeks after trauma (Gronwall and Sampson, 1974). This effect is a slowing down of the rate at which information is processed by the central nervous system. Thus, although simple reaction times may be within the normal range, the concussion patient diverges more and more from the control as the number of items to be dealt with simultaneously is increased.

Using a paced auditory serial addition task (PASAT) as a measure of information processing rate, it is possible to quantify changes in performance during recovery from concussion. PASAT scores, and the time taken until normal scores are recorded, are both related to severity of injury, as measured by duration of post-traumatic amnesia (PTA). It has also been shown that patients with persistent post-concussional symptoms show a reduction in information processing rate which is inappropriate to the time elapsed since injury, and which persists beyond the average recovery time (Gronwall and Wrightson, 1974).

The present paper examines the relation between post-concussion symptoms and PASAT scores further, to determine how well self-reports of recovery from concussion patients correlate with recovery in information processing rate. A related question is how accurately either measure might reflect performance in a practical setting, on a structured occupational therapy (O.T.) programme.

METHODS

Subjects: Thirty patients aged from 16 to 33 years were studied. None had had skull fractures, intracranial haematoma or history of previous head injury or psychiatric illness. Eighteen patients in the mildly concussed (MC) group had durations of PTA of less than one hour. The 12 patients in the more seriously concussed (SC) group had PTAs ranging from two hours to six days.

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Materials: (i) PASAT: The test has four trials of 61 digits (the numbers 1-9 used in the same random order on each trial) recorded every 2.4, 2.0, 1.6 and 1.2 secs respectively. At each trial the appropriate series of digits was played to the patient, who was instructed to add each digit he heard to the one immediately preceding it, and to give his answer aloud. Thus in the digit string 2, 4, 8, 9, 3, correct responses would be 6,12,17,12. The average time taken for each correct response on the four trials is averaged again to give a composite time score.

(ii) Symptom rating scale: The patient was asked to rate each of five common post-concussional complaints on a five-point rating scale, where number I presented 'no problem', and number V meant an 'extremely bad problem'. To help him, he was given a card with each number qualified in this way. The symptoms checked were headache, concentration, tiredness, memory and irritability. The five ratings were then totalled to give a composite symptom score.

Procedure: Each patient was given PASAT as soon as possible after recovery of consciousness. The test was repeated at regular intervals until the time score had returned to the normal level of approximately one correct response every two and a half seconds. Instructions and procedure were those used in the earlier investigations (Gronwall and Wrightson, 1974, 1975).

At the end of each PASAT test session the symptom rating scale was administered, and on the same day the occupational therapist concerned with that patient was asked whether performance had improved, was the same as, or was worse than it had been in the previous week.

RESULTS

Group MC

Rank difference correlations between PASAT and symptom ratings were calculated for each patient. Values of rho ranged from .879 to .981, all significant at $p<.05$ or higher. Figure 1 shows results from the patient whose rho value was nearest the group mean of .918. For comparison with O.T. performance both the PASAT and symptom data were also classified as improved, the same, or worse than at the previous week. Table I gives contingency coefficients (Siegel, 1956) between PASAT and therapy, and between symptom ratings and therapy. Both comparisons show statistically significant correlations.

Group SC

No patient in this group had symptom rating scores which significantly correlated with PASAT, and rho values ranged from −.326 to .511. Figure 2 shows changes in symptom ratings and PASAT during the recovery period for the patient whose correlation between the two measures was exactly on the mean for the SC group (rho = −.090). This graph is typical of results from the more seriously injured patients. In the early stages the patient's account of how many problems he had bore no relation to his objective performance, and S4 gave a symptom rating of 6 (the same as he gave when he had recovered) for the first 23 days after his accident. Nor was there a significant correlation between symptom ratings and O.T. performance (Table II). As with the MC group, however, changes in PASAT time scores during recovery were significantly ($p<.001$) related to changes in therapy performance.

All cases in group SC initially recorded low symptom scores, which rose to a peak and then typically fell consistently with improvement on PASAT. Eight of the 12 patients reached the symptom peak when the PASAT time score was close to four seconds for each correct response, but there was considerable variation among the remainder (time scores varied from 2.9 to 5.6 secs).

DISCUSSION

From mildly concussed patients self-ratings based on the five post-concussional symptoms correlated significantly both with performance during a therapy programme, and with information processing rate, as measured by PASAT. This result is not surprising, as the rating scale was always presented immediate-

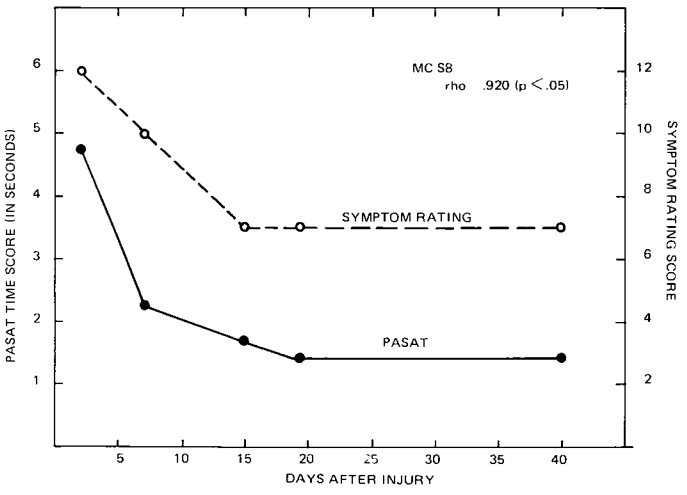

Fig. 1. Changes in symptom ratings and PASAT time scores during recovery from mild concussion (S4, group MC).

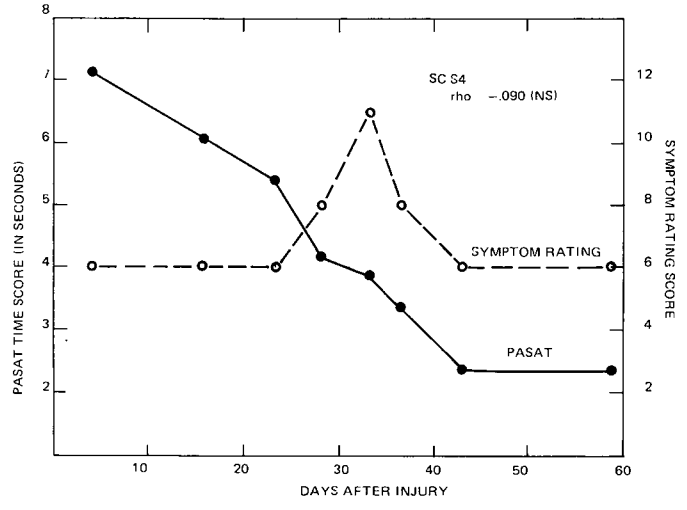

Fig. 2. Changes in symptom ratings and PASAT time scores during recovery from moderately severe concussion (S8, group SC).

TABLE I

Correlations between symptom ratings, PASAT and therapy in the mildly concussed group

		PASAT				SYMPTOMS		
		Improved	Same	Worse		Improved	Same	Worse
O.T.	Improved	25	0	0	Improved	27	4	0
	Same	11	18	0	Same	6	17	0
	Worse	0	0	0	Worse	0	0	0
		C = 0.395 ($p < .01$)				C = 0.305 ($p < .05$)		

TABLE II

Correlations between symptom ratings, PASAT and therapy in the seriously concussed group

		PASAT				SYMPTOMS		
		Improved	Same	Worse		Improved	Same	Worse
O.T.	Improved	48	0	0	Improved	15	9	12
	Same	30	12	0	Same	30	12	12
	Worse	0	0	0	Worse	0	0	0
		C 0.387 ($p < .001$)				C 0.135 (NS)		

ly after the PASAT test had been completed, which should favour the patient making an accurate estimate of his own progress.

PASAT performance in all patients was significantly correlated with performance on a practical structured O.T. Programme. However, PASAT scores were not related to patients' reports of problem symptoms in the more seriously injured group. Nor were symptom ratings from this group an indication of progress in therapy. It was not until PASAT scores had improved to some level (usually, but not always, when the patient needed approximately four seconds for each correct response) that changes in symptom ratings began to reflect changes in PASAT. In other words, patients in the SC group felt better when they were worse, and felt worse when they began to get better. This has important practical implications. It suggests that asking a patient who has had more than a minor injury how he feels will not necessarily give accurate information about the degree of recovery. Self-reports of recovery from such patients may not be adequate grounds for determining return to work, for example.

If reports from mildly concussed patients reflect improvement during recovery reasonably accurately, but reports from more serious cases do not, one possible reason may be that the latter had poorer memories. That is, the patients may have had such bad memories that they could not remember how they had been performing. However, after the period of PTA was over, none of the patients in the SC group had deficits in immediate memory, although three of the 12 did have lower than average verbal learning ability in the early stages. This may have influenced their symptom ratings to some extent, but is unlikely to be the whole answer.

An important factor might be related to limbic system involvement following concussion, leading to a type of frontal lobe euphoria. The patient may know he cannot concentrate as well as he normally does, and that his memory is not very good, but it does not worry him. so he can truthfully report it is 'no problem'. Certainly changes in affect are frequently noted after more serious concussions. Patients may be emotionally quite flat, or may be markedly euphoric, even if they have no other clinical signs of frontal lobe dysfunction.

A third factor derives from what is meant by functioning at a slower than normal rate. Not only does it mean that it takes longer to do something, but also that doing it takes up all available capacity, so that other information cannot be processed at the same time. Thus, feed-back from actions may not be available to allow accurate evaluation of performance. Feed-back, whether from outside sources or internal, would be lost in the system, because there would be no spare circuits available to monitor this information at the same time as doing the task. It would not be until the rate at which information is processed had increased to an adequate level that the patient would be able to notice that he was not functioning as efficiently as he normally did. This would explain why the mildly injured patients, whose reduction in information processing rate was not as great as the more seriously injured group, could give reasonably accurate estimates of recovery. The SC group only began to complain of problems with concentration, memory, and so on, when their PASAT scores approached values typical of MC patients in the early port-traumatic period.

Finally, one of the most compelling reasons why post-concussion symptoms such as headache, concentration problems, fatigue and irritability have been considered to have a neurotic rather than an organic basis, is that the patients who complain have mostly had only minor injuries. Perhaps this is not necessarily paradoxical. As with the SC group in the present study, reports of freedom from post-concussional complaints may in some cases be evidence of lack of insight, rather than evidence of full functional recovery.

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THE CONTINUAL ADMINISTRATION OF NEOSTIGMINE AND THE NEUROMUSCULAR JUNCTION

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INTRODUCTION

Myasthenia gravis is usually treated by the continual administration of anticholinesterases. However excessive dosage of this type of drug may induce muscle weakness. The therapeutic benefit of neostigmine is due to its acute effect of reducing acetylcholinesterase activity, thus producing an increase in both degree and duration of action of acetylcholine (ACh). Little is known of the chronic effects of neostigmine administration. Roberts and Thesleff (1969) found that the amplitude of miniature end-plate potentials (MEPPs) was reduced after the continual administration of neostigmine, suggesting that the ACh receptors are partially blocked or that the amount of ACh per quantum is decreased. The former suggestion is supported by the demonstration of reduced binding of α-bungarotoxin to receptor sites (Chang, Chen and Chuang, 1973). The number of quanta per nerve impulse is also reduced after chronic administration of neostigmine (Roberts and Thesleff, 1969), but these authors also found that the neuromuscular junction would not respond at rates above 20/sec, suggesting that at physiological motor discharge rates there is presynaptic failure of the junctions. Such a mechanism could account for the weakness observed in man from continual administration of large doses of anticholinesterases. The experiments described here were designed to confirm the findings of Roberts and Thesleff and assess their physiological significance.

METHODS

White Wistar rats weighing 150-200 gm were injected subcutaneously with 100 μg of neostigmine twice daily for 3-7 days. Atropine sulphate (1 mg) was injected subcutaneously twenty minutes prior to the neostigmine, to minimise the muscarinic effects of the anticholinesterase. The muscarinic effects progressively decreased with each successive dose of neostigmine so that after the first three doses of neostigmine, atropine was no longer given. The animals were killed by exsanguination at least 15 hours after the last dose of neostigmine and the hemidiaphragm and attached phrenic nerve were removed, placed in Krebs solution and washed for one hour. When end-plate potentials (EPPs) were recorded, d-tubocurarine (0.8-1.4 μg/ml) was added to the Krebs solution to prevent muscular contraction. MEPPs and EPPs were recorded intracellularly with 6-40 MΩ glass micropipettes filled with 3M KCl. Only potentials with rise-times of less than 1.5 m.sec were accepted for analysis. Initially the nerves were stimulated at a rate of 1/sec and the amplitude of 200 successive EPPs recorded on 35 mm film. After correcting for a transmitter equilibrium potential of -15 mV, the quantal content of the EPPs was calculated by the method of variance (del Castillo and Katz, 1954; Martin, 1955) on 10 groups of 20 EPPs (Figure 1). The quantal content at other repetition rates was calculated by comparing the mean amplitude of EPPs with the amplitude at a stimulus rate of 1/sec. MEPPs were recorded on an ultraviolet recorder and the amplitude of 100 consecutive MEPPs measured and plotted as a histogram.

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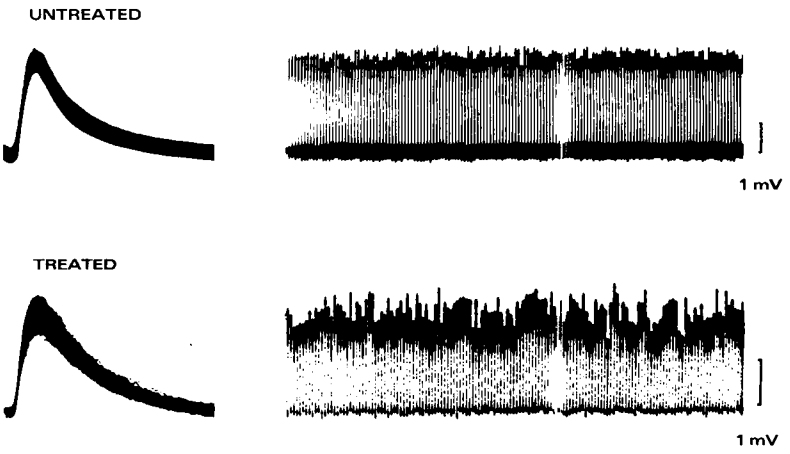

Fig. 1. Recording of several superimposed EPPs and of individual EPPs on s owly moving film. In the latter case only the portion of oscilloscope trace comprising the entire rising phase of each EPP was recorded, so that the length of each individual line represents the peak to peak amplitude of a single EPP. The variation in peak to peak amplitude is greater in the treated preparation, indicating a lower quantal content.

RESULTS

During treatment with neostigmine the rats were less active and stood with a more flexed posture than untreated animals. After 3-7 days of treatment the non-fasting weights of treated rats were reduced by up to 10% of their pre-treatment weight. The membrane potentials were similar in both groups, being 64.9 ± 1.3 mV (mean ± S.E.) in untreated and 64.4± 1.3 mV in treated rats. The rise and decay times of EPPs were similar in both groups of animals.

Quantal content of end-plate potentials

At a stimulus repetition rate of 1/sec the mean quantal content of EPPs at 12 neuromuscular junctions from 4 untreated rats was 248 quanta of ACh per nerve impulse. A mean of 126 Quanta per nerve impulse were released at 17 junctions from rats treated with neostigmine. This reduction to 51% of untreated values is statistically significant ($P<0.001$).

The effect of varying the stimulus frequency on the number of quanta of ACh discharged per nerve impulse was studied by using stimulus frequencies of from 1/sec to 100/sec. As the repetition rate was increased, there was a progressive reduction in EPP amplitude. This reduction was more marked in the treated group. When the logarithm of the EPP amplitude at a stimulus frequency of 1/sec was plotted against the time interval between successive stimuli, the relationship was found to be linear (Figure 2). Both regression lines were statistically linear on the log-log scale and the difference in slope between the two lines was significant ($P<0.001$).

At each end-plate, under stable experimental conditions, the number of quanta released is directly proportional to the EPP amplitude, after corrections have been made for membrane potential and transmitter equilibrium potential. When the quantal content of EPPs had been estimated at a particular neuromuscular junction at a stimulus frequency of 1/sec, the quantal content of EPPs at differing repetition rates was calculated by the ratio of amplitude of EPPs. Corrections for membrane potential and transmitter equilibrium potential were only applied to the EPP amplitude at 1/sec. The error in quantal content tent estimations at other repetition rates arising from this procedure was less than 2%. The relationship between repetition rate and quantal content is shown in Figure 3. As the stimulus interval decreased, the discrepancy between untreated and treated preparations increased. This increasing discrepancy indicated that at physiological repetition rates the reduction in quantal output was greater than that predicted by

comparing the quantal content of EPPs at 1/sec. For example, at a stimulus frequency of 30/sec, the mean number of quanta released per impulse was 96 in untreated and 43 in treated preparations. This reduction to 45% is greater than the reduction to 51% estimated at a stimulus frequency of 1/sec.

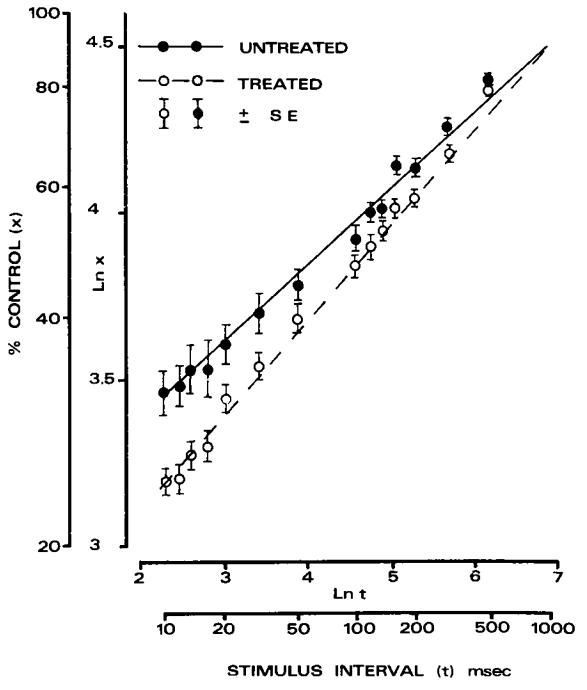

Fig. 2. The logarithm of the stimulus interval has been plotted against the logarithm of the EPP amplitude calculated as a percentage of its amplitude at a stimulus frequency of 1/sec. Each point is the mean of at least 12 estimations. Both regression lines are statistically linear and the difference in slope between the lines is statistically significant ($P < 0.001$). As the stimulus interval decreases the end-plate potential amplitude decreases. This decrease occurs at a greater rate in the neostigmine treated animals than in the untreated animals.

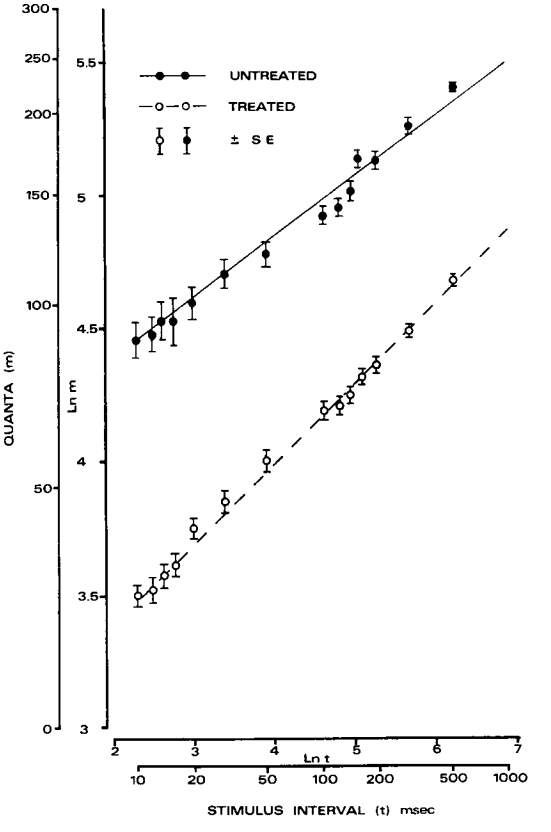

Fig. 3. The logarithm of the number of quanta discharged per nerve impulse has been plotted against the logarithm of the stimulus interval. As the stimulus interval is decreased the number of quanta released per nerve impulse decreased. This decrease was greater in the neostigmine treated animals than in the untreated animals.

Miniature end-plate potentials.

Spontaneous MEPPs were recorded at 46 neuromuscular junctions from 3 untreated rats and at 46 junctions from 3 treated rats. The resting membrane potential was 66 ±1 mV (mean ± S.E.) for untreated and 68 ± 1 mV for treated fibres. One hundred consecutive MEPPs were recorded from each end-plate and the time taken for these 100 spontaneous MEPPs to occur used to calculate their frequency. The mean amplitude for untreated preparations was 0.53 ± 0.03 mV (mean ± S.E.) compared with 0.39 ± 0.02 mV for treated preparations, a significant reduction to 75% of normal MEPP amplitudes ($P < 0.001$). The frequency of spontaneous MEPPs was 6.6 ± 0.5 /sec (mean ± S.E.) at untreated junctions compared with 2.3 ± 0.2/sec at treated junctions, again a significant reduction ($P < 0.001$).

DISCUSSION

The chronic administration of neostigmine decreased the number of quanta of ACh released per nerve impulse by nerve terminals to 51% of the untreated value at 1/sec. This did not appear to be due to free neostigmine. At least sixteen hours had elapsed since the last dose of neostigmine and the preparation was washed for at least one hour prior to any recording. Under these conditions, it was unlikely that any free neostigmine was present. The finding of normal decay times of EPPs in treated animals further indicated that no effective free neostigmine was present. The normal decay time also indicated that effectively no neostigmine was bound to acetylcholinesterase. This did not, of course, exclude the possibility that neostigmine was bound to sites other than acetylcholinesterase.

No evidence of presynaptic failure was observed in either untreated or treated preparations, even at repetition rates of 100/sec. This is in contrast to the experience of Roberts and Thesleff (1969). Since presynaptic block was not found at more than two hundred junctions, it was very unlikely that this mechanism contributed to the weakness associated with chronic neostigmine administration. The decrease in quantal content was greater at high repetition rates, such that within the physiological range of motor fibre activity, the quantal output per nerve impulse was less than half of normal. Chang *et al.* (1973) estimated the total amount of ACh produced by 5 second bursts of impulses at 100/sec using preparations similar to those described in this paper (Chang *et al.*, 1973). They found that the continual administration of neostigmine reduced the total ACh output of a rat diaphragm to 50% of normal. This figure was similar to the reduction in quantal output described here, suggesting that the decrease in ACh output could be accounted for entirely by reduction in quantal output. The amount of ACh per quantum was therefore probably normal.

The amplitude of MEPPs was reduced to 75% of normal values by chronic neostigmine administration. This reduction in MEPP amplitude might have been a result of either a postjunctional reduction in end-plate sensitivity to ACh or a reduction in the amount of ACh contained in each quantum. The latter possibility is unlikely, for the reasons outlined above. The end-plate sensitivity could be reduced if some receptor sites were effectively blocked. This possibility is supported by the finding that, using α-bungarotoxin (Chang *et al.* 1973), the total number of ACh receptor sites was found to be reduced from 2.1×10^7 per end-plate to 1.2×10^7 by chronic neostigmine administration. This chronic neostigmine administration reduced the number of quanta released per nerve impulse as well as the frequency of spontaneous release of quanta. Two mechanisms which may cause this reduction are, the interference with the release mechanism for quanta and a reduction in size of the releasable pool of quanta. The experiments described in this paper do not distinguish between these two possible mechanisms.

The reduction in quantal output to less than 50% of normal would potentiate the neuromuscular defects in myasthenia gravis. The chronic effects of continual administration of neostigmine in rats persist for at least sixteen hours after the last dose, outlasting the acetylcholinesterase inhibition by many hours. For this reason, a patient with myasthenia gravis taking neostigmine would initially have a greater weakness on cessation of neostigmine than if no treatment had been given.

SUMMARY

The effect of continual administration of neostigmine on the neuromuscular junction of the rat diaphragm was examined by determining the number of quanta of acetylcholine released by each nerve impulse, the effect of differing repetition rates on quantal release and the amplitude and frequency of miniature end-plate potentials.

The number of quanta of acetylcholine released at a nerve impulse repetition rate of 1/sec was reduced to 51% of normal in treated animals. This reduction was greater at faster repetition rates. The amplitude of miniature end-plate potentials was reduced to 75% of normal. This reduction appears to be due to blocking of receptor sites rather than the reduction in the amount of acetylcholine in each quantum. The frequency of spontaneous miniature end-plate potentials was reduced in treated animals.

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