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Business enquiries and subscriptions to be directed to

DR. GEORGE SELBY
Suite 5, 5th Floor.
NORTH SHORE MEDICAL CENTRE
66–80 PACIFIC HIGHWAY,
ST. LEONARDS.
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THE AUSTRALIAN ASSOCIATION OF NEUROLOGISTS – A REVIEW OF TWENTY-FIVE YEARS

JOHN GAME*

It is an honour to be asked on the occasion of the twenty-fifth year of the Australian Association of Neurologists to speak about our history. It is to be hoped that one day a fully documented history of the Association will be written. My comments today must be regarded as being merely some reflections of a member who has been a participant in the activities of the Association from the beginning.

I think it is fair to say that an Association which has been alive and growing for twenty-five years has now reached maturity and is here to stay. Thus I think we can reasonably rejoice and celebrate the occasion with modest satisfaction and some real confidence that our Association is, in fact, an adult and vigorous body capable of making a worthwhile job of doing what its founders hoped it would do. The act of conception is normally a very private human activity and the details surrounding it are very often not available to historians. So it was with the origin of the Association.

In the Minutes of the Inaugural Business Meeting of the Originating Members, held in the Anatomy Department of the University of Melbourne on Wednesday, 25th October 1950, it is stated that "Dr. Graeme Robertson then moved that it be recorded in the Proceedings of the Association that the Originating Members greatly appreciated Dr. Cox's work in forming the Association". I think it is apt that this quotation brings to notice the first two names to be mentioned by me in this review: Leonard Bell Cox, a man of independent and strong mind and Edward Graeme Robertson, a quiet and modest man of disciplined and dedicated mind. Their personalities did not bring them together as close friends but each held respect for the other's qualities and attributes.

Leonard Cox had experienced the adversities of service in the First World War, personal ill health and the Depression. His indomitable spirit and independence of nature had surmounted these difficulties by a fascination with the human mind which led him first to an interest in psychiatry and through that to the study of neuro-pathology and clinical neurology, in relative solitude. His tissue culture studies and classification of glial tumours was a remarkable individual contribution. By 1950 he had been established for some years as Honoary Neurologist to the Alfred Hospital, Melbourne, and in private consultant practice. Graeme Robertson had trodden a different path of individual initiative. He had submitted himself to the discipline of Queen Square where his capacity was recognised and his future assured on the staff of that Hospital and one of the great Teaching Hospitals of London. However he had chosen to return with his training and consummate skill to serve with loyalty his old Hospital, the Royal Melbourne, and a strictly consultant private neurological practice. Thus each in his own way had demonstrated a streak of strong individuality and initiative and between them they had established neurology as a discipline in its own right in Melbourne. The sound confidence of each in what he was doing allowed them to see the importance of looking to the future and so, I believe, this brought them together in founding our Association.

There were at the same time in Sydney two men, also of differing personalities but of equally strong spirit, who had had training in neurology at Queen Square but in the mode of the times were practising and teaching as general physicians. They were Kenneth Beeson Noad and Eric Leo Susman. They added their stature and fibre to the initiative of their Melbourne colleagues and shared in the foundation of our Association. Eric Susman was well recognised, not only as

*MELBOURNE

a personality but as a character in medicine in Sydney, about whom stories will be told for generations to come. His own sense of fun would undoubtedly wish that to be so.

Gerald Moss of Perth was a classical scholar and this perhaps in no small way influenced his attraction to neurology, which was his greatest love in medicine. By circumstance he practised as a general physician, although he had become senior neurologist when the Neurosurgical Unit was established in the Royal Perth Hospital as recently as 1949.

Sydney Sunderland, Professor of Anatomy at Melbourne University and said to have been the youngest man ever to attain a Chair in an Australian University, was already distinguished as a neuro-anatomist and associated with Leonard Cox in the clinical study of peripheral nerve injuries. He joined the group and provided the first and lasting link between town and gown in our Association. John Billings and I were recently arrived back in Melbourne, having both had an opportunity of training in neurology at Queen Square in the first group of post-graduates to go to London after the War. We had been accepted as neurologists at our Hospitals and with a small handful of others had taken the slightly bold decision for the time to practise in a purely consultant capacity.

This made eight who became the Foundation Members and all except Gerald Moss were at the Inaugural Meeting on 25th October 1950. Leonard Cox was appointed First President and I had the honour to be appointed Honorary Secretary and Treasurer. There was much discussion amongst us about the name to be given to our Association. Many were considered but we all agreed that the Australian Association of Neurologists identified us geographically but placed no limit on the breadth and scope of our membership. Of great importance was the question of who should be eligible to be members. The liberal view of including all physicians who had some interest in neurology was decided to be less important than the concept that we were seeking association of those who accepted occupation with the problems of the nervous system as their primary interest. That is not to say that sound training and experience and qualification in medicine at a senior degree level and some continuing contact with general medicine were not desirable. In fact they became pre-requisites, but it was decided that the forum for association and scientific exchange with those who were primarily physicians (but with an interest in neurology) was in our participation in the activities of the Royal Australasian College of Physicians. It is interesting to note in passing that this College had been formed only a matter of twelve years before our Association, a period of time which will proportionately diminish when viewed in retrospect in the many years which we hope to lie ahead of both Bodies.

The objects of our Association were legally stated in the Constitution, which was not completed and signed until October 1954. The thing that really matters is what was in the minds of the Foundation Members. The record in my personal memory is that the predominant intentions were four.

First was the personal fellowship of those throughou Australia primarily interested in neurology.

The second was the scientific association and collaboration of these same people.

The third was the recognition and establishment of neurology in its broadest and proper sense, which meant the bringing together not only of clinicians but of all those whose primary activity was the study of the nervous system.

Finally and not least was the determination to establish and maintain the highest possible standard of the practice of clinical neurology in Australia.

It seems, therefore, fitting to try to review our pursuit of these objectives over the last twenty-five years.

PERSONAL FELLOWSHIP

As a result of our experiences in the Armed Services, notions of State parochialism had dissolved into a broader concept of fellowship as Australians. The history of our Association and its activities speaks for itself in showing that this notion has persisted. I do not think any of our Members would doubt that we are a truly national, Australian, Association without any real concern for

State boundaries. Our horizons have broadened into the international sphere more than they have ever narrowed to the trivialities of State jealousies.

New Zealand neurologists have always been welcome members and at their invitation we have twice met in New Zealand.

SCIENTIFIC ACTIVITIES

The Greeks many centuries ago realized the importance of the mind in the activities and affairs of men. So it is that I believe that a school of thought is more enduring and indestructible than any physical edifice. I believe there lies within us an unspoken sense of responsibility to carry into the eastern hemisphere the high standards and discipline of mind which were cultivated in neurology in Europe, particularly in London, in the last century. That has found expression in the standards which we have set and striven to attain, not only in the practice of neurology in Australia but also in the scientific work and, equally important, in the presentation of the results of that scientific work in the form of papers read at the Meetings of our Association. Despite limited resources we have never failed to be able to find Members who have been able to produce papers for our Scientific Meetings which compare favourably with work done and papers produced in older and better endowed countries.

A natural evolution was the obvious need for a proper record of this work reported in these papers. The achievement of this goes to the credit of our second and most distinguished President, Graeme Robertson, who was undoubtedly the motivating force in the publication of the first issue of the Proceedings of the Australian Association of Neurologists in 1963.

As an aside it warrants recording that the publication of our Proceedings was in turn the stimulus to the adoption of an insigne for the Association. This was discussed in 1962 but it was not until 1964, once again from Graeme Robertson's imaginative mind, that there came the proposal and the adoption of the Waratah, a distinguished native Australian flower, as our emblem. He showed the Council a plate in the book "A Specimen of the Botany of New Holland" by James Edward Smith, M.D., F.R.S., printed by J. Davis in 1793 and published by J. Sowerby of 42 Paternoster Row, London. The plate was prepared by Dr. Smith from drawings made on the spot and sent to England by John White, Esq., the first Surgeon General of the Colony. The insigne thus had medical as well as national association and is additionally appropriate in its resemblance to the crest of the National Hospital, Queen Square, London. Arrangements were made for a stylised version of this drawing to be prepared by Miss Margaret Stones, an Australian, who was then associated with the Kew Gardens, London. This has remained our insigne ever since.

The continued publication of the Proceedings strained our financial resources almost to breaking point on several occasions over the years. But the tireless work of Graeme Robertson, its Editor, constantly stimulated the Council to find ways and means, which were mostly found with the aid of three leading pharmaceutical firms – Ciba-Geigy, Roche and Sandoz. We are, I believe, the only special medical group in Australia which has consistently published its own journal and the quality of its contents and presentation has earned wide recognition and praise at home and abroad. It is a great joy to report that there are signs that large publishing firms are now seeking the right to publication. Thus there is real hope that the journal will stand on its own feet. Up to the present we have acted as our own publishers and distributors, a field of business activity in which we could naturally have little expertise.

The extension of the direct scientific association of the A.A.N. to our neighbouring countries of Asia came in 1962 when the First Asian and Oceanian Congress of Neurology was held in Tokyo and the Asian and Oceanian Association of Neurology was formed. Generous finance from the United States of America made this possible and our Japanese colleagues, headed by Professor Shigao Okinaka, the Emperor's physician, called Graeme Robertson, our President, to their aid in planning the Congress, which was an outstanding success and was followed by the Second Asian and Oceanian Congress in Melbourne in 1967. This Congress was planned and organized by the collaborative efforts of the Members of the A.A.N. with Graeme Robertson as President. It is

now established practice for this Congress to be held every four years somewhere in Asia. Before that, the World Federation of Neurology had been formed in 1957, also with generous funds from the United States of America, and Professor Ludo van Bogaert, the distinguished Belgian neuropathologist, was its first President. We became a member Society.

The activities of the World Federation of Neurology were largely centred in Europe and North America, which made it difficult for us to participate directly. Nevertheless the World Federation became the sponsoring body for the World Congress of Neurology, which is held every four years. Our delegates have held office in both the planning bodies of the Congresses and the Council of the World Federation. On two occasions Vice-Presidencies of the World Federation were held by Graeme Robertson and myself.

The concern of the Australian Association of Neurologists with scientific research in neurology in Australia has been expressed in our policy to include in our Association all scientists, medically qualified or otherwise, who are primarily engaged in research into the nervous system. We have always had a close association with the John Curtin School of Medicine of the Australian National University and have been proud to have amongst our members Sir John Eccles, Nobel Prize Winner of 1964,and Professor David Curtis, awarded Fellowship of the Royal Society in 1974. Their papers presented at our meetings have been frequently published in our Proceedings, together with those from various other neurological scientists from universities and institutions throughout Australia.

Whilst clinical neurology has been established at a high standard in Australia and pure neurological research, such as that at the Australian National University, has also flourished we have long been aware of the limited availability of suitably trained and qualified neurological scientists to support the clinical activities of neurologists and neurosurgeons in the diagnosis and treatment of their patients and in research into the causes of their diseases. In seeking ways of remedying this situation in Australia and to help extend the potential benefits to our Asian colleagues who seek training in Australia, we have realised that there are three fields of medical endeavour which are inseparable. These are patient care, gaining knowledge (research) and dissemination of knowledge (education). We believe that the overall position in Australia is not helped by the fact that the Government instrumentalities which are necessarily the major source of funds for all these activities are divided not only between State (patient care) and Commonwealth (finance for education and research) but within the Commonwealth Government there are again two separate departments, the Department of Health and the Department of Science and Education.

After some years of careful thought and discussion it was decided that we may help to bring together, in neurology at least, these three separately funded activities by the creation of an Australian Neurological Foundation for the purpose not only of seeking funds for these activities but also for increasing the public and Governmental awareness of the needs. So it was in 1970 that the Australian Neurological Foundation was established under the Presidency of The Right Honourable Lord Casey of Berwick in Victoria and the City of Westminster, K.G., P.C., G.C.M.G., C.H., D.S.O., M.C., K. St.J., supported by a small but now increasing group of distinguished and energetic laymen with a highly developed sense of community service. These basic reasons for the establishment of the Foundation had been outlined in a letter to the then Prime Minister, The Right Honourable John Gorton, M.P., dated 16th May 1969.

In forming the Foundation it was our belief that the most effective single step towards the aim of improving the overall standard of neurological and neurosurgical services in Australia would be the establishment of Chairs in Neurology and Neurosurgery in the major universities. However, in fund raising, tax exemption for donors is almost a *sine qua non* and in order to qualify as a Public Benevolent Institution for the purpose of receiving donations we have had to make our more immediate objectives more directly and apparently related to the treatment of patients and research into the causes of their diseases and their treatment.

Nevertheless, under the umbrella of the Foundation, Trusts have been set up in each State of Australia to receive gifts by Will free of Probate where allowable. As an irony of bureaucracy the establishment of Chairs can remain a primary objective of these Trusts.

Before leaving the discussion of our objective of stimulating scientific association amongst neurolo-

gical scientists in Australia, I mention last but not least the high value we place upon our fellowship with the Neurosurgical Society of Australasia. Many visitors to our country have expressed amazement when we speak of our neurosurgeons as our friends, but I firmly believe that it is true to say that in our daily practices as well as in our conjoint scientific meetings a most healthy and happy state of collaboration and friendship has always existed. Like many of the matters raised in this brief review much more could be said of this. Their ready collaboration in our efforts through the Australian Neurological Foundation is a further manifestation, if any is needed, of this continued and fruitful association.

RECOGNITION OF NEUROLOGY

Many of our activities about which I have already spoken have clearly contributed towards the establishment of neurology in its broadest clinical, medical, surgical, and scientific sense as an entity not only in medicine but in our society. A simple, perhaps naive, illustration of the trends of thought may be the fact that cessation of function of the brain rather than the heart is becoming recognised as the cessation of life.

The emergence of neurology as a discipline in its own right has not been univerally welcomed in some medical circles. There has long lingered a school of thought that general physicians should be all things to all men and that any declared specialisation beyond that represented a fragmentation of medicine to the detriment of the art. Much could be said on this subject but probably one fair answer is to point to the extensions of the boundaries of medicine and to those who have pushed them forward. In this era of expanding education and knowledge it seems inevitable that concentration of at least a major part of one's capacity in a particular field is necessary if expertise is to be achieved or new scientific boundaries advanced. Some of our earlier Members had to expend a good deal of their endeavour in justifying their existence or attaining and maintaining their position as neurologists, and even now there are some institutions within the country which seek to make the neurologist subservient to the almost mythical figure of the complete general physician.

MAINTENANCE OF CLINICAL STANDARDS

In the initial decades of our Association the great majority of those admitted as Ordinary Members had been trained in Britain, particularly at the National Hospital, Queen Square, London. This, I believe, is the main reason why we consciously strove to emulate and disseminate the clinical excellence and intellectual integrity which characterize that institution. Over the years we became increasingly concerned by the fact that training in neurology for Australians could only be found overseas, mostly in Britain and in later years to a steadily increasing extent, in the United States of America.

In 1966 the Association decided to try by its actions and influence to develop ways and means for the training of neurologists within Australia, hopefully including those who sought it from Asia, and also to help and foster neurological research in Australia. We wrote to the Royal Australasian College of Physicians telling them of our awareness of the needs and our hope to develop plans for neurological training and invited the collaboration of the College. At the same time we set up our own Education Committee and our own Scientific Advisory Committee. A lot of hard work was done by those concerned and by 1968 we had planned a course of training which would effectively cover the field by sending trainees to those hospitals or institutions in Australia where facilities and resources were sufficiently developed for the various aspects of training.

In 1970 the Royal Australasian College of Physicians announced their recognition of the fact, long recognised by our Association, that very few physicians could become expert in all fields of internal medicine and that provision should be made for training and accreditation of physicians in the various branches of medicine, including neurology. To give effect to this new outlook the College announced plans for the training and accreditation of physicians which would eliminate the established examinations for Membership of the College and instead set up plans for preliminary

basic training in general medicine. This was to be followed by more specialized training in various selected fields of medicine which would lead directly to the admission to Fellowship of the College of those who attained the necessary standards of training and experience in those fields.

As would be disclosed by our records, it would be false of me to say that we were prepared to comply with the College plans without qualification. Like the psychiatrists, paediatricians and dermatologists in relation to their own specialities, we wanted to continue to be primarily responsible for the training of neurologists and the determination of who would become fit to practise consultant neurology. As a result we made proposals to the College in which we recognised the indisputable right of the College to determine for itself who would become Fellows of the College. At the same time these proposals would allow us to continue to be primarily responsible for the training and accreditation of neurologists by our nominating, and the College appointing those who were to carry out the functions of training and accrediting physicians in neurology. Over the years harmonious discussions and agreements to give effect to the aspirations of both Bodies have been achieved, but we have not yet succeeded in obtaining formal documented confirmation of this. Thus the matter at present remains unresolved. It is my personal belief that the inalienable rights of both organizations can be preserved without any destruction of the authority of either. I firmly believe that it would be to the benefit of both the College and ourselves to resolve this problem on the basis of equal collaboration. Maybe if the College had been prepared to go one step further and re-constitute itself as a confederation of the various branches of medicine the objectives would have been more easily achieved.

At the Second Asian and Oceanian Congress of Neurology in 1967 a resolution was passed by the Delegates which sought to establish Australia as the major centre for neurological training in the eastern hemisphere. This would not prevent the necessary development of neurological centres in the individual countries of the members of the Asian and Oceanian Association of Neurology but rather would foster and nourish them. It is this type of responsibility and our desire that we should remain the body that ultimately determines who is fit to practise consultant neurology in Australia which have been the important motives in our desire to collaborate with the College of Physicians in the manner discussed.

Just as I have mentioned that the breadth of horizon of our founders allowed them to see into the future, so do I believe that our Association will continue to have the foresight to be the major motivating and unifying force in directing the future expansion of neurology in Australia.

GENICULATE HEMIANOPIAS: INCONGRUOUS VISUAL DEFECTS FROM PARTIAL INVOLVEMENT OF THE LATERAL GENICULATE NUCLEUS

WILLIAM F. HOYT*

The lateral geniculate nucleus (LGN) remains an enigma in clinical neurology. Clinico-anatomical studies correlating patterns of homonymous visual defects and necropsy findings in the LGN have been recorded in only 3 cases (Henschen, 1898; Mackenzie, Meighan and Pollock, 1933; and Balado, Malbran and Franke, 1934) but no identifying perimetric features of geniculate hemianopia were published until Gunderson and Hoyt's report in 1971.

The present report describes the incongruity of the homonymous hemianopias in four patients with partial LGN involvement and discusses these perimetric findings in terms of the retinotopic laminar anatomy of the nucleus. Fundoscopic signs of retrograde atrophy in the retinal nerve fiber layer were recognized in three of the patients and were recorded photographically in one of them.

CASE REPORTS

CASE 1

Slowly progressive incongruous left homonymous hemianopia and progressive left hemiplegia in a man with 19-year-long temporal lobe epilepsy from astrocytoma that slowly invaded the right LGN and neighboring structures.

When aged 24 years a soldier experienced the first of many episodes of staggering giddy spells lasting several minutes. At age 36, he had three grand mal seizures and thereafter received daily primidone (Mysoline®) and phenytoin (Dilantin®). At age 43 he noted some subtle clumsiness of his left arm and difficulty reading.

Ocular Findings. Vision was 20/20 in each eye and pupillary reflexes, eye movements, and ocular fundi, including the optic discs, were recorded as normal. Visual field examination revealed a unique pattern of homonymous field defects (Fig. 1).

Neurologic Evaluation. Rapid alternating movement of the left hand was slow without other motor or sensory disturbance. Results of radiographic and encephalographic studies, including brain scan, were normal.

Clinical Course. The patients visual defects slowly enlarged and the left hemiparesis gradually worsened (Fig. 2). Again complete neuroradiologic studies were interpreted as normal. Two months later, following a major seizure, he died.

Neuropathologic Examination. The brain contained two foci of tumor, one in the right temporal lobe, and the other in the right thalamus, rostral midbrain, and pontine tegmentum (Fig. 3). A grayish zone bridged the two tumor foci in the area of the right LGN. Microscopic examinations showed diffuse pilocytic astrocytoma in which areas of malignant degeneration replaced completely the right rentrolenticular zone and the area of the right LGN. The right hippocampus was minimally involved but contained signs of neuronal degeneration and glial reaction typical of Ammon's horn sclerosis.

* The Neuro-Ophthalmology Unit of the Departments of Neurology, Neurosurgery, and Ophthalmology, University of California (San Francisco) San Francisco, California, USA, 94143.

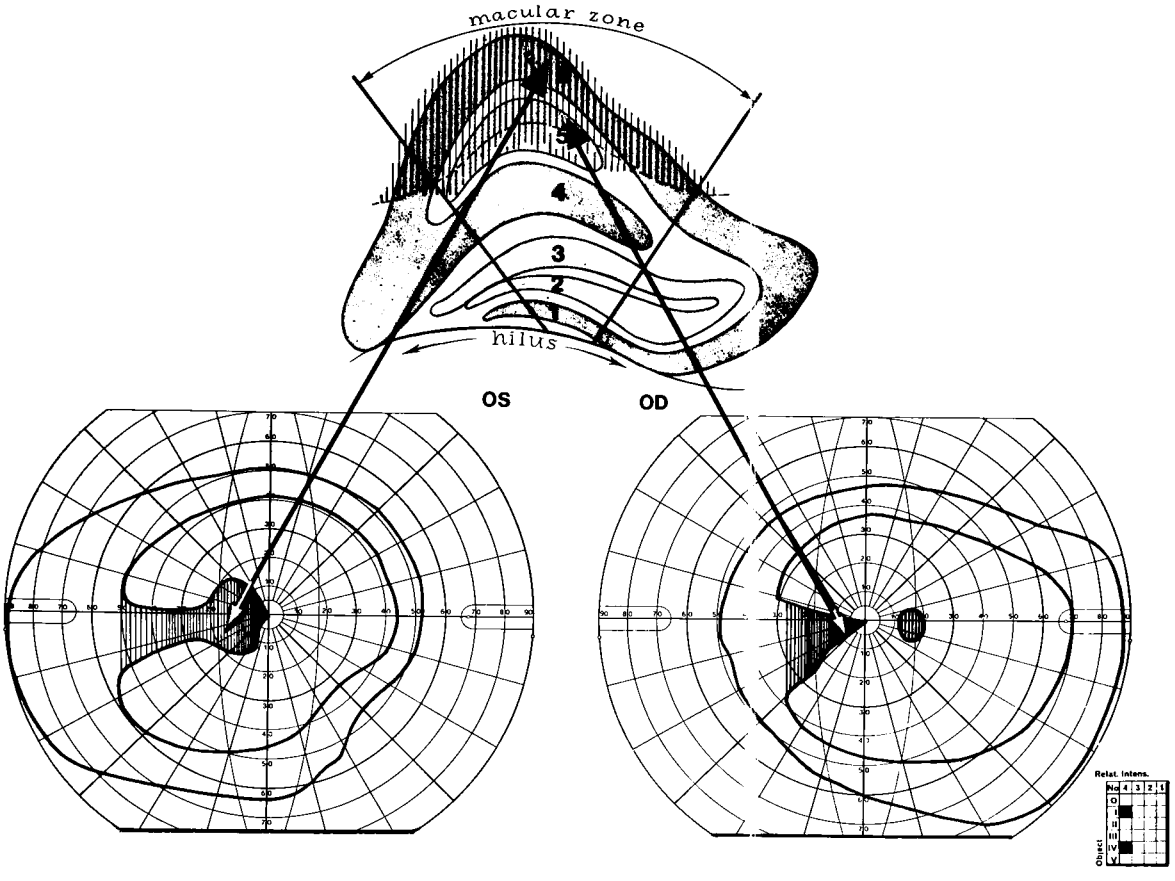

FIG. 1 (Case 1). Progressive geniculate hemianopia from astrocytoma involving the right lateral geniculate nucleus.

Initial visual defects were relative and grossly incongruous. In the temporal field there was a "keyhole-shaped" defect and in the nasal field, a smaller wedge-shaped defect.

The schematic diagram of the laminae in the right geniculate nucleus (at the top) indicates, in a mid-coronal section, how a lesion at the dorsal crest of the LGN produces greater involvement of lamina 6 and a larger visual defect in the paracentral temporal field of the contralateral eye.

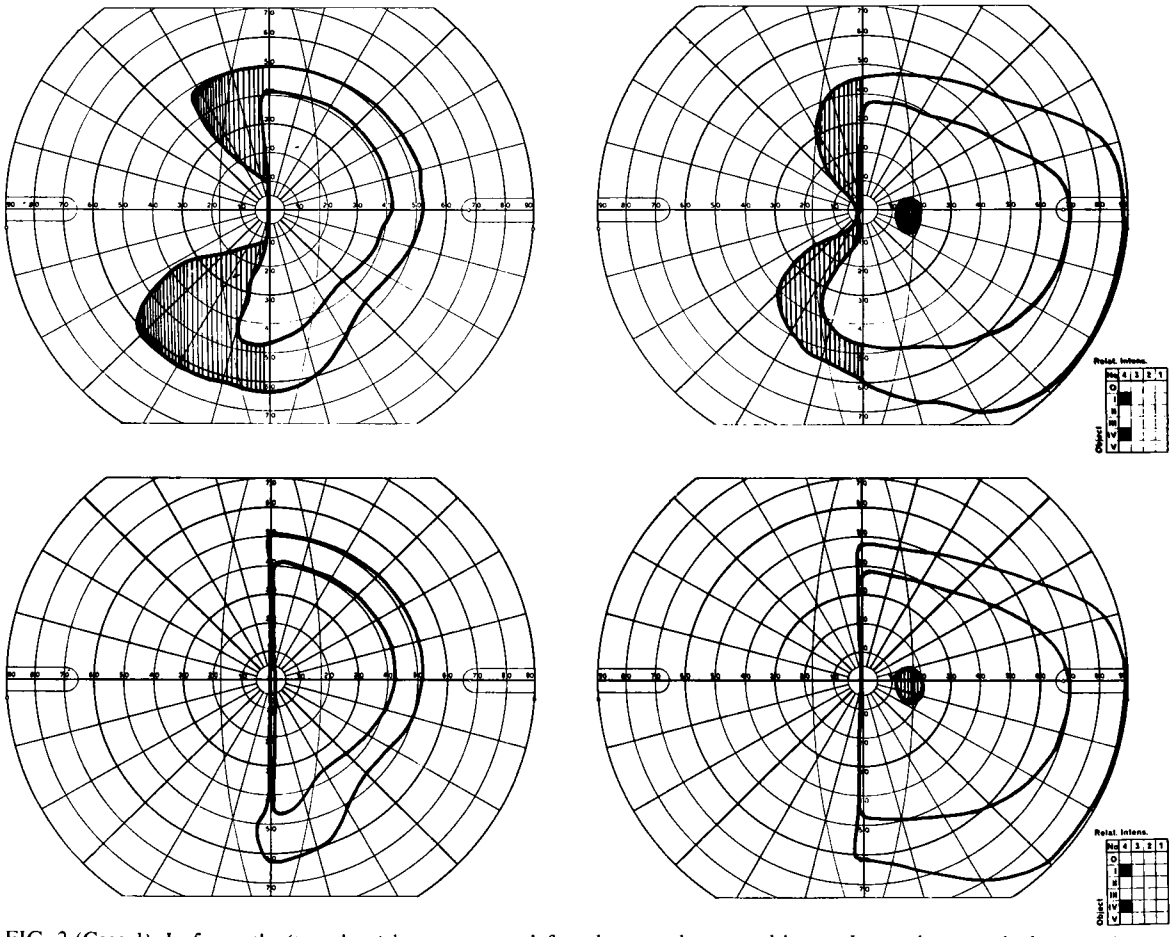

FIG. 2 (Case 1). In 5 months (top chart) homonymous defects became denser and larger. In another month (bottom chart) hemianopia was total.

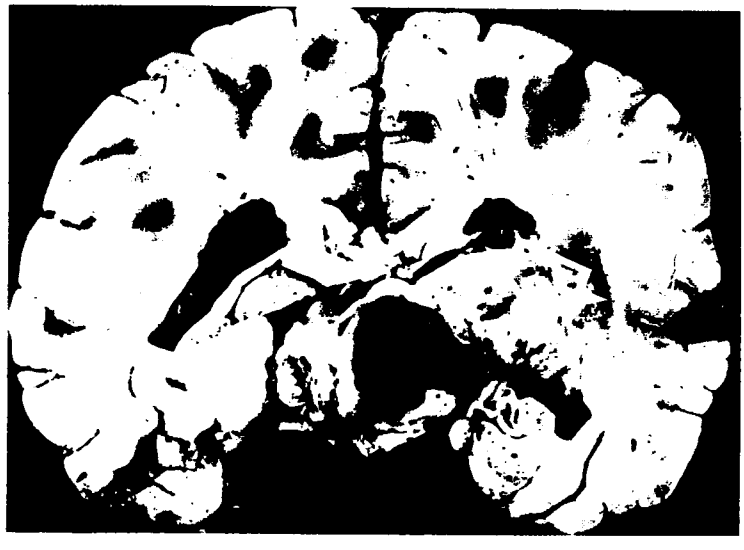

FIG. 3 (Case 1). Coronal section of brain showing tumor in the right temporal lobe, the temporal isthmus, the LGN (arrow), and the brain stem.

CASE 2

Right incongruous hemianopia in a girl with arteriovenous malformation in the area of the left LGN.

A 16-year-old girl complained of mild frontal headache and hazy vision seven months after a spontaneous subarachnoid hemorrhage.

Ocular Findings. Vision was 20/20 in each eye. Pupillary size and reactions were normal, without hemianopic pupillary akinesia or afferent pupillary defect. The nasal and temporal edges of the right optic disc were pale. Peripapillary arcuate nerve fibre reflexes were visible only above and below the right disc. Such reflexes were visible in all quadrants around the left disc.

Visual fields (Bjerrum screen and Goldmann perimeter) showed a dense, grossly incongruous right homonymous hemianopia. The defect in the right eye obliterated all of the temporal field except for a slim 10 degree central area. The defect in the left eye consisted of an upper quandrantopia with a sloping inferior border that extended to 3 degrees from fixation (Fig. 4).

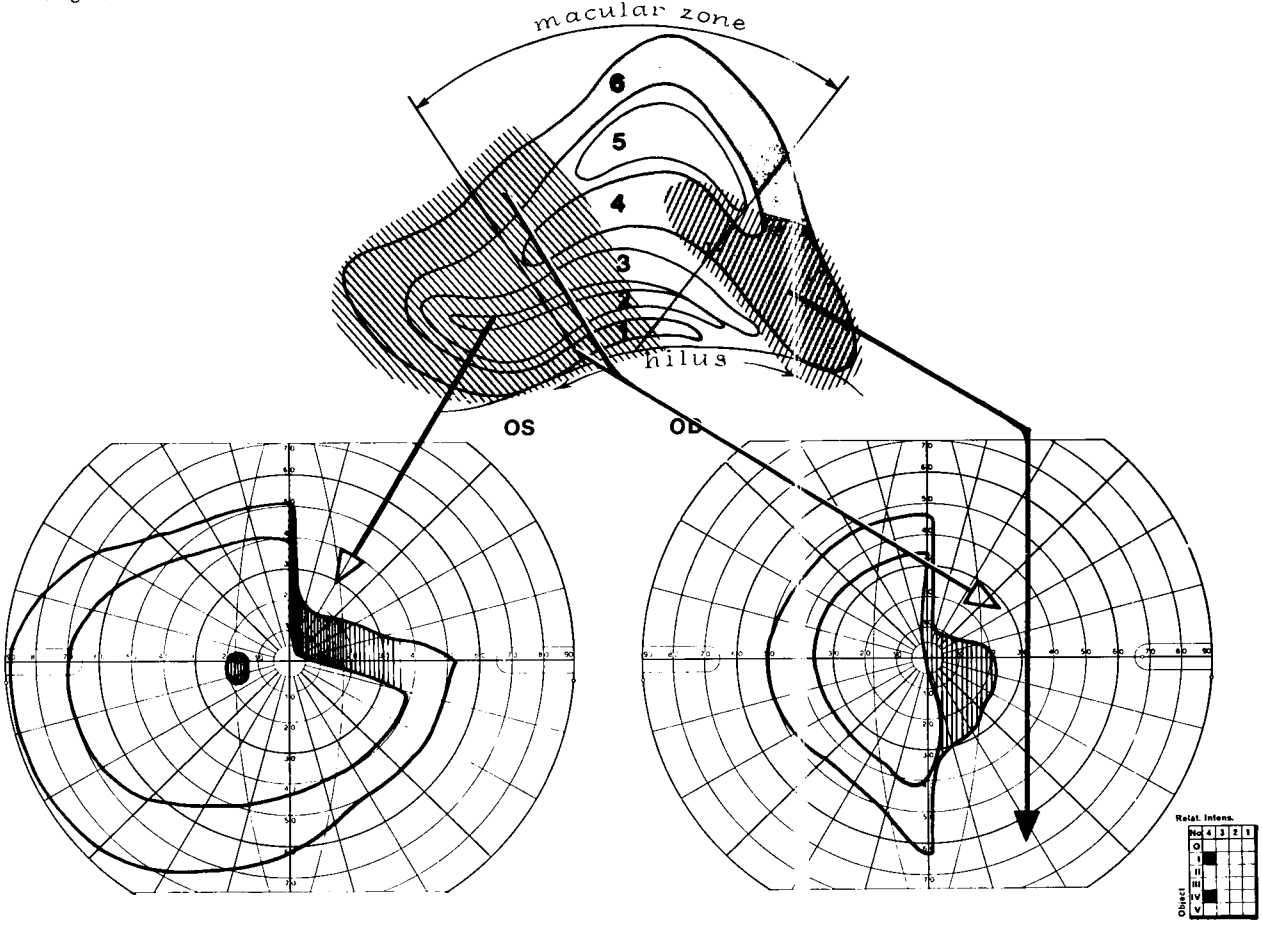

FIG. 4 (Case 2). Incongruous geniculate hemianopia from arteriovenous malformation in the left LGN. Geniculate diagram (above) shows area of laminae 6 and 4 (shaded area on right) where a lesion could account for the monocular inferior quadrant defect (black arrow). The multi-laminar area on left (shaded area) could account for the bilateral upper quadrantanopia (open arrow).

Neurologic Evaluation. The patient was alert and healthy, without limb weakness, reflex asymmetry, sensory loss, incoordination, or postural disturbance. Vertebral angiography demonstrated a 0.50 x 0.40 x 1.0 cm arteriovenous malformation supplied from the ambient segment of the left posterior cerebral artery. The malformation projected upward and laterally into the area of the left LGN (Fig. 5).

Clinical Course. The patient's headaches were mild and seemed unrelated to the geniculate angioma. One year and three years later, visual field defects were unchanged and there were no new neurologic findings.

FIG. 5 (Case 2). Geniculate arteriovenous malformation (arrow) in vertebral angiogram (Towne projection). The malformation arises from the ambient segment of the left posterior cerebral artery and extends posterolaterally into the area of LGN and the pulvinar.

CASE 3

A 62-year-old man had trouble seeing to his left because of a left sided incongruous homonymous hemianopia. He was mildly hypertensive and had fundoscopic signs from atrophy of the right post-chiasmal pathway.

This 62-year-old physician recalled only "slight" difficulty seeing to his left for 3 or 4 years. He was totally unaware that he had a visual field defect but admitted that he had several "near misses" and one accident in his automobile when he failed to notice other cars approaching on his left. An ophthalmologist found a left-sided homonymous hemianopia during an examination for glasses.

Ocular Findings. Visual acuity was 20/20 in each eye. Ocular movements were conjugate. Pupillary reactions to light and accommodation were brisk and equal. In the ocular fundi the choroidal pattern was prominent, the pigment epithelium was thin, and the retinal vessels were slightly narrowed. The left optic disc was pale with sparse capillaries except in the upper and lower sectors where arcuate fibre bundles entered it. Nerve fibre striations were absent nasal to the disc and temporally, in a horizontal band. The right disc was slightly pale temporally and retinal zones normally containing arcuate fibres were thinned. Elsewhere around the disc nerve fibre refexes were visible.

Visual fields showed an unusual incongruous left homonymous hemianopia. The temporal defect consisted of a horizontal dense sector that spared fixation. Dim remnants also were spared above and below along the vertical meridian. The corresponding nasal defect contained a blind horizontal sector that extended to fixation and spared areas in the upper and lower quadrants beside the vertical meridian (Fig. 6).

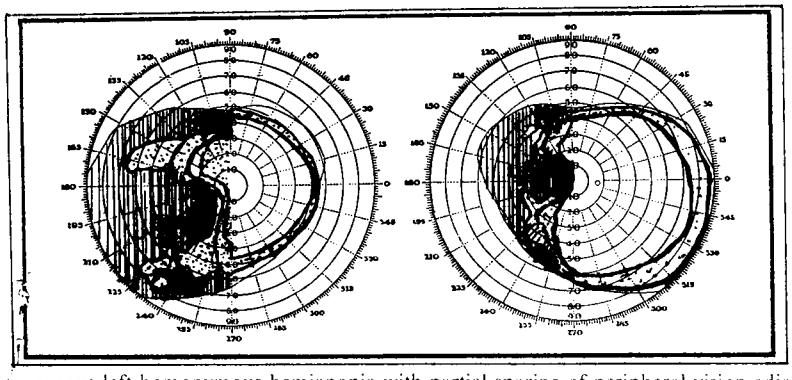

FIG. 6 (Case 3). Incongruous left homonymous hemianopia with partial sparing of peripheral vision adjacent to the vertical meridian in the upper and lower quadrants. Note the sparing of central (macular) vision only in the left field. This monocular type of macular sparing is a feature of LGN involvement.

Neurologic Evaluation. The patient appeared in good health. His blood pressure was 150/95. Carotid bruits were not heard. He had no sign of limb weakness, imbalance, reflex asymmetry, or sensory change. Radiologic examinations of the skull were normal except for bilinear opacities in the carotid siphon. No other neuroradiologic studies were performed.

Course of Disease. The left-sided homonymous hemianopia has remained unchanged for 4 years.

CASE 4

Markedly incongruous left homonymous hemianopia and fundoscopic signs of retrograde atrophy as sequelae of a hypertensive vascular accident.

A 50-year-old business executive with systemic hypertension experienced several transient attacks of slurring of speech, dropping of the left side of his mouth, and numbness in the left face and hand. Four months later he became angry while addressing a business meeting; suddenly his vision blurred in both eyes, he felt nauseated, and he noted a "pulling sensation" of his face on the left. He did not fall but needed help to reach a chair. Five minutes later his vision cleared on the right side but not on the left side of vision. This deficit caused him difficulty with reading.

Ocular Findings. Visual acuity was 20/20 bilaterally, color perception was normal, and eye movements were full and conjugate. Pupillary reactions during light and near stimulation were brisk and equal. The left pupil failed to dilate fully in darkness, but the left upper lid did not droop and there was no anhidrosis of the left forehead. Perimetric examination (Goldman perimeter) defined a markedly incongruous inferior quadrantanopia on the left (Fig. 7). Red-free fundoscopic examination showed hemi-retinal nerve fibre layer atrophy in the upper homonymous quadrants of the ocular fundi (Fig. 8).

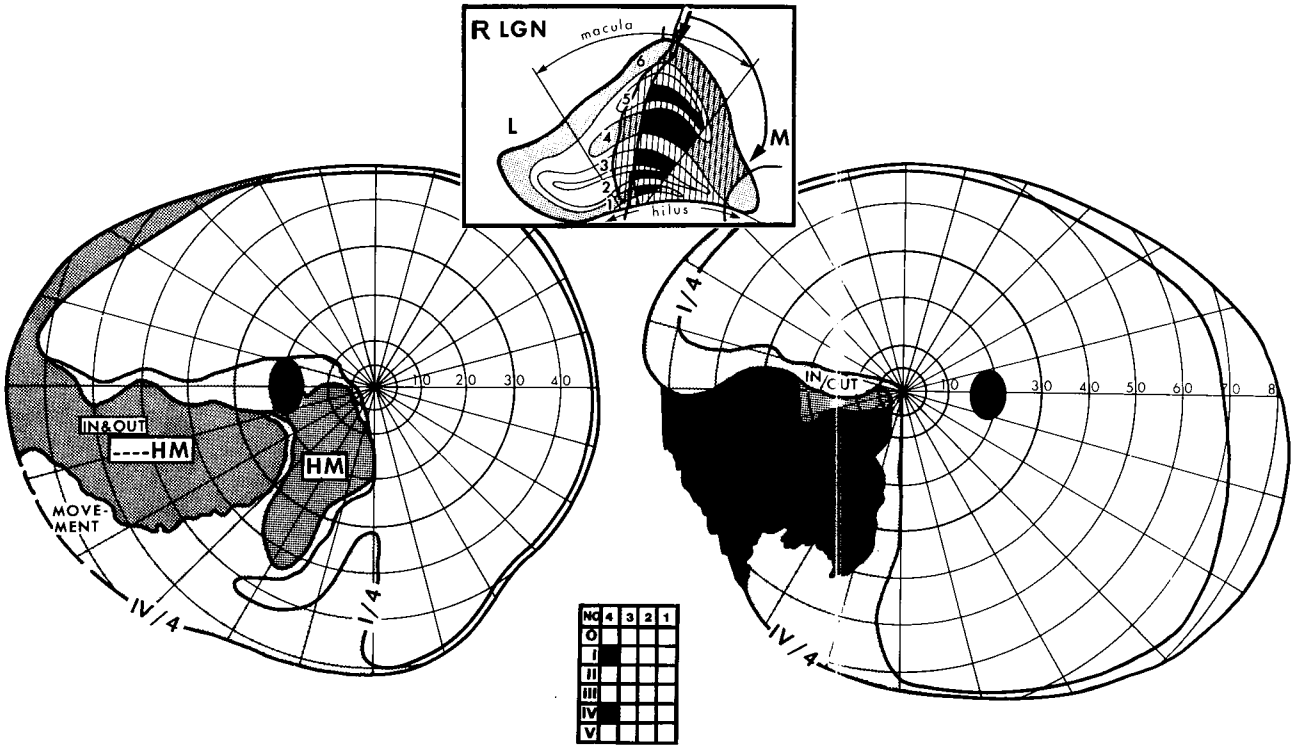

FIG. 7 (Case 4). Geniculate hemianopia from vascular complication of systemic hypertension. The homonymous defects in the left visual fields are incongruous with regard to their edges and density. Points of importance are (1) macular sparing in left temporal defect and macular splitting in the right nasal defect, (2) relative sparing of areas along the vertical meridian, and (3) the peculiar retention of "normal" peninsula of field in the inferior temporal quadrant. The diagram (inset above) depicts the right LGN in mid-coronal section (viewed from front). The postulated lesion involves the medial (M) half of the nucleus in all layers. The crest of lamina 6 is spared, corresponding with the spared "macula" in the left monocular field. The medial horn of the nucleus is only partially involved, corresponding with the spared peripheral portion of the lower quadrants. All of the laminae for the ipsilateral eye (5, 3, and 2) are involved, corresponding with the absolute defect in the nasal field.

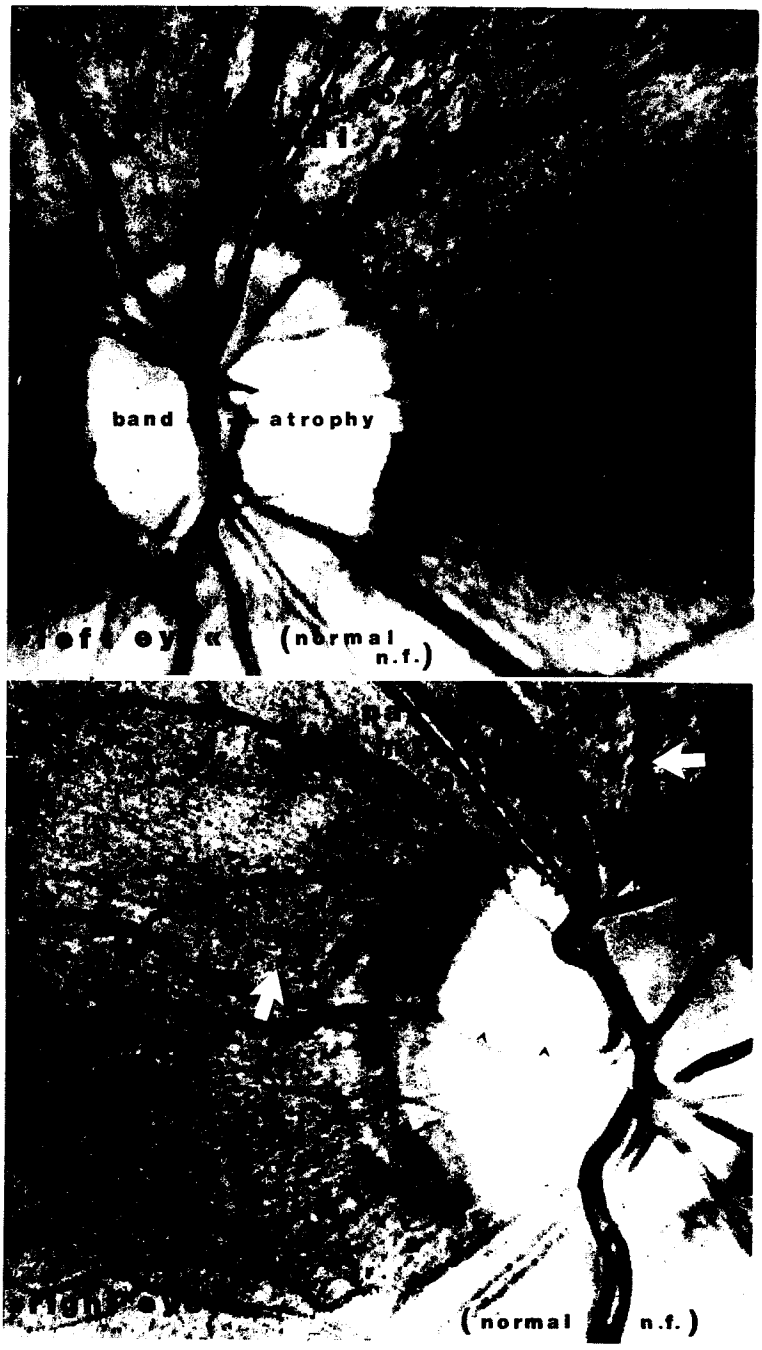

FIG. 8 (Case 4). Homonymous retrograde atrophy in the retinal nerve fiber layer from involvement of medial side of right LGN. In the left fundus (above), the eye with temporal inferior quadrantopia, the disc and retina show a horizontal band of nerve fibre atrophy. The superior margin of the disc is abnormally sharp, indicating that the nerve fibres overlying it are thinned out. The inferior disc margin and adjacent retina is blurred and opaque with a normal nerve fibre layer.

In the right fundus (below), the eye with the nasal inferior quadrantopia, the disc is pale in the upper temporal sector. Superiorly, the nerve fibre layer is abnormally thin (between white arrows), exposing the upper disc margin and the trunks of the superior arteries and veins. The upper retina is darker than the inferior retina because the thinned (atrophic) retina reflects less light.

Neurologic Evaluation. Blood pressure was 170/110. No bruits were heard in the neck. The heart rate was normal, without arrhythmia. He had no sign of congestive heart failure. Although he complained of slight residual numbness in the fingers of his left hand, sensory testing showed no abnormality. There was no weakness or reflex asymmetry in the face, arms, or legs. Mentation and speech were normal. The clinical diagnosis was hypertensive vascular disease with multifocal lacunar infarctions in the brain, including the right LGN.

Clinical Course. The transient neurologic symptoms stopped and the blood pressure was lowered to 135/90 on a regimen of hydrochlorothiazide (50 mgm/day) and a small dose of hydrallazine three times daily. The left homonymous hemianopia regressed slightly over a period of 4 months.

DISCUSSION

Incongruity of the homonymous field defects in geniculate hemianopias deserves consideration clinically and anatomically. The field defects in the clinico-anatomical case studies of Mackenzie *et al.* (1933) and Balado *et al.* (1934), and the clinical reports of Smith, Nashold and Kreshon (1961) and Fite (1967) showed this feature. The occurrence of incongruity from lesions at the level of the LGN disobeys a time-honored axiom of perimetric diagnosis. Since the time of Salomon Eberhard Henschen (1898), it has been a clinical rule that incongruity of homonymous field defects is greatest with lesions near the chiasm and that the incongruity diminishes progressively with more posterior involvement of the visual pathway (Kearns and Rucker, 1959). This formulation derives from the belief that visual projections from corresponding points in each retina gradually line up, one fibre with the other, as the afferent pathway approaches the striate cortex.

A logical anatomical basis for incongruity in homonymous hemianopias from subtotal geniculate lesions stems from two accepted principles of retinotopic organization in the LGN. The first principle is Minkowski's (1921) landmark discovery that crossed retinal projections terminate in geniculate laminae 6, 4, and 1, while uncrossed projections terminate in laminae 5, 3, and 2. The second is the principle that corresponding "points" in the two retinae are represented in the LGN in vertically oriented lines or columns of cells from all six laminae. In this way the two-dimensional (monocular) assembly of receptor cells in the back of the eye is transformed into a three-dimensional (binocular) assembly in the lateral geniculate laminae, with the majority of cells being concerned with "macular" vision (Brouwer and Zeeman, 1925; Le Gros Clark and Penman, 1934; Kupfer, 1962). From these elementary considerations about the organization of crossed and uncrossed retinal ganglion cell connections in the 6-layered LGN, it is apparent why partial lesions of geniculate laminae might produce differing effects on vision in each eye.

Neuropathologic observations of LGN involvement by adjacent disease in thalamus, medial temporal lobe, or rostral brain stem are frequent in the laboratory. If clinical records of perimetric findings are available, they usually show total homonymous hemianopia (Lillie, 1930). Subtle changes in the LGN pass unnoticed unless the neuropathologist has specific interest in this structure. Lindenberg (1965) and Lindenberg, Walsh and Sacks (1973) illustrated and discussed ischemic changes that occur in the lateral geniculate nucleus, including discrete zones of laminar necrosis.

From current knowledge that cells of the LGN have a stable retinotopic arrangement and that diseases, particularly vascular diseases, can destroy only part of the nucleus, we might anticipate the occurrence of some unique perimetric signs in the fields of one or both eyes. Certain anatomical obstacles diminish the possibilities for precise intra-geniculate localization. Among these is the fact that most geniculate involvements destroy axons along with the cells in the nucleus. However, topographic diagnosis is possible in certain cases. A lesion in lamina 6 in the crest of the LGN should produce a monocular hemianopic scotoma in the central field of the contralateral eye (see Fig. 9). A geniculate hemianopia with this character has not been recognized. A lesion of the medial horn (lamina 6) should also produce a monocular defect in the contralateral eye, e.g. an inferior quadrant defect sparing the macular area (see Case 2 of this report). Larger, bilaminar lesions in the geniculate crest (laminae 5 and 6) should produce incongruous scotomas or horizontal wedge defects of the type illustrated in Fig. 1 (Case 1). Similar perimetric findings have been recorded by Oosterhuis, Ponsen, Jonkman and Magnus, (1969), by Smith (1970), by Kearns and Rucker (1959) and by Spalding (1952) without recognising their origin. Fig. 6 (Case 3) may exemplify a multilaminar geniculate crest lesion that spares the lateral horns of the nucleus. Fig. 7 (Case 4)

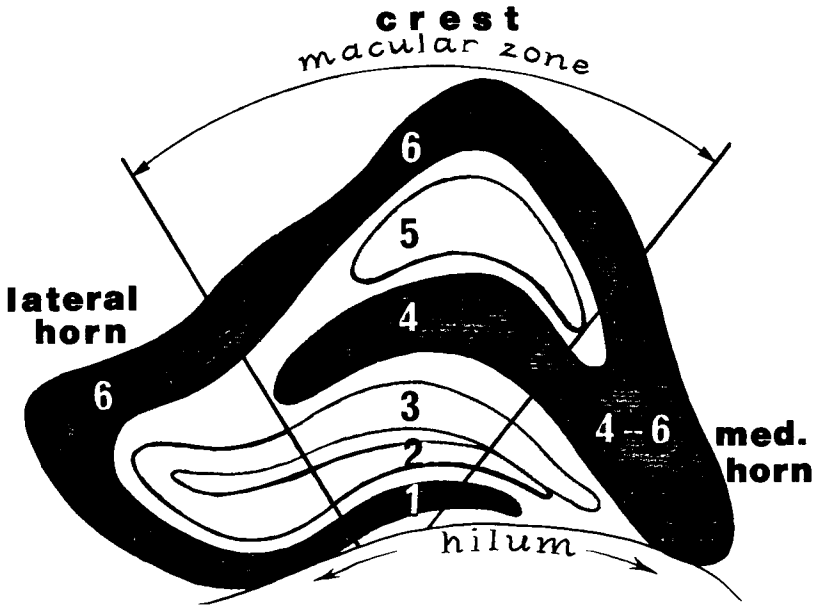

FIG. 9. Coronal sectional schema of the LGN laminae. The outer lamina, like a capsule with a shelf-like invagination, receives the crossed projections from the contralateral retina (Laminae 6, 4, and 1). The laminae receiving the uncrossed retinal projections occupy the core of the nucleus (Laminae 5, 3, and 2). The macular portion of the laminae is large and centrally located. Afferent optic tract fibres enter the nucleus between the laminae and geniculate axons exit from the lateral side of the nucleus, above and below the lateral horn.

illustrates a more compact multilaminar geniculate lesion involving only the medial half of the nucleus. This type of hemigeniculate lesion with quadrantic homonymous hemianopia may show asymmetrical macular sparing as occurred in the upper quadrants of the visual fields of Case 2 (Fig. 3) and Case 3 (Fig. 6). Kearns and Rucker (1959) recorded a similar finding (their Fig. 18).

Fundoscopic signs of retrograde atrophy in the nerve fibre layer of the retina in three of the cases in this report (Case 2, 3, and 4) have not been previously recorded in patients with geniculate hemianopia. The pattern of fibre loss was typical of optic tract atrophy (Hoyt and Kommerell, 1973). These findings indicate associated injury of primary visual axons by the disease causing the geniculate dysfunction. The signs are indistinguishable from signs produced by more anterior optic tract lesions. It is probable that these signs were present but went unrecognized in Case 1, the patient with astrocytoma involving the LGN. In any patient with neurologic signs suggesting lateral geniculate disease, signs of hemiretinal atrophy support the diagnosis and exclude an acquired occipital cause of the hemianopia. When a question arises as to whether a hemianopia is both geniculate and suprageniculate, the absence of nerve fibre abnormality from a blind quadrant of the retina suggests suprageniculate localization. This kind of diagnostic question arises in evaluating patients with thalamic tumors or proximal posterior cerebral artery occlusions.

The present report provides guidelines for neuro-ophthalmologic diagnosis of lesions in the LGN. If the monocular and retinotopic principles of LGN organization are recalled in future evaluations of incongruous hemianopias, new patterns of geniculate hemianopia will be discovered. As illustrated here in cases of geniculate hemianopia, fundoscopic examination for retrograde atrophy adds an important dimension to clinical diagnosis of all homonymous hemianopias.

SUMMARY

Quantitative perimetric studies in four patients with involvement of a lateral geniculate nucleus revealed strikingly incongruous defects in the corresponding homonymous fields of vision. The

patterns of these hemianopias are analysed and correlated anatomically with established retinotopic projections on the six cellular laminae of the geniculate nucleus. Incongruous wedge-shaped field defects appear to be pathognomonic of focal disease in the dorsal crest of the geniculate nucleus. Other patterns typify lesions of the medical or lateral horns of the nucleus. On theoretical grounds monocular hemianopic defects should result from unilaminar geniculate lesions, but this perimetric sign awaits confirmation. In each case of geniculate disease where the retinal nerve fibre layer has been examined specifically for evidence of retrograde homonymous atrophy, typical hemiretinal signs were found to be present.

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CERTAIN NEURO-OPHTHALMOLOGICAL ASPECTS OF MULTIPLE SCLEROSIS

JOHN M. SUTHERLAND*

Symptoms and signs referable to the visual system are commonly encountered in multiple sclerosis (M.S.) and their occurrence not infrequently ushers in the clinical disease. Thus, Poser (1965) in 25 autopsy proven cases of M.S. reported visual manifestations as occurring as the first symptom in 48%, and during the course of the disease in 80%. The present paper, based on personal experience of 558 patients with M.S., and on a review of the more recent neurological literature, discusses some of the ocular manifestations of the disease.

DIPLOPIA

Diplopia occurred as an initial symptom in 67 patients (12%) in this series of 558 M.S. cases and was present in a further 110 (20%) at the time of examination. The sixth cranial nerve was usually implicated, the third less frequently, while the fourth was rarely affected. Involvement of the third cranial nerve was usually only of partial degree. Indeed, although an overt ocular palsy might be an initial sign of M.S., in my experience an obvious stabismus was uncommon.

Patten, Hart and Lovelace (1972) drew attention to a myasthenic-like fatiguability which may occur in M.S. and to the improved functional capacity which sometimes follows the use of anticholinesterase drugs. In similar vein, Lumsden (1972) referred to the antisynaptic effect of M.S. serum and suggested that transient clinical manifestations of the disease may relate to the effects of this 'antisynaptic factor'. In my experience, injections of edrophonium ('Tensilon') or therapy with neostigmine ('Prostigmine') had a beneficial effect in occasional M.S. patients complaining diplopia but the results were never as clear cut as in patients with myasthenia gravis. However, this effect, when observed, may have diagnostic implications in an early case of M.S.

INTERNUCLEAR OPHTHALMOPARESIS AND OPHTHALMOPLEGIA

Many years ago, Adams, Sutherland and Fletcher (1950) referred to the diagnostic importance of ocular imbalance, a condition which suggests a dissociated action of the extrinsic ocular muscles, in M.S. Subsequently, this finding was observed in 52% of 100 consecutive cases (Sutherland, Tyrer and Eadie, 1961). This ocular imbalance appears to be due to paresis of the internal rectus muscle in lateral conjugate movement. It is best described as internuclear ophthalmoparesis or ophthalmoplegia, and in fully developed degree comprises: (1) failure of the medial rectus muscle on the side of the lesion to act on horizontal gaze to the opposite side; (2) nystagmus of the abducting eye; (3) ocular dysmetria – overshooting of the eyes on attempting rapid fixation movements.

According to Smith and David (1964), when these signs are unilateral a vascular lesion is responsible in some 70% of cases, whereas bilateral internuclear ophthalmoplegia is virtually diagnostic of M.S. Cogan and Wray (1970), however, emphasized the occurrence of internuclear ophthalmoplegia as an early sign of brain stem tumours.

* Department of Neurology and University Department of Medicine, Royal Brisbane Hospital

NYSTAGMUS

Nystagmus occurred alone or in combination with other components of Charcot's triad in 38 (48%) of 79 patients hospitalized with M.S. (Table I), a figure identical with that reported by Scott (1961). In a later series of 100 consecutive patients this sign was present in 63% of cases (Sutherland *et al.*, 1961).

TABLE I

The occurrence of nystagmus, scanning speech and intention tremor (Charcot's triad) in 79 consecutive hospital patients.

	No. of Patients	% of Series
Nystagmus + Scanning speech + Intention tremor	12	15
Intention tremor alone	12	15
Nystagmus alone	11	14
Nystagmus + Intention tremor	10	13
Scanning speech alone	7	9
Scanning speech + Nystagmus	5	6
Scanning speech + Intention tremor	4	5

Nystagmus in M.S. is usually of the horizontal type. When it is monocular (Harris' ataxic nystagmus) or has a rotatory, jelly-like component, a diagnosis of M.S. should be suspected (McAlpine, 1972). Wybar (1975) considered ataxic nystagmus is a limited degree of internuclear ophthalmoplegia not sufficiently marked to cause limitation of adduction but sufficient to cause nystagmoid jerks of the abducting eye.

THE PUPILS

In 100 consecutive hospital patients with M.S. the pupils were generally of average size or somewhat dilated, being of more than 4mm diameter in 90% of cases. In only 6% of instances were they regarded as miotic. Pupillary reactions to light and on convergence were generally brisk and in 38% of patients hippus was observed. This finding is in marked contrast to the loss of normal pupillary unrest which may be an early ocular mainfestation of neurosyphilis.

The concurrence of mydriasis (90%), internuclear ophthalmoplegia (52%) and hippus (38%) constitute a triad of importance in the clinical recognition of M.S.

OPTIC NEURITIS

The vulnerability of the optic nerves, chiasm and tract to M.S. is well known. As emphasized by McAlpine (1972) it is probable that during the full course of the disease the majority of patients will develop symptoms and signs referable to optic neuropathy. Thus Lumsden (1970) found typical plaques in the optic nerves, chiasm or tracts in each of 36 consecutive cases of M.S. In the present series of 558 patients, 75 (13%) experienced dimness or loss of vision as an initial symptom and a further 83 (15%) developed these symptoms later in the course of the disease, or had them at the time of examination.

Characteristic Optic Neuritis

The characteristic clinical situation is that of a young patient who presents with impairment of vision in one eye of sudden onset. A central field defect may be described. There is often discomfort on movement of the eye or on pressure on the eyeball. The pupil is often dilated and reaction to light may be sluggish. Ophthalmoscopically, there may be no change in the nerve head. In some 20% of cases the disc is pinker than on the normal side and there may be florid papillitis

with a swollen nerve head, distended veins and small haemorrhages. In occasional cases these appearances may render differentation from papilloedema due to increased intracranial pressure extremely difficult. In distinguishing between the swollen disc of optic neuritis and that of papilloedema, the following features may be of assistance: (1) pain in the affected eye on movement or pressure is common in optic neuritis; (2) visual acuity is diminished in optic neuritis but may be normal until late in papilloedema; (3) the papillomacular bundle of fibres is particularly vulnerable in demyelinating diseases, hence a central or paracentral scotoma is characteristic of optic neuritis; (4) if visual field testing proves unreliable or if the scotoma spares fixation so that visual acuity is essentially unimpaired, two further signs have been found useful by Daroff and Smith (1965):

(a) the Marcus Gunn pupillary sign – direct stimulation by light on the affected side produces less miosis than the consensual reaction and the pupil on the affected side dilates slowly after constriction compared with the normal side – so that the pupil may actually appear to dilate as it changes from an intact consensual to a relatively impaired direct response.
(b) cells in the vitreous – this, however, can only be seen by slit lamp biomicroscopy.

Bilateral Optic Neuritis

With the exception of Japanese patients (Kiroiwa, 1968; Shibasaki and Kuroiwa, 1973) bilateral optic neuritis (i.e. symptoms affecting both eyes simultaneously or successively within an interval of less than one week) is uncommon. My experience, suggesting a figure of under 10%, has been confirmed by Bradley and Whitty (1968) who reported bilateral optic neuritis in 7% of their series. It is of considerable interest that whereas in Japan bilateral optic neuritis is typical of M.S. this was not found in Hawaii (Alter, Good and Okihiro, 1973) when optic neuritis was studied in the Oriental and Caucasian populations of that State.

Spillane (1972) considered that neuromyelitis optica is being increasingly recognised as an acute form of M.S. However, my own experience of patients with bilateral optic neuritis (with signs of myelopathy at the time or shortly afterwards) suggests that most cases are better regarded as having acute disseminated encephalomyelitis. I would suggest that in Australia Devic's disease is usually a manifestation of acute disseminated encephalomyelitis but that in some 7-10% of cases the subsequent course is that of M.S.

Slowly progressive visual impairment

As long ago as 1881, Parinaud noted that visual impairment might be gradual rather than sudden in M.S. and Scott (1961) reported the occurrence of insidious progressive optic neuropathy in three cases (4.6%) of his series of 65 M.S. patients. Certainly cases occur in which visual impairment has been so gradual as to pass unnoticed by the patient until found by chance during a routine examination or only when the other eye becomes involved. McAlpine (1972) while agreeing that slowly progressive demyelination of the optic nerve or nerves might occur in M.S. advised that other causes such as compression or Leber's disease should be considered.

Linked to this discussion is the significance to be attached to the finding of pallor of the temporal half of the optic disc in a patient with M.S. who has had no visual symptoms. Kahana, Leibowitz, Fishback and Alter (1973) reported that 182 patients (70%) in their total series of 259 patients had optic nerve involvement and that 75 of this group (41%) had no visual symptoms; atrophy or pallor of the disc were the most commonly observed signs. I have always had reservations as to the significance to attach to pallor of the disc, particularly the temporal half, in the absence of supportive evidence such as a history of visual impairment, or unless objective signs are also present such as impaired visual acuity, impaired colour vision or the presence of a scotoma. Employing these criteria, the optic nerve was regarded as pathological in only 17% of 558 patients at the time of examination.

Effect of fatigue

Reference has already been made to a myasthenia-like fatigability which may be encountered in M.S. Further, blurring of vision or an increase in the size of a scotoma may occur in relation to exertion and McAlpine (1972) considered that in a young adult a history of blurred vision on exertion should rouse suspicion of M.S.

It might be that vasomotor responses are responsible for these fluctuations. In my own series there was a tendency for a lower than average blood pressure while vasomotor symptoms such as unduly cool hands and feet, chilblains and acroparaesthesia were frequently encountered. Similarly, Watkins and Espir (1969) in a series of 100 consecutive patients with M.S. compared with a similar series of matched controls, found the incidence of migraine to be 27% in the M.S. group compared with 12% in the control series. The possibility of vasospasm being responsible for transient neurological symptoms, including visual disturbance, in M.S. patients should not be overlooked.

However, other mechanisms underlying paroxysmal symptoms in M.S. may be operative in some instances. Espir and Millac (1970), discussed paroxysmal disorders in M.S. such as dysarthria, tonic spasms and pain including trigeminal neuralgia. They suggested that demyelination of a degree insufficient to produce a permanent defect but rendering axons hyperexcitable might be the underlying mechanism. In such instances the use of carbamazepine ('Tegretol') may be of value and its administration in paroxysmal diplopia or impaired vision merits a trial.

Prognosis

In the absence of other evidence of neurological involvement, the significance of monocular acute retrobulbar neuritis is difficult to assess. Retinal vascular occlusion, compression, Leber's disease, toxic causes, neuromyelitis optica (acute disseminated encephalomyelitis) may merit consideration. However, the most common cause is M.S. and if cases are followed up over a period of 20 years, it is probable that about 50% will have further evidence of demyelination elsewhere.

The immediate prognosis for recovery of vision in acute optic neuritis is good. Both Bradley and Whitty (1967) and Rischbieth (1968) have shown that normal vision will be restored after some six months in about 75% of cases. The outlook is, however, worse in patients over 45 years of age than under this age (Earl and Martin, 1967), and patients who experience an insidious and progressive optic neuropathy may suffer severe impairment of vision (Scott, 1961). The usual sequelae when present include decreased visual acuity, impaired colour vision, scotomas (particularly for colours) and atrophy or pallor of the disc.

PERIPHLEBITIS RETINAE

Rucker (1944) of the Mayo Clinic first described sheathing of the retinal veins in M.S. and in 1972 he reviewed the relevant literature. A critical analysis of the significance of periphlebitis retinae in M.S. has been made by McAlpine (1972).

Rucker (1972) described two varieties: a flimsy sheathing of veins which might remain unchanged over long periods of time, and small, oval shaped, cloud-like patches which may persist for a few weeks or a few months. McAlpine (1972) emphasized that at least clinically, periphlebitis retinae in M.S. differs from vasculitis seen in relation to other disorders such as tuberculosis, sarcoidosis, and choroiditis due to various causes, in that haemorrhages, venous retinal thrombosis, pigmentation and vitreous haemorrhages are rarely seen. Rucker (1972) considered that in classical form periphlebitis retinae occurs in some 20% of cases of M.S. Conversely, if evidence of choroiditis or syphilis is lacking this finding is, 'about 90% reliable for M.S.'. Despite this, in the present series of 558 patients with M.S. periphlebitis retinae was rarely encountered. In explanation, Rucker (1972) stated that 'examiners conducting ophthalmoscopy with a brilliant light beam through undilated pupils in a partially darkened room will fail to see it ... for a satisfactory view ... the pupils must be widely dilated, the room dark and the light of the ophthalmoscope only moderately intense'. This

might account for the fact that Wybar (1952) found sheathing of retinal veins in 9 cases of M.S. in a series of 91 patients the majority of whom had previously been examined by me.

McAlpine (1972) summarizes the situation thus: '... it would seem that the association of M.S. and periphlebitis retinae is significant ... this group of conditions is obviously in urgent need of further planned study by opthamologist, neurologist and experimental pathologist, working as a team'.

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A FAMILY WITH CHARCOT-MARIE-TOOTH DISEASE AND LEBER'S OPTIC ATROPHY

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

Optic atrophy is a well recognized complication of Friedreich's ataxia and hereditary spastic paraparesis (Bell and Carmichael, 1939; Greenfield, 1954) but is rarely associated with Charcot-Marie-Tooth disease. Vizioli (1889), Ballet and Rose (1904), Taylor (1912), and Schneider and Abeles (1937) have all described families with Charcot-Marie-Tooth disease in which one or more members developed optic atrophy, and sporadic cases have been reported by other authors (Gordon, 1903; Krauss, 1906; Eisenbud and Grossman, 1927; Cavanaugh and Tucker, 1928; Piton, 1941; Brihaye, Nenquin-Klaassen and Bertholet, 1956; Hoyt, 1960). More recently, two families have been described in which both optic atrophy and deafness were associated with the condition (Rosenberg and Chutorian, 1927; Iwashita, Inove, Araki and Kuroiwa, 1970).

The family to be described in the present report appears to be unique in that Leber's optic atrophy and Charcot-Marie Tooth disease were inherited independently and were associated in two members of the family.

FAMILY HISTORY

The pedigree of the family is shown in Fig. 1.

The propositus, IV_2, a girl aged 17, awoke one morning with numbness and footdrop of the left foot. She wound found to have a left lateral popliteal nerve palsy and at the same time was observed to have mild bilateral pes cavus and weakness of dorsiflextion of the right foot. There was no muscle wasting, deep tendon reflexes were normal, and there were no sensory abnormalities. Motor conduction velocities in the right median, ulnar and lateral popliteal nerves were 69 M/sec, 34 M/sec, and 34 M/sec respectively. Sensory action potentials were reduced in amplitude and lateral popliteal mixed nerve action potentials were absent.

The father, (III_3), aged 57, had suffered from progressive weakness of the lower limbs since the age of 22. On examination, he was found to have pes cavus, marked distal wasting and weakness of upper and lower limbs, absent deep tendon reflexes in the lower limbs, and impaired sensation distally in the upper and lower limbs. Motor conduction velocity in the right ulnar nerve was 30 M/sec.

Sural nerve biopsy was performed on father and daughter. There was a reduction in the density of large diameter fibres, teased single fibre preparations revealed segmented demyelination and remyelination, and on electron microscopy onion bulb formations were seen around well myelinated fibres. These appearances were typical of the hypertrophic form of Charcot-Marie-Tooth disease.

Several other members of the family (II_4, II_6, II_7, III_4, III_5, III_{10}, IV_4 and V_9) were similarly affected, and the inheritance of the chronic peripheral neuropathy appeared to be autosomal dominant.

In addition to having Charcot-Marie Tooth disease, the uncle of the propositus, III_1, aged 50, had developed at the age of 16 a sudden onset of progressive loss of vision which had proceeded to almost total blindness over a period of 6 weeks. On examination he was unable to count fingers at 10 cms with either eye. He had bilateral optic atrophy. Because of severe impairment of vision, fields were difficult to chart but a dense paracentral scotoma was present in the left eye.

Altogether, 10 members of the family had been afflicted by an acute onset of visual failure which progressed rapidly

* Department of Medicine, University of Sydney, Sydney Hospital and Royal Prince Alfred Hospital

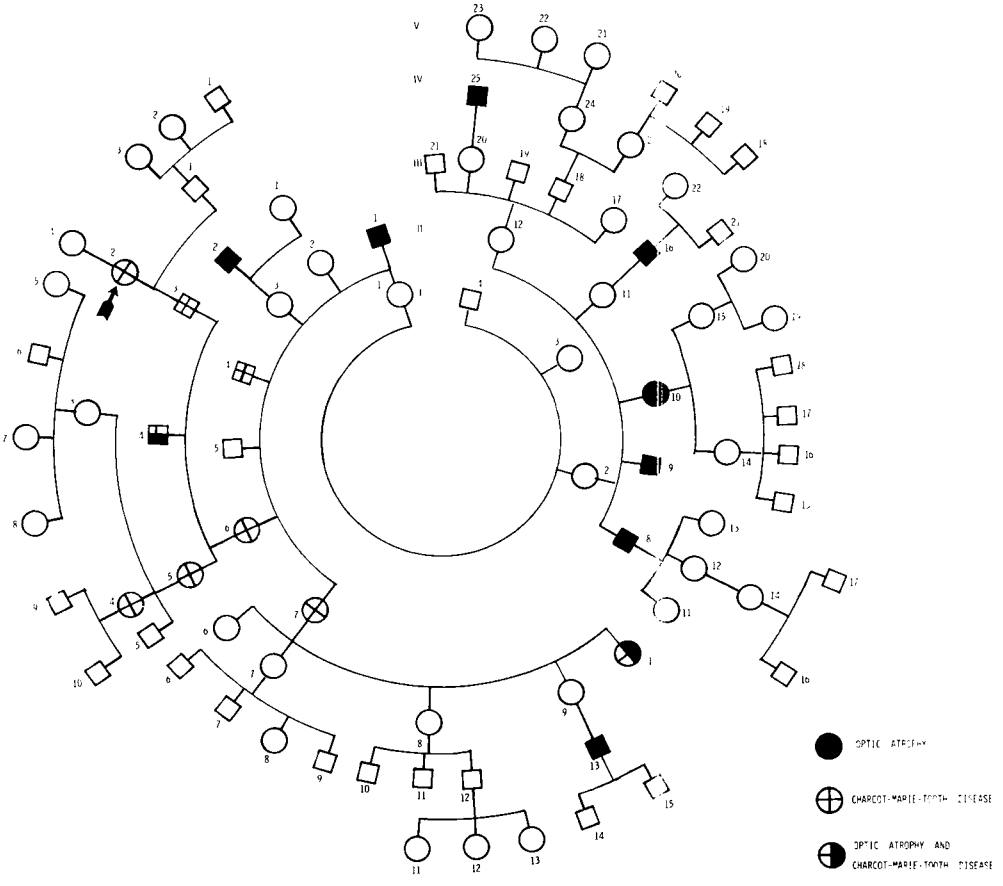

FIG. 1. The pedigree here reported. Persons affected by optic atrophy are shown in solid black. Those with Charcot-Marie-Tooth disease are indicated with crosses, and those with both disorders are designated by a half black and half crossed representation. The index case is indicated by an arrow.

over a period of up to six months. The age of onset of blindness ranged from 16 to 33 years. Eight males and 2 females were affected, and the inheritance was invariably maternal. Two patients who were seen during the acute stage ($IV_{1,}$ and IV_{25}) had visual acuity less than 6/60 bilaterally, and bilateral central scotomata. Two patients (III_{1} and III_{10}) suffered from both Charcot-Marie-Tooth disease and visual failure.

DISCUSSION

In previous reports of optic atrophy associated with Charcot-Marie-Tooth disease, there has been no electrophysiological or pathological confirmation of the diagnosis. All the subjects with chronic peripheral neuropathy who were examined in the family here reported had the clinical, electrophysiological, and histopathological features of the hypertrophic type of Charcot-Marie-Tooth disease (Dyck and Lambert, 1968; Dyck, Gutrecht, Bastron, Karnes and Dale, 1968). There was an autosomal dominant mode of inheritance, pes cavus, distal wasting and weakness of muscles of upper and lower limbs, depressed or absent reflexes in the lower limbs and mild distal sensory impairment. There was marked slowing of motor conduction. The density of myelinated fibres in the sural nerve was reduced. There was evidence of segmental demyelination and remyelination in teased nerve fibres, and onion bulb formations were clearly visible on electron microscopy.

The clinical and genetic features of the visual failure in the 10 affected members of the family were those of Leber's optic atrophy. There was an acute or subacute onset of impairment of vision, first in one eye and then in the other, which progressed for several months. Central scotomata

and disc pallor were found on examination. Males were affected much more commonly than females and the mode of inheritance was maternal, the mother being unaffected (Meadows, 1970).

Optic atrophy is a very uncommon complication of Charcot-Marie-Tooth disease. In the cases described by Ballet and Rose (1904) and Hoyt (1960), optic atrophy developed rapidly over a period of six months or less. In all the other cases, optic atrophy was slowly progressive or full clinical details were not provided. In the case described by Schneider and Abeles (1937), Piton (1941), Brihaye *et al.* (1956) and Hoyt (1960) bilateral central scotomas and optic atrophy were noted, and these might represent cases of Leber's optic atrophy.

In the family described in the present report, there seems little doubt that Leber's optic atrophy and hypertrophic Charcot-Marie-Tooth disease were associated in the same family, and appeared to be transmitted independently.

SUMMARY

A family has been studied in which members of four generations were affected by the hypertrophic type of Charcot-Marie-Tooth disease. The diagnosis was confirmed by electrophysiological studies and by sural nerve biopsy. Ten members of the family, 8 males and 2 females, developed optic atrophy of acute onset with progression over a period of two to six months. The history of visual failure, its maternal inheritance, and the neuro-ophthalmological findings of optic atrophy with bilateral central scotomata were typical of Leber's optic atrophy. Two members of the family suffered from both Charcot-Marie-Tooth disease and Leber's optic atrophy. There have been a few previous reports of optic atrophy associated with Charcot-Marie-Tooth disease, and in the present family both conditions appeared to have been inherited independently.

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SUPERIOR OBLIQUE MYOKYMIA

K.M.R. GRAINGER and S.S. GUBBAY*

The term "superior oblique myokymia" was first used by Hoyt and Keane (1970) to describe the isolated finding of intermittent, unilateral, intorsion rotatory nystagmus. Two patients with this condition are here presented and the response to treatment with carbamazepine is described.

CASE REPORTS

CASE I:

A 23 year old woman presented in September, 1973, with a five-month history of transient blurring of vision in the right eye with images moving up or down. Episodes were brief, lasting approximately 10 seconds, and occurred in the right eye only. They occurred irregularly at frequencies up to 60 times per hour. They were more noticeable when reading, typing, or driving her car. Alcohol had been noticed to aggravate the movements. In the past she had suffered from attacks of migraine since the age of 12 years. These consisted of scintillating teichopsia in both eyes followed by unilateral or bifrontal headache. These had ceased some six months previously and had not recurred.

Examination revealed brief episodes lasting between 2 and 15 seconds during which there was clockwise rotatory nystagmus of the right eye. These episodes occurred irregularly but appeared to be precipitated at variable intervals by reading when her eyes looked downwards and converged. Normal saccadic eye movements were then seen to be interrupted by the rotatory nystagmus. No other abnormalities were found; in particular, her visual acuity was normal, fields were normal, pupils were normal with normal reactions and eye movements including convergence were all normal. Optico-kinetic nystagmus was seen in all directions, and fundoscopy revealed no abnormalities. Neurological examination was, likewise, entirely normal.

The following estimations or investigations were performed, and all showed normal or negative results: haemoglobin, white cell count, erythrocyte sedimentation rate, serum electrolytes, serum calcium, serum albumin and globulin, blood urea, liver function tests, microscopic examination of urine, radiographs of skull including optic foramina, caloric tests, audiogram, electroencephalogram, cerebrospinal fluid (no cells, protein 43mg%, IgG 3.6mg (8.2%), glucose (66mg%), serological tests for syphilis, brain scan (static and dynamic), fluorescein angiography, arch aortogram and vertebral angiogram.

CASE II:

A 56 year old male presented in February, 1973 with a 10 year history of "twitching and quivering" in the right eye associated with vertical displacement of the images. These movements had come on gradually, but there had been little change over 10 years. He felt they were precipitated by sudden movements of the eyes to the left. He observed diplopia lasting some 3-4 seconds with quivering going on for 12-15 seconds. These episodes could occur frequently or be absent for periods of up to 2½ weeks.

Examination revealed internal rotatory nystagmus of the right eye occurring intermittently with some intorsion movements but, as with the first patient, no other abnormality was found.

TREATMENT

Carbamazepine was administered to the first patient but was ceased because of initial drowsiness. Subsequent reintroduction

* The Neurological Services, Perth Medical Centre, Shenton Park, Perth 6008, and the Royal Perth Hospital.

to a dosage of 200mg per day caused the complete cessation of the movements. On two occasions when carbamazepine was ceased, the symptoms recurred within 3-4 days.

Carbamazepine was administered to the second patient on two occasions but in both instances produced a sensitivity reaction and had to be ceased. Diazepam and phenytoin were also given, without therapeutic benefit.

DISCUSSION

In 1906 Alexander Duane of New York under the heading, "Unilateral Rotatory Nystagmus" described a 24 year old woman with episodes of vertical diplopia. She described one object arising vertically out of the other with the objects dancing up or down. The patient had observed in a mirror that the left eye oscillated. Examination was normal except for anti-clockwise rotatory and vertical nystagmus in the left eye. This appeared to be more marked when the left eye was used alone for fixating or if the eyes were converging.

Sogg and Hoyt (1962) reported a father and son with intermittent vertical nystagmus and oscillopsia. These authors felt this was possibly an inheritable supranuclear problem in the brain stem. They commented on causes of episodic nystagmus, viz. vestibular disturbances such as in streptomycin toxicity, vestibular neuronitis, acute labyrinthitis, and Ménière's disease. All these conditions are frequently associated with one or all of the following characteristics: horizontal nystagmus and associated vertigo, nausea, tinnitus, hearing loss and illusionar movement of the environment. In oculogyric crises of post-encephalitic Parkinsonism, nystagmoid jerks may occur with rhythmic spasm of the lids. Voluntary nystagmus is always horizontal and very rapid. None of these conditions appeared to be present in the patients described.

Hoyt and Keane (1970) described five cases of intermittent unilateral, vertical or rotatory eye movements. In one patient the eye movements could only be observed when magnification was used. They related the movement to the superior oblique muscle on the grounds of the intorsion of the eye, the EMG findings of intermittent phasically discharging muscle fibres in the superior oblique synchronous with the movements, the absence of reciprocal inhibition from the inferior oblique muscle and, finally, the cessation of the movement following tenotomy of the superior oblique tendon with recession of the inferior oblique. They proposed the term "superior oblique myokymia". This term was subsequently used by Susac, Lawton Smith and Schatz (1973) to describe a further seven cases with relief of symptoms by carbamazepine in five patients. The movements did not return in one patient when the carbamazepine was ceased after two months, and in a second patient after six months' therapy. This latter patient initially had a short-lived response to carbamazepine. One patient was refractory to medical treatment.

Patients have presented describing their symptoms in a wide range of terms. These include terms related to the movement such as twitching, twittering, quivering, tremulousness, vibration, and a pulling sensation in the eye. Terms used to describe the alteration in vision include blurred, jumping, shimmering, tilting, and flickering. Examination may quickly reveal the movements of the eye during the symptomatic periods, but occasionally magnification may be required. The condition occurs in both sexes with a wide age range (14 to 61 years). It appears to be benign as no other neurological deficits have developed although one patient has been described with the symptom of vibration in his ipsilateral great toe, similar to the vibration in the eye, and a further patient with clumsiness in the contralateral hand. One patient had a family history of disseminated sclerosis and amyotrophic lateral sclerosis, and two patients had migraine, but no evidence to incriminate any of these diseases in the aetiology of the myokymia was found.

Therapeutically, carbamazepine is usually successful, but if ineffective, tenotomy of the superior oblique muscle may be considered.

SUMMARY

Two instances of superior oblique myokymia are described. In one the abnormal eye movements responded to carbamazepine therapy. The relevant literature is reviewed.

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THE LOW INTRACRANIAL PRESSURE SYNDROME

J.J. BILLINGS, E.J. GILFORD, and J.K. HENDERSON.*

The characteristic symptom of low intracranial pressure is headache which is aggravated by the assumption of the upright position. The spinal fluid pressure in the lateral recumbent position is less than 70mm. Nausea, vomiting, dizziness, pallor, sweating and vertigo may accompany the headache. Relief occurs quickly on lying down.

The syndrome may appear in a variety of circumstances: (1) after lumbar puncture or nerve sleeve tears, where continued leakage of cerebrospinal fluid develops. The "difficult" lumbar puncture, where there is repeated perforation of the arachnoid membrane, is more likely to result in subsequent leakage of fluid than the single puncture with a fine needle. (2) following head injury, with or without mainfest external loss of cerebrospinal fluid. (3) following intracranial operations, especially the evacuation of a subdural haematoma. (4) following meningitis, especially viral meningitis.

In any of these circumstances vomiting, dehydration and hypotension are possible contributing factors. Some neurologists have formed the opinion that subdural haematoma may be caused by intracranial hypotension, the haematoma occurring either as the result of reactionary engorgement of the cerebral vessels and rupture of one of these, or of rupture of a small vessel running across the subdural space following downward displacement of the brain.

CASE REPORT

A married woman aged 50 years who had suffered from pulmonary tuberculosis in her early twenties, with a satisfactory recovery, was admitted to St. Vincent's Hospital, Melbourne, in July 1973. She gave the history of the rather acute onset of pain at the back of the neck and in the occipital region three weeks earlier, accompanied by stiffness of the neck. The pain had improved after a few days but then relapsed. Manipulation of the neck under general anaesthesia was carried out by her local medical practitioner, after which the headache became considerable worse. At about this time it was noticed that the headache tended to be more severe in the erect posture and could be relieved by lying down. When severe, the headache was accompanied by vomiting.

By the middle of the second week of the illness the patient had found it necessary to lie flat in bed throughout the day to avoid distressing headache and vomiting. She was then admitted to a hospital close to her home, where radiographs of the chest, blood count, erythrocyte sedimentation rate, urinalysis and lumbar puncture were performed. The cerebrospinal fluid was under very low pressure; it contained 10 lymphocytes/ml and 110mgm% of protein, culture being sterile and a search for acid-fast bacilli and torula negative. Cultures for tubercle bacilli subsequently gave negative results. During the next week the symptoms remained unchanged, but she was observed to have developed nystagmus, which prompted her admission to St. Vincent's Hospital with the suspicion of a posterior fossa tumor. This admission took place on the 21st day of the illness.

On admission she looked tired and pale, was rather depressed and was complaining of headache. Slight neck stiffness was present, and irregular, ill-sustained nystagmus on horizontal gaze. She was not obviously dehydrated. The serum electrolyte values were normal but the blood urea was slightly elevated. A radio-isotope brain scan was normal. The clinical diagnosis was that of intracranial hypotension, probably secondary to benign viral meningitis. She was nursed in a head-down position and a large fluid intake was encouraged. Within a few days there was considerable improvement, but progressive elevation of the head, even when undertaken gradually, caused a recrudescence of symptoms.

* St. Vincent's Hospital, Melbourne.

On the 36th day of the illness a further lumbar puncture was performed. It was found that the pressure was so low that fluid could be obtained only by aspiration, when it passed freely into the syringe. The CSF protein value was then 133mgm%. During the next several days the symptoms fluctuated to some extent, but she was unable to endure elevation of the head for more than a few hours at a time. The body temperature remained normal and a further estimation of the erythrocyte sedimentation rate was also normal. After another 18 days the third lumbar puncture was performed, and again the fluid was readily obtained but only by aspiration. On this occasion the protein was 118mgm%, the chloride and glucose values being normal. There were 10 red blood cells and 21 white blood cells (60% lymphocytes) per ml. No organisms were visible nor could organisms be isolated by culture. Subsequently cultures for torula and tubercle bacilli proved negative.

Because of the protracted clinical course a pneumoencephalogram was performed seven weeks after the commencement of the illness (Figs. 1 and 2). The lateral ventricles were normal in size, as were the subarachnoid spaces over the cerebral hemispheres. The third ventricle was unusual in appearance with a diverticulum projecting downwards into the interpeduncular cistern, involving the region of the tuber cinereum. The supra-sellar cistern and the interpeduncular cistern were seen to be reduced in size as a result of the downward displacement of the thalamic region and the cerebral peduncles. The whole appearance was that of caudal displacement of the cerebral hemispheres and brain stem towards the tentorial opening. The pontine cistern and the posterior fossa cisterns, including the cisterna magna, were small in size but were otherwise normal. There was no evidence of cerebellar tonsillar herniation, and the fourth ventricle was not abnormal.

It was then postulated that the original diagnosis of intracranial hypotension following mild infection was correct, the caudal dislocation of the brain shown in the air studies being interpreted as a natural consequence of the combination of low intracranial pressure and a reduced volume of cerebrospinal fluid. Such a combination would require some expansion of the cerebral vascular bed in accordance with the Monro-Kellie law which states that the total bulk of the intracranial contents, namely the nervous tissue, blood and cerebrospinal fluid must always be constant. In other words, some degree of "cerebral swelling" is a necessary result of a reduced volume of cerebrospinal fluid. Accordingly, an injection of 60ml of Ringer's solution was given into the subarachnoid space at a further lumbar puncture. For about 20 minutes afterwards there was complaint of rather severe headache, after which the patient became completely comfortable. From that time onwards her recovery was uninterrupted, and when reviewed some four months following her discharge from hospital she had remained entirely free of symtoms.

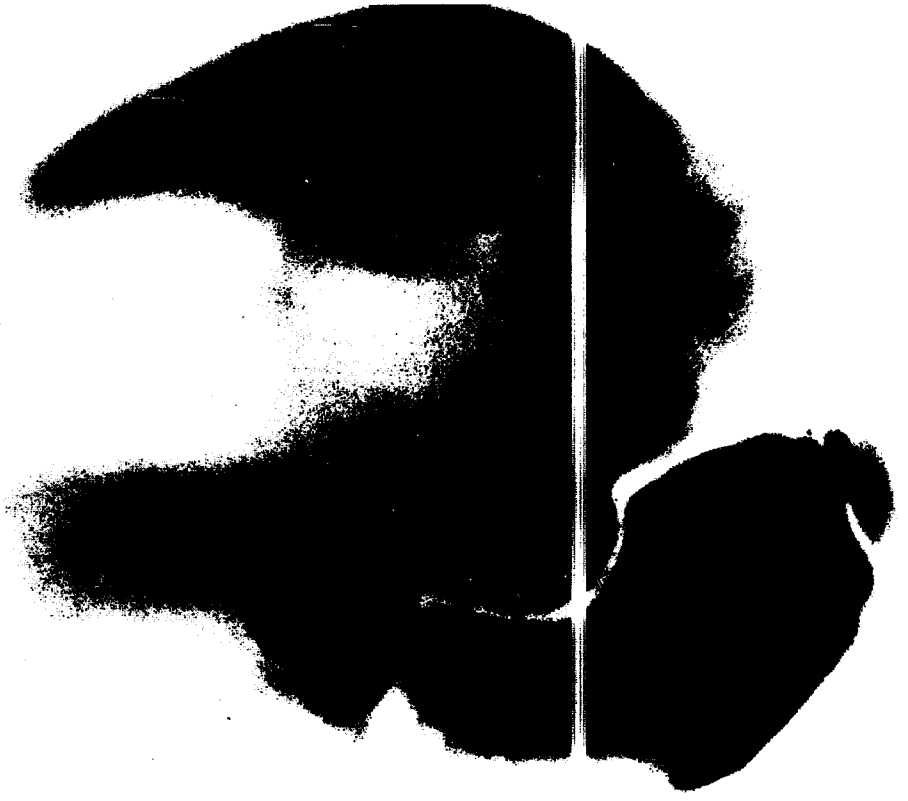

FIG. 1. Lateral tomogram of the anterior end of the third ventricle demonstrating the downward herniation of the floor of the third ventricle (arrows) producing partial obliteration of the interpeduncular cistern.

FIG. 2. Coronal tomogram taken through the third ventricle and lateral ventricles showing downward herniation of the brain with bilateral uncal herniation. (arrows).

DISCUSSION

There was concern at first regarding the continued elevation of the cell count and protein level in the cerebrospinal fluid. However it was recognized that the values had to be interpreted in conjunction with the judgment that the total quantity of cerebrospinal fluid, as well as its rate of formation and reabsorption, were considerably reduced. The immediate and permanent cure of the disorder following injection of the Ringer's solution was accepted as evidence that the abnormalities in the cerebrospinal fluid did not have serious significance.

The localised diverticulum of the floor of the third ventricle projecting down into the interpeduncular cistern was a very unusual finding, particularly as there was no displacement of the third ventricle from the mid-line. It was presumed that this appearance was due to supratentorial swelling resulting in a general downward displacement of the supratentorial structures, so as to partially obliterate the interpeduncular cistern, and to produce the deformity of the floor of the third ventricle. The size of the lateral ventricles and the very narrow width of the third ventricle would suggest compression of these structures, and both the pineal and habenular calcifications were seen to be displaced downwards.

Although some separation of the convexity of the cerebral hemispheres from the vault of the skull may be expected to occur in the early development of this low intracranial pressure syndrome when it follows lumbar puncture, such a sequence seems unlikely when the syndrome results from viral meningitis. Certainly by the time the air studies were undertaken in this case, the appearances were those of general swelling of the hemispheres, without any increase in size of these subarachnoid spaces superiorly. Although the occurrence of subdural haematoma following lumbar puncture may be due to the rather rapid development of low intracranial pressure, it is difficult to understand how the reverse sequence may occur, and a cerebral tumour or subdural haematoma be responsible for low pressure.

Minor examples of the syndrome described in this patient have been observed on a number of occasions in association with viral meningitis, and have been quickly relieved by the injection of Ringer's solution or normal saline intra-thecally. In our patient the disorder was unusually severe and protracted in its course. The radiological features do not seem to have been documented previously.

SUMMARY

The syndrome of low intracranial pressure may develop in a variety of circumstances, e.g. after lumbar puncture, following head injury and intracranial operations. It sometimes occurs after viral meningitis. The case history is described of a woman in whom the disorder was unusually severe and persistent. Interesting radiological features were observed, the appearances being those of herniation of the brain towards the tentorial opening. Simple measures of treatment produced dramatic and lasting relief.

ACKNOWLEDGEMENT

Thanks are due to Dr. Paul Mestitz who referred the patient to hospital, having made the provisional diagnosis which was subsequently confirmed.

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MECHANISMS IN CEREBRAL LESIONS IN TRAUMA TO HIGH CERVICAL PORTION OF THE VERTEBRAL ARTERY – ROTATION INJURY

P.F. BLADIN and J. MERORY*

The role of the vertebral artery in cervical trauma has long occupied a central place in the consideration of clinicians concerned with spinal injuries. Involvement of this vessel in fractures and dislocations of the cervical vertebrae has been documented by many authors, notably Schneider and his colleagues (1970; 1972) whose researches into football injuries in the U.S.A. have highlighted the aetiologic mechanisms. In addition Schneider and his co-workers (1958, 1959, 1961, 1966) examined the role of the vertebral arteries in the production of both spinal cord and brain stem injuries in cases of cervical injury without disruption of the bony architecture. They have suggested the mechanisms of "pinching" the vertebral artery, and transient dislocation of the atlas.

The present communication considers various aspects of vertebral artery lesions occasioned by acute rotational injury to the neck. Three illustrative cases are presented to help elucidate the mechanisms of vertebral artery injury.

CASE I

(This case has been described previously – Bladin, 1974)

A young male motor mechanic presented with a history of two separate attacks of vertebro-basilar ischaemia preceded by some weeks of occipito-nuchal headache. Some 2½ months previously he had suffered an acute rotational (probably to the right) hyperextension injury to the neck in a rear-end collision in a motor vehicle. He had a stiff neck for some time but kept working. His first episode consisted of an acute attack of vertigo, diplopia and increased nucho-occipital ache which forced him to rest in bed but which subsided after several days. Three days before admission the second attack occurred. This consisted of drowsiness, dysarthria, amnesia and diminution of visual acuity throughout his visual fields, with weakness and inco-ordination in all limbs. For 24 hours after admission the patient was too drowsy to co-operate in detailed examination and the clinical history had to be obtained from his spouse. Over the next 3 days surprisingly rapid recovery was noted. At the end of this time the patient was left with total amnesia for the event and an easily detectable right homonymous hemianopia, much denser in the upper quadrant than in the lower.

Angiography showed a 3-4 cm long segment of irregularly narrowed left vertebral artery which tapered above and below the lesion which was the C_1 and C_2 level (Fig. 1). In addition the left posterior cerebral artery was occluded some distance along its course (Fig. 2). It was surmized that because of its site and appearance the vertebral artery lesion was a dissecting aneurysm which had caused the vertebral-basilar embolic episodes culminating in left posterior cerebral artery occlusion.

Operative interference to stop further embolic episodes confirmed the pathologic diagnosis but effective surgical amelioration of the lesion was not technically possible. Anticoagulant therapy was considered but was rejected after much discussion.

* Department of Neurology, Austin Hospital, Melbourne.

FIG. 1. Lateral view of vertebral angiogram of Case I, showing a narrowed segment of artery in the region of C1 – C2.

FIG. 2. Axial vi w of vertebral angiogram of Case I. The left posterior ce ebral artery is occluded part of the way along its course.

CASE II

A 31 year old female who complained of some neck stiffness occasioned by fa ling asleep in a chair 10 days beforehand, sought relief in chiropractic manipulation. She was placed on a couch face d wn, told to relax and then her head was suddenly twisted sharply to the left, followed in breathtaking succession by a rist to the right. Rotational displacement was such as to occasion sharp discomfort, and "seconds later" intense vertigo a d flashes of light all over the visual fields. Then, within the minute, she noted that the right lower half of her visual fiel s had "blacked out". She communicated her distress to her manipulator. He in turn, somewhat discomforted by all this, astily summoned help. His manipulatory colleague arrived within the half minute, allowed that it was all most puzzling, and promptly remanipulated the patient's neck, twisting it sharply to the left. This produced no relief; indeed now the p ient noted paresthesiae in both arms and legs, found her face going numb – the right side very much so – and her ton ue was clumsy to the extent of rendering her inarticulate and dysphagic. She was dizzy, nauseated, and quite prostrate and arrangements were set in train for her removal to hospital.

By the time the ambulance arrived (some 30 minutes later) she had recover d somewhat. The facial paresthesiae had regressed and she could swallow and talk, albeit in a dysarthric fashion. On a mission to the Casualty Department she was somewhat drowsy and complained of severe occipito-nuchal pain and inten e vertigo. She veered sharply to the right when attempting to walk.

Examination revealed limitation of neck movements in all directions, bilater l ptosis worse on the right than the left, ataxia of the right arm and leg, and rotary nystagmus accentuated on the lef lateral gaze. There was a right upgoing plantar but tendon jerks were brisk and equal. Visual fields, motor power, and ensation were normal.

Radiographs of the skull and cervical spine, including functional films, were normal. In view of the experience of Case I it was surmized that damage to the vertebral arteries had probably occurre . Angiography was performed somewhat less than 48 hours after the trauma. This revealed a 3-4 cm irregularly attenu ted segment of the right vertebral artery in the C_1 to C_2 region, with very little flow into the skill (Fig. 3). The resem lance to the picture seen in Case I was immediately obvious and the diagnosis of dissecting aneurysm was accepted.

In order to prevent the embolic complications, the patient immediately started th rapy with heparin, aspirin and dipyridamol (Persantin). The heparin was administered over only 48 hours, but the aspirin a id Persantin were continued as long term therapy.

Check angiography a week later confirmed that the lesion was essentially th same, indicating an anatomic disruption of the vessel wall. It was obvious that long-term therapy was necessary and she was kept on her anti-embolic regime for

FIG. 3. Subtraction film of vertebral angiogram of Case II. The segment of artery at C1 and C2 level is narrowed.

FIG. 4. Lateral view of vertebral angiogram of Case II, taken 3 months after the initial angiogram. The previously narrowed segment of artery now appears virtually normal.

a further 3 months. At that juncture angiography showed virtual resolution of the lesion with good flow intracranially (Fig. 4). Her therapy was ceased and she has remained symptom free ever since. Either *post hoc* or *propter hoc* no embolic (or iatrogenic) complications had occurred.

CASE III

A 47 year old male was involved in a motor accident. His head seemingly was jerked to the right and backwards and then forwards, so that he lacerated his left frontal region upon the interior vehicular bodywork. He was somewhat stunned by this, but when he appeared in Casualty the same night, his only complaint was of a sore stiff neck. After an overnight stay under observation he had recovered enough to enable discharge on the morrow. No neurological deficit was recorded. Radiographs of the skull and cervical spine were normal, including functional films.

After 2 days, the neck stiffness had subsided, allowing him to turn his head from side to side once again. He was alarmed to note that on rotation of his head to the right, intense vertigo ensued. Repeat radiology of the cervical spine showed some slight narrowing in the disc region of C_6 to C_7; otherwise there was no abnormality, and he was reassured. But when he reappeared some 5 months later, still complaining of these symptoms, he was referred for neurological opinion.

Examination then revealed no abnormality until an attempt was made to reproduce his symptoms. Three to 4 seconds after the patient assumed the supine position with his head turned to the right an intense vertigo was produced and a very coarse nystagmus with a prominent vertical component was seen. However, details of this could not be verified at leisure – the patient immediately made frantic and successful attempts to reassume his "eyes front" position and would allow no further testing. Vertebral angiography showed that the patient had only a left vertebral artery. This appeared to be a congenital anomaly judging by the lack of any right vertebral artery at the arch of the second cervical vertebra (Figs. 5 & 6). The patient refused surgery and even refused to wear a collar, maintaining that he had learned *not* to turn his head to the right; even in sleep. He has remained symptom free since.

FIG. 5. Lateral view of left vertebral angiogram of Case III, showing normal vertebro-basilar flow.

FIG. 6. Lateral view of left vertebral angiogram of Case III, with the subject's head turned to the right. Vertebral artery flow now ceases at C2 level.

DISCUSSION

There have been reports of patients who have undergone torsional chiropractic manipulation of the neck and who have sustained various degrees of brain stem ischaemia, some fatal (Blane, 1925; Pratt-Thomas and Berger, 1947; Ford and Clark, 1956; Schwarz, Geiger and Spano, 1956; Green and Joynt, 1959). Furthermore brain stem ischaemia due to cervical rotation has been reported as a consequence of positioning during surgical operation (Holzer, 1955) and industrial trauma (Murray, 1957). However, angiographic evidence has been somewhat lacking in giving insight into the mechanisms of this process. From the case described here, it would seem that both acute, subacute and chronic effects may be produced.

Acute Effects:

The lesion in the vertebral arteries of all 3 patients was in the area of maximal cervical vertebral disalignment, the C_1 to C_2 region. Consideration of the physiology of atlanto-axial movement (Tatlow and Bammer, 1959) has shown that in normal easy head turning movements the arc of rotation of the atlas is somewhat restricted. The lateral atlanto-axial joint on the side to which the head is turned is virtually locked by surrounding muscles and the contralateral atlanto-axial joint slides forward and down. An additional arc of movement (Fig. 7 (a & b)) is accomplished by backward rotation at the hitherto locked ipsilateral joint. Thus violent excursion of vertebral artery is eliminated. Rotation of the atlas does produce deformation of the vetebral artery (Fig. 7a and b) – and indeed De Kleyn and Nieuwenhuyse (1927) maintained that even in normal movements this caused arterial compression. Tatlow and Bammer (1957) in cadaver studies demonstrated by angiography a thinning of the upper end of the vetebral artery during head rotation. If their results are compared with the *in vivo* angiograms in the present series it will be seen that

FIG. 7. (a and b). Showing the effects rotation of C1 on C2 would have on the left vertebral artery (represented by the white cord).

this effect occurs precisely in the same region of the artery — that portion between C_1 and C_2 vetebrae. Sudden passive cervical rotation will thus have a stretching, tearing, shearing effect on the vetebral arterial wall and it is little wonder that intramural dissection and haemorrhage can be demonstrated in such patients. Furthermore spasm would be likely to occur as an immediate effect.

Subacute effects:

The role of embolisation is dissecting aneurysm has been discussed before (Bladin, 1974). There have been previous reports of patients in whom late onset post-traumatic brain stem ischaemia has occurred (Ford and Clark, 1955; Suechting and French, 1955; Green and Joynt, 1969). Furthermore multiple thrombi have been found in various parts of the vertebral basilar territory; this is possible evidence of embolisation (Pratt-Thomas and Berger, 1957; Ford and Clark, 1956). Such embolisation may present a life threatening complication which demands preventative therapy of some sort. This was the rationale for prolonged aspirin and dipyramidol (Persantin) treatment in the second patient — who, *post hoc* or *propter hoc*, suffered no embolic episodes. Further, the therapy did not exacerbate the arterial lesion.

Chronic effects:

The lesion is the third patient, both by its site and causation, clearly established its relationship to the other two cases. No doubt mural disruption of the artery, perhaps together with the surrounding osseous and ligamentous structures, caused total luminal obliteration of the left vertebral artery on rotation of the head to the right. Obviously the chronicity and potential danger of this lesion seemed to demand surgical therapy. One can only admire the confidence and sang froid of the patient, whose faith in his self-training proved justified. The actual pathological mechanisms whereby the relationships of vertebral arteries to surrounding bony and ligamentous structures can be so permanently and radically altered is illustrated very elegantly in the communication of Yates (1959) who showed just who widespread can be the traumatic haemorrhage occasioned by obstetrical manipulation during foetal extraction.

SUMMARY

Three cases have been described illustrating the mechanisms and effects of lesions from acute rotation injury to the vertebral artery. These indicate that the portion of artery at risk is in the C_1 to C_2 region, where stretching and shearing strains can produce intramural dissection and haemorrhage. Such changes can radically alter flow to produce acute arterial obliteration or later cerebral embolism. Such alteration can also produce a change in relationships between artery and surrounding structures and thus cause intermittent occlusion of a vertebral artery upon cervical rotation.

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AMINE TURNOVER IN MIGRAINE

M. ANTHONY and H. HINTERBERGER*

The question as to whether certain articles of food can precipitate migraine remains, as yet, unresolved. The incidence of dietary migraine where patients relate their attacks to eating a particular food, such as cheese, alcohol, fatty meals, oranges or chocolates, varies in published studies from 5% (Hanington, Horn and Wilkinson, 1970) to 25% (Selby and Lance, 1960). Hannington (1967) separated out a group of patients with dietary migraine and demonstrated that the intake of 125mg tyramine orally would precipitate a migraine attack in 78% of these (65 out of 83 patient sessions).

The mechanism of these induced headaches has been thought to be the release by tyramine of other vaso-active amines, in particular serotonin, noradrenaline, adrenaline and histamine. The studies published so far have been concerned with biochemical investigations of migrainous patients after tyramine loading during headache freedom only (Sandler, Youdim, Southgate and Hannington, 1970; Smith, Kellow and Hannington, 1970). In the absence of information in the literature on tyramine turnover during migraine, the urinary excretion of tyramine as well as of serotonin, catecholamines and histamine was estimated before, during and after attacks of migraine. The study was designed to elucidate the role of endogenous tyramine as a trigger for migraine headaches, acting either directly or by the release of other amines.

At the same time blood levels of the above amines were assessed under similar circumstances. Estimation of tyramine was omitted, because large quantities of blood are required for its estimation and these were not available to us at the time. Further, it was considered more relevant to assess blood levels of the amines that tyramine is supposed to release from storage sites, as this would provide more information on the role of tyramine in migraine.

MATERIALS AND METHODS

Ten patients suffering from severe and frequent attacks of migraine were admitted to hospital for investigation. Three days before admission all medication was suspended, including ergotamine preparations, but simple analgesics were permitted if they were needed. Urine was collected in 4-hourly periods from the time of admission until the headache developed and then throughout the headache period and for at least 24 hours and, at times, 48 hours, after the end of the migraine attack.

Urinary amines were estimated by the methods mentioned below:—

a) total tyramine – by organic extraction as described by Udenfriend (1962).
b) serotonin – by the resin extraction method of Arterberry and Conley (1967).
c) noradrenaline and adrenaline (free) – by the alumina method of Weil-Malherbe (1968).
d) histamine – by the resin extraction method of Huff, Davies and Brown (1966).

* The Divisions of Neurology and Clinical Chemistry, Prince Henry Hospital; Schools of Medicine and Pathology, University of New South Wales, Sydney

Blood was collected 3 times daily until the headache developed, at 4-hourly intervals throughout the migraine attack and again 3 times daily for at least 24 hours after the headache ended.

Plasma serotonin was estimated by the fluorometric technique of Crawford and Rudd (1962), plasma noradrenaline and adrenaline by the method of Haggendal (1963) and whole blood histamine by the method of Shore, Burkhalter and Cohn (1959).

Statistical analysis was by Student's "t" test on dependent means; differences were considered significant if the probability was 5% or less.

RESULTS

A) Urine

(All values are expressed in μug. of amine excreted in 4-hourly periods.)

1. *Tyramine* – mean values (together with their standard errors) for the preheadache, headache and postheadache periods were 34.76 ± 12.142, 22.43 ± 4.301 and 31.15 ± 4.798, respectively. Nine patients showed a rise of urinary excretion when the postheadache period was compared with the headache phase; the rise ranged from 15% to 44%, the mean rise for the group being 30%. Statistical comparison of headache and postheadache values reached significance at the 0.2% level. On the other hand comparison of preheadache and headache values did not reach statistical significance, although the mean excretion was higher during the preheadache rather than the postheadache period. This result is due to the smaller number and greater variance of observations during the preheadache period.

2. *Serotonin* – mean values (± standard errors) for the 3 periods were 8.72 ± 1.155, 12.04 ± 1.699 and 10.65 ± 2.306, respectively. Statistical analysis shows that comparison of preheadache and headache values reached significance at the 1.2% level. Similar comparison between headache and postheadache values did not reach statistical significance. This is probably due to the fact that released serotonin during the migraine attack continued to be cleared in the urine during the early postheadache phase, as the mean excretion during that period is 22% higher than during the preheadache phase (8.72 as against 10.65). During migraine 8 of the 10 patients showed a rise of urinary serotonin excretion ranging from 16% to 113%, the mean rise for the group being 41.5%.

3. *Noradrenaline* – mean values (± standard errors) for the 3 periods were 3.98 ± 0.473, 3.29 ± 0.357 and 3.38 ± 0.349, respectively. Statistical comparison of the preheadache, headache and postheadache phases showed no significant difference between the 3 periods, either when values were analysed for the individual patient or for the group as a whole.

4. *Adrenaline* – mean values (± standard errors) for the preheadache, headache and postheadache phases were 0.74 ± 0.261, 0.92 ± 0.279 and 0.91 ± 0.194, respectively. Statistical comparison of results for the 3 periods showed no significant differences.

5. *Histamine* – mean values (± standard errors) for the 3 periods were 4.96 ± 0.764, 5.64 ± 1.276 and 5.05 ± 0.964, respectively. Statistical comparison of the values for the 3 periods again showed no significant differences.

Mean 4-hourly excretion values for all 5 amines during preheadache, headache and postheadache periods are summarised in Table 1, which also includes the results of the statistical analysis.

B) Blood

Mean values for the 10 patients are expressed as follows:– serotonin in $\mu g/10^9$ platelets (since 99% of plasma serotonin is present in platelets); noradrenaline and adrenaline in ng/ml plasma and histamine in ng/ml whole blood. Results are summarised in Table II, which also includes the statistical analysis.

It can be seen that in the case of plasma serotonin there is a highly significant difference when headache values are compared with either those of preheadache or postheadache periods, where in each case the significance reaches the 0.1% level. All 10 patients showed a fall in plasma serotonin during migraine, whilst 8 of these showed a simultaneous rise in urinary serotonin excretion ranging from 16% to 113% (Table III).

TABLE I

Urinary Amine Excretion in Migraine
10 Patients

	Mean Values (μg/4 hours)			Statistical Significance		
	Pre-HA	HA	Post-HA	HA-PreHA	HA-PostHA	PostHA-PreHA
Tyramine	34.76	22.43	31.14	NS	0.2%	NS
Serotonin	8.72	12.04	10.65	1.2%	NS	NS
Noradrenaline	3.98	3.29	3.38	NS	NS	NS
Adrenaline	0.74	0.92	0.91	NS	NS	NS
Histamine	4.96	5.64	5.05	NS	NS	NS

NS = not significant

TABLE II

Blood Changes in Biogenic Amines in Migraine
10 Patients

	Mean Values (4 hourly)			Statistical Significance		
	Pre-HA	HA	Post-HA	HA-PreHA	HA-PostHA	PostHA-PreHA
Serotonin (μg/10⁸ plats)	0.62	0.47	0.66	0.1%	0.1%	NS
Noradrenaline (ng/ml plasma)	219.7	285.3	263.3	NS	NS	NS
Adrenaline (ng/ml plasma)	21.6	13.9	19.4	NS	NS	NS
Histamine (ng/ml, whole blood)	39.1	42.4	48.2	NS	NS	0.1%

NS = not significant

TABLE III

Comparison of Changes of Plasma and Urinary Serotonin in Migraine – 10 Patients

											Mean
% Fall in Plasma 5HT	13	40	33	25	24	30	37	44	20	39	30.5%
% Rise in Urinary 5HT	80	113	20	20	75	46	16	45	9% Fall	NC	41.5%
Correlation	+	+	+	+	+	+	+	+	–	–	

Plasma noradrenaline and adrenaline values showed no remarkable change during headache and statistical analysis showed no significant differences between the 3 periods.

On the other hand whole blood histamine values continued to rise from the preheadache, through

the headache to the postheadache periods, mean values being 39.1, 42.4 and 48.2 ng/ml whole blood, respectively. Whilst comparison of preheadache and headache values show no significant statistical difference, similar comparison between the preheadache and postheadache values shows the difference to be highly significant at the 0.1% level.

DISCUSSION

The reports by Hanington (1967) and Hanington *et al.*, (1970) that the majority of patients with a history of dietary migraine will develop a typical migraine attack following the ingestion of tyramine, has not, so far, been confirmed by subsequent work. Moffett, Swash and Scott (1972) found that of their 8 patients with a history of dietary migraine, half developed headache after tyramine ingestion and half after placebo capsules. In another study (Ryan, 1974) comprising 40 patients with a history of dietary migraine, more patients responded with a migraine headache to placebo than to tyramine.

It has been suggested that the mechanism of tyramine headache was the slow inactivation of the amine and its consequent accumulation in the blood where it could release a variety of pharmacologically active agents having as their end point the migraine attack. This could be so, since there are reports that monoamine oxidase activity of platelets is reduced during migraine, with subsequent delay in inactivation of the amine (Sandler, *et al* 1970; Sicuteri, Buffoni, Anselmi and del Biancho, 1970). If this were the case, the reported decreased excretion of both free and conjugated tyramine in migrainous subjects after tyramine loading (Smith, Gordon, Hanington, Marsh and Wilkinson, 1973) is difficult to explain and is certainly not in accord with the results of the present study. In fact, our patients did not suffer from dietary migraine so the lower excretion of tyramine during migraine appears to be a feature of all migrainous patients and not confined to those with a dietary history. Further, urinary tyramine in man is mostly of endogenous origin, as shown by experiments during which partial sterilization of the gastro-intestinal tract in normal humans led to an increase in urinary tyramine, suggesting that the gut bacteria themselves consume tyramine or its precursor, tyrosine. On the other hand, inhibition of decarboxylase by alpha-methyl dopa produces a decrease of urinary tyramine (De Quattro and Sjoerdsma, 1966). It is, therefore, very likely that variation in urinary tyramine excretion in man is mainly a reflection of the plasma concentration of its precursor amino acid and the activities of tissue decarboxylase and monoamine oxidase enzymes. Under these circumstances metabolic studies of tyramine in migrainous subjects, following the exogenous administration of the substance, have little value in elucidating its role in the production of migraine headaches. Rather, estimation of its precursor tyrosine as well as of the amine itself in the blood and urine during headache and headache freedom are likely to prove more fruitful.

The results of this study suggest that decreased tyramine excretion is a feature of most migrainous attacks and that it is not confined to patients with dietary migraine. It is, therefore, conceivable that the amine may precipitate migrainous headaches in some patients under certain, as yet not defined, circumstances. It may have this action in conjunction with other pharmacologically active agents, be they amines, lipids, hormones or changes in activity of various enzymes.

It is relevant that neither noradrenaline nor adrenaline excretion was significantly increased during migraine, suggesting that there cannot be a significant accumulation of tyramine in the circulation during headache with the characteristic releasing effect of the amine on catecholamine stores.

On the other hand, the fall in plasma serotonin during migraine with the subsequent rise of its urinary excretion, could reflect the releasing effect of tyramine on serotonin storage sites, but relevant information on this point is lacking. The question cannot be resolved until both tyramine and its precursor tyrosine are estimated in the blood during the various phases of the migrainous process – a study which is currently in progress.

SUMMARY

Urinary excretion of the vaso-active amines tyramine, serotonin, noradrenaline, adrenaline and

histamine and blood levels of serotonin, noradrenaline, adrenaline and histamine, were estimated in 10 patients before, during and after an attack of migraine. During the headache process there was a statistically significant fall in the excretion of tyramine and a similarly significant rise in the excretion of serotonin. Excretion of the other 3 amines showed no significant fluctuation during the various phases of the migraine attack.

Blood levels of serotonin were significantly lower during headache than during freedom from headache, whilst whole blood histamine was significantly higher only during the postheadache phase. The meaning of the latter observation is not obvious.

The above results are discussed in the light of recent reports that tyramine is the substance responsible for headache attacks in patients who have a history of dietary migraine. Reasons are offered as to why this is unlikely to be the case.

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THE HEADACHES OF PHAEOCHROMOCYTOMA

J.W. LANCE and H. HINTERBERGER*

Although phaeochromocytomas are uncommon tumours, they give rise to a constellation of symptoms which may cause the patient to be referred to a neurologist for the diagnosis of headache or "funny turns".

Phaeochromocytomas arise from chromaffin cells, so-called because of their affinity for staining with chrome salts. The neuroectodermal cell which is the precursor of the sympathetic nervous system, the sympathogonia, differentiates into ganglion cells and chromaffin cells which have the potential of synthesizing catecholamines. At birth, chromaffin tissue is widely distributed from neck to pelvis along the line of the sympathetic chain and plexuses, the largest collection apart from the adrenal glands being the organ of Zuckerkandl near the origin of the inferior mesenteric artery. About 60% of phaeochromocytomas arise in the adrenal glands and the remainder from chromaffin rests scattered from chest to scrotum. Some 6% prove to be malignant (Page and Copeland, 1968).

The enzyme responsible for converting noradrenaline to adrenaline depends on a steroid co-factor which normally occurs in sufficient concentration only in the adrenal medulla, so that tumours arising elsewhere do not usually produce adrenaline. The aim of the present study was to correlate the catecholamine production of phaeochromocytomas with the symptoms of each patient, particularly in relation to headache.

METHODS

The case histories of 27 patients with proven phaeochromocytoma, 14 male and 13 female, aged from 9 to 59 years, were analysed. Catecholamine excretion in 24 hour specimens of urine had been studied in all patients before operation, with noradrenaline (NA) and adrenaline (A) being estimated separately in 19. Specimens of the tumour were made available post-operatively in 24 cases, and NA and A were estimated separately in 19 of these. On the basis of these investigations, tumours were classified into 4 groups.

Group 1. Tumours synthesizing mainly NA (tumour content of NA 84-100%: urinary excretion of NA 82-100% of free amines).

Group 2. Tumours producing both NA and A (tumour content of NA 48-66%: urinary excretion of NA 30-95%).

Group 3. Tumours containing mainly A. There were only 2 in this group. In one, content of NA was approximately 20% in urine and tumour tissue. In the other NA represented 67% of free amines in the urine specimen examined but only 20% of tumour amines.

* The Divisions of Neurology and Clinical Chemistry, The Prince Henry Hospital, Sydney, and the School of Medicine, University of New South Wales

Group 4. Those in whom no differential studies had been done.

Techniques of chemical analysis are given in detail by Hinterberger and Bartholomew (1969), Hinterberger and Wilcken (1974) and Lance and Hinterberger (1976).

RESULTS

Site of tumour

Of 21 tumours in the adrenal gland, 13 were on the right, 5 on the left and 3 were bilateral. Seven tumours were found in extra-adrenal sites. Two were para-aortic, one of which was additional to a right adrenal phaeochromocytoma included above. One was in the lower pole of the left kidney and may well have arisen from adrenal tissue. Two tumours were in the bladder. Another was a recurrent malignant thoracic tumour which was investigated during the fourth recurrence. The remaining tumour arose from the organ of Zuckerkandl, but the patient had previously had another phaeochromocytoma removed from the scrotum.

Associated abnormalities

Two patients had neurofibromatosis. One had a medullary carcinoma of the thyroid gland and mucosal neuromas (Sipple's syndrome) and was described separately by Bartley and Lloyd (1975). Another had a pluriglandular syndrome of which acromegaly was a presenting feature.

Symptoms and Signs

Of the 27 patients, 8 were found to be hypertensive on routine examination, 2 during pregnancy. On questioning, many of these patients had also experienced headache, palpitations, sweating and other symptoms which were related to the presence of phaeochromocytoma. Seven patients complained of headache and 12 patients of "funny turns" as the mode of presentation.

"Funny turns" had recurred episodically for periods varying from 1 month to 25 years, with a frequency varying from one every few months to 6 times a day or "almost continuously". The symptoms in these turns comprised palpitations (11 patients), pallor (10), headache (9), sweating (9), tremor (6), flushing (4), anxiety (4), weakness (4) and episodes of collapse with focal neurological signs (2).

Many of these symptoms were also experienced by patients presenting primarily with hypertension or with headache. A comprehensive list of symptoms in all patients is correlated with catecholamine production of their tumours in Table I. It can be seen that sustained hypertension was more common in the NA secreting group and pallor and tremor in groups 2 and 3 in which adrenaline was also produced in signficant quantities. Headache and sweating occurred with much the same frequency in all groups.

"Collapses", usually with focal neurological symptoms and signs, were reported by 6 patients. One had experienced two episodes of prolonged circulatory collapse early in her history and mental confusion was always a feature of her paroxysms. Another had lost consciousness on several occasions while standing during an attack. Her arms always felt "paralysed" in the attack and her vision blurred. Her hands remained weak and she was unable to read for 30 minutes after the attack, suggesting an episode of vertebrobasilar insufficiency. Another patient had suffered involuntary movements of the right hand before becoming unconscious. She experienced wide fluctuations in blood pressure during operation, was confused, agitated, and unable to see for 3 days post-operatively. On recovery of vision, she was unable to recognise familiar faces for several days. "Collapses" with loss of consciousness and pallor were also reported in 3 patients in whom headache was the main presenting symptom. Two of these had also suffered focal cerebral symptoms with loss of consciousness; there was left hemiparesis in one and aphasia in another.

TABLE I

Correlation of Symptoms with Catecholamine Production

	Mainly NA secretion	Mixed	Mainly A secretion	Undifferentiated	Total
Total in group	11	6	2	8	27
headache	8	4	2	6	20
palpitations	6	6	1	3	16
sweating	6	2	2	6	16
pallor	3	4	1	4	12
flushing	0	3	0	2	5
tremor	1	5	1	1	8
anxiety	1	1	1	3	6
weakness	3	1	1	0	5
collapse	2	1	1	2	6
CNS symptoms	2	1	1	1	5
hypertension:					
sustained	8	2	0	4	14
paroxysmal	7	5	2	7	21

Analysis of headache

Of the 27 patients, 20 had experienced episodic headache, usually in association with other symptoms. Two had a past history of migraine. The headaches were bilateral, with the exception of one patient who reported a left-sided headache on occasions. In two patients the headaches were occipital and radiated to the vertex but in the remainder they were bifrontal, radiating to the temples or "all over the head". They were described as throbbing, pulsating or bursting and were moderate to very severe in intensity. The headaches usually came and went with the other paroxysmal symptoms, lasting 5 minutes to 2 hours. In one patient, headache twice persisted for 24 hours. Several patients reported that the headache was present for a few seconds or minutes only at the beginning of the attack and one patient said that it appeared only at the end of the episode. Nausea and vomiting accompanied the headache in 7 patients, only one of whom had a past history of migraine. Two patients noticed blurred vision, and one of these was unable to read for several hours after the attack. The two patients with bladder phaeochromocytomas had a distinctive syndrome in which headache started 10-30 seconds after micturition ceased and lasted 1-3 minutes.

In 10 patients, blood pressure recordings were made just before and during a typical paroxysm with headache. Resting levels of blood pressure varied from 100/80 mm Hg to 180/130 mm Hg. Readings during headache were 200-300 mm Hg diastolic and 100-205 mm Hg diastolic. It should be noted that diastolic readings of 140 and 150 mm Hg were recorded in two such patients at times when they were free of headache so that the trigger factor for headache appeared to be the rate of change in blood pressure rather than the absolute value.

Of the 7 patients who did not have headache as a symptom of phaeochromocytoma, 4 had sustained hypertension and only 3 were subject to "funny turns". Four of the seven patients had been prone to other forms of headache in the past; one migrainous, one with vascular headaches on exertion in hot weather, one with premenstrual vascular headache and one with tension headache. Blood pressures as high as 190/270 mm Hg systolic and 110-170 mm Hg diastolic were recorded at various times in these headache-free patients.

Two patients who suffered from typical migraine headache had experienced a "funny turn" during a migraine attack. One patient, in Group 3 (mainly adrenaline production), described how this left-sided migraine became severe and pounding while palpitations persisted. The other patient, in Group 1 (mainly NA production) did not notice any change in the nature or intensity of her

headache while the other paroxysmal symptoms were present. She volunteered the information that the frequency of her migraine had diminished from once every 2-3 weeks to 3 times in 12 months since her funny turns began.

After the removal of the phaeochromocytoma, the distinctive headaches disappeared but one patient has continued to have attacks of migraine.

DISCUSSION

Headache is recognised as a common symptom of the paroxysms caused by phaeochromocytoma but it is not invariably present. Thomas, Rooke and Kvale (1966) reviewed the clinical histories of 100 patients with proven phaeochromocytoma seen at the Mayo Clinic in the preceding 20 years. Headache was a feature of attacks in 80%. It was usually of rapid onset, bilateral, severe, throbbing and was associated with nausea in about half the cases. The headache lasted for less than an hour in 70%, and was accompanied by other symptoms of catecholamine release in 90%.

In the present series of patients, headache appeared to be caused by sudden elevation in blood pressure and bore no relation to sustained systolic or diastolic hypertension. Of the 7 patients who did not experience headache as a symptom of phaeochromocytoma, 3 had been subject to other paroxysmal symptoms and only 2 to spells which suggested a rapid increase in the degree of hypertension. The headache-free patients were all hypertensive and 4 had suffered from other forms of headache in the past.

The intravenous infusion of NA into migrainous subjects in sufficient concentration to raise the systolic blood pressure 10-40 mm Hg is not sufficient to produce headache. The late Harold G. Wolff (1963) administered such infusions on 116 occasions to 35 patients with vascular headaches of the migraine type, with abolition or reduction in intensity of the headache in 93 instances. In 3 cases, the diameter of the temporal artery and the amplitude of its pulse waves was observed to diminish as the headache abated. However, when NA was infused too rapidly, there was a sudden increase in blood pressure of 40-60 mm Hg systolic and the vascular headache was intensified. Wolff also observed that the subcutaneous injection of adrenaline (0.6 ml of adrenaline hydrochloride 0.001%) in two migrainous subjects decreased headache and reduced temporal artery pulsation for a short period. He attributed the headache of phaeochromocytoma to the sudden rise of blood pressure in the attacks, comparable with that of violent exercise, sexual excitement or great anger. There have been recent reports of severe headaches, explosive in onset, occurring at the time of orgasm which are comparable to those of phaeochromocytoma, thus bearing out Wolff's observation (Lance, 1974; Paulson and Klawans, 1974).

It thus appears that there are two competitive factors operating in the mechanism of the headache of phaeochromocytoma: the pressor and vasoconstrictor effects of NA and A. In those patients with predominant pressor effects, the headache develops rapidly and may be sustained throughout the paroxysm. In other patients, vasoconstriction of the cranial vessels may terminate the headache within a few minutes, despite hypertension being maintained for longer periods. Two patients in this series experienced paroxysmal symptoms of phaeochromocytoma while suffering a typical migraine headache. In one, the migraine headache did not alter in quality but, in the other, the headache was intensified and throbbed violently for the duration of the paroxysm.

It was not possible to identify syndromes distinctive for tumours producing NA, A or both amines. Sustained hypertension was more prominent in the former group while pallor and tremor were more common when A was produced in significant amounts as well as NA. Certain symptoms such as palpitations and sweating usually attributed to circulating levels of A, were encountered frequently in mainly NA secreting tumours.

Finally, it is of interest to consider the possible mechanisms of amine release. Being without innervation, the tumour does not excrete its products by exocytosis of storage granules but is thought to continue production of NA and A beyond its storage capacity. The amines diffuse from the cell into the circulation continuously or intermittently (Winkler and Smith, 1968). High levels of circulating catecholamines cause uptake and increased storage in other adrenergic tissue including

the adrenal medulla from which they are released on nervous stimulation. The latter can account for paroxysmal symptoms being triggered by anxiety or excitement, as well as by compression of the tumour.

SUMMARY

Of 27 patients with phaeochromocytoma, 20 were subject to headaches as a part of their symptom complex and 7 were not, in spite of the fact that 4 of the latter had experienced other forms of headache at other times. There was no correlation between the proportion of noradrenaline to adrenaline produced by the tumour and the presence or absence of headache or the nature of the headache. Liability to headache appeared to be linked with the rate of change in blood pressure and was not related to absolute values of blood pressure.

Two patients experienced a "funny turn" typical of catecholamine release during a spontaneous migraine headache. The migraine headache became pulsatile and severe in one patient but was unaltered in the other. The variable duration and intensity of the headache in different patients can be explained by the pressor and cranial vasoconstrictor effects of the secreted amines which respectively enhance and diminish vascular headache.

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SODIUM VALPROATE IN THE MANAGEMENT OF INTRACTABLE EPILEPSY: COMPARISON WITH CLONAZEPAM

J.W. LANCE and M. ANTHONY*

This study was stimulated by the report last year (Tomlinson, 1974) of a patient with myoclonic epilepsy which had been controlled by treatment with sodium valproate (Epilim, Depakine). Supplies of the drug were made available for the trial only five months ago, and this accounts for the preliminary nature of the present report.

Sodium valproate has been used as an anticonvulsant in Europe since 1963 but the first account appeared in the English literature only last year (Jeavons and Clark, 1974). Sodium valproate is the sodium salt of dipropylacetic acid, a branched-chain fatty acid. It has an average elimination half-life of 10 hours and is excreted in the urine. Five years of European experience was summarised by Dumon-Radermecker (1969) who quoted the findings of Lebreton and others in 1964 that sodium valproate increased brain levels of gamma-amino butyric acid (GABA) by inhibiting GABA transaminase. Duman-Radermecker reported that 18 of 25 patients with *petit mal* absences resistant to other treatment were improved by sodium valproate, 11 becoming free of seizures. A double-blind crossover trial was conducted by Meinardi (1971) who concluded that one-third of 42 patients with various forms of resistant epilepsy benefited from the use of sodium valproate. The general impression from the open trials conducted in Europe is that sodium valproate is free from toxicity and is helpful in the management of all forms of epilepsy with the exception of tonic seizures in childhood.

Jeavons and Clark (1974) treated 63 patients, hitherto unresponsive to therapy, for 4 to 11 months. Control became complete in 12 of 17 patients with *petit mal* absences, 10 of 19 patients with *grand mal* and 8 of 10 patients with myoclonus. The response was poor in children with both myoclonus and akinetic attacks (Lennox syndrome), temporal lobe epilepsy and other focal seizures.

In the present report, we have taken the opportunity to compare the effect of sodium valproate with that of clonazepam which we have been using in previously uncontrolled epileptic patients for the past three years.

METHODS

At the time of writing, 35 patients, 18 male and 17 female, ranging in age from 10 to 43 years, had been admitted to the trial. All patients had suffered from intractable epilepsy which had not been controlled by full doses of conventional anticonvulsant agents, alone or in combination. Sodium valproate was added to preexisting medication in 8 patients, substituted for clonazepam in 11, ethosuximide in 6, carbamazepine in 6, primidone in 2, diazepam in one and acetazolamide in one.

* The Division of Neurology, The Prince Henry Hospital, Sydney, and the School of Medicine, University of New South Wales.

The initial dose was 200 mg. orally morning and night and the patient was given instructions to increase the dosage by one tablet (of 200 mg.) daily at intervals of 3 days up to a total of 6 tablets daily unless the seizures were completely controlled or side-effects supervended. They were instructed to telephone immediately if any problems arose, and to report to the clinic each month. Three patients were given higher doses after one month (up to 9 tablets, 1800 mg., daily) since they had not responded completely and were free from side-effects. The blood pressure was recorded at each visit. A full blood count and partial thromboplastin time with kaolin (PTTK) or blood coagulation time was obtained at the onset of the trial, and one month and three months after starting medication. Biochemical investigations at the same times included blood urea, serum bilirubin, serum alkaline phosphatase (SAP) serum glutamic pyruvic transaminase (SGPT) and random blood glucose levels.

The types of seizures and electroencephalographic (EEG) findings are shown in Table I. The 13 patients with more than one type of seizure are shown in the mixed group. The EEG demonstrated classical 3 Hz spike and wave paroxysms in 6 patients, a typical spike and wave or multiple spike and wave complexes in 9, focal changes in 14, non-specific slow wave changes bilaterally in 6 and was completely normal in 2 patients. In Table I, the symbol (+1) indicates that this EEG change was additional to that of the primary classification. One patient with consistent focal changes showed occasional paroxysms of a typical spike and wave and the reverse was noted in another patient.

TABLE I

	Type of seizure							EEG					
								spike and wave		focus		non-epileptic	
	GM	PM	M	A	T	F	Total	3Hz	Atyp.	single	multiple	abnormal	normal
Grand mal	4						4			1	1	2	
Petit mal		3					3	3					
Myoclonus			3				3		3				
Akinetic				1			1					1	
TLE					5		5			3	1		1
Other focal						6	6		(+1)	1	4		1
Mixed, GM, PM	5	5					5	2	3	(+1)			
GM, PM, A	2	2		2			2	1	1				
GM, A	2			2			2			1	1		
GM, T	2				2		2					2	
GM, M	1		1				1					1	
PM, A		1		1			1		1				
	16	11	4	6	7	6	35	6	9	7	7	6	2

The cause of seizures appeared to be genetic in 9, birth trauma in 9, possible birth trauma in 7, encephalitis in 2, meningitis in one, possible hypoxia during anaesthesia in one, head injury in one and was unknown in 5.

The observation period has been 4 months for 3 patients, 3 months for 10 patients, two months for 15 patients and only one month for 7 patients.

RESULTS

Sodium Valproate

Of the 16 patients with *grand mal* as one manifestation of epilepsy, 5 were subject to seizures

of insufficient frequency to warrant analysis, so that only 11 are shown in Table II. One patient had regularly experienced 3 seizures daily and the remainder 1-8 each month. Six of the 11 patients suffered major fits in the first few weeks during the withdrawal of previous medication (clonazepam 5, primidone one) and the substitution of sodium valproate. Three of these patients have now remained free of seizures for 2 and 3 months respectively and the fourth has continued to have 4 attacks each month (half the previous frequency). Two other patients, one with myoclonus and one with focal adversive seizures, experienced their first *grand mal* fit for 5 and 7 years respectively, while clonazepam was being replaced by sodium valproate.

In Tables II and III, the classification '100% improvement' indicates that the patient has been free of seizures during the observation period. Of the 11 patients with a regular major seizure pattern before the trial, 8 have improved as shown in Table II. From the same Table it can be seen that improvement was noted in 7 of 11 cases of *petit mal*, all 4 with myoclonus, 3 of 5 with akinetic attacks, 4 of 7 with temporal lobe epilepsy and only 3 of 6 with other focal attacks. The Table excludes one patient with infrequent akinetic attacks in whom the response cannot yet be assessed.

TABLE II

Sodium Valproate: Follow-up 1-4 Months
(35 Patients)

	% Improvement					
	0	25	50	75	100	Total
grand mal	3	1	3	3	1	11
petit mal	4	2	2	3	0	11
myoclonus	0	0	1	2	1	4
akinetic	2	0	1	1	1	5
T.L.E.	3	2	0	2	0	7
other focal	3	0	2	0	1	6
	15	5	9	11	4	44

Two of the 4 patients with myoclonus have familial myoclonic epilepsy and were virtually confined to wheel chairs because of repetitive myoclonic jerking on attempted movement in spite of partial control by large doses of clonazepam. On starting sodium valproate, their condition fluctuated in a remarkable fashion throughout the day but has now settled down to sustained improvement as the dose was gradually increased to 1600 mg. daily. One of them now walks freely around the house and down the street, in a way that has not been possible for 5 years and rarely has any myoclonic jerking (classed at 75% improved). The other is able to walk with the aid of a walking machine but still has severe myoclonus at the time of her periods (classed as 50% improved). A third patient who was incapacitated by continuous myoclonus for 30 minutes in the early morning and continued to have intermittent attacks throughout the morning has had only a few mild isolated jerks in the past 3 months and is classified as 100% improved. The fourth patient suffered severe myoclonic jerking before *grand mal* seizures and both manifestations disappeared with the increase in dosage from 1200 mg. to 1800 mg. daily.

Side-effects

Gastrointestinal side-effects were experienced by 7 patients on increasing medication dosages to 1200 mg. daily, there being nausea in 6 (of whom 2 also vomited and 2 had diarrhoea) and persistent mucus in the bowel motions in the seventh patient. Eleven patients complained of drowsiness in the first week or so, but 9 of them became exceptionally well and bright without reduction in dosage. Two remained very drowsy until the daily dose was lowered to 400 mg. and 600 mg. respectively. Two noticed giddiness and ataxia, and one complained of diplopia on 1200 mg. daily.

One patient, who had transferred from treatment with clonazepam, stated that his mind seemed to be racing and that he was unable to sleep. These sensations disappeared when the dose was brought down from 1200 mg. to 800 mg. daily.

One patients with temporal lobe epilepsy arising from the left hemisphere noticed myoclonic jerking of the right arm and leg for the first time in his life when sodium valproate 1200 mg. daily was added to his previous medication with carbamazepine, although his temporal lobe seizures were reduced to 25% of their former frequency. The addition of clonazepam 3 mg. daily completely abolished the temporal lobe episodes and the right-sided myoclonus. Another patient with *petit mal* suffered fewer attacks on sodium valproate 1200 mg. daily but developed 'shuddering' with each episode, which she had not done for many years. The shuddering disappeared when the dose was lowered to 1000 mg. daily.

One patient developed an eczematous eruption in the axillae, elbow flexures and fingers, which she had experienced 2 years before. A second patient reported a rash on the forearms which resembled a folliculitis. In neither case is the association of the rash with the medication certain. One patient commented that his urine appeared to be greasy in the first month of treatment but that he had not noticed this in the second month.

Thirteen patients commented that they felt very much brighter and more able to concentrate on the new medication. In one of these, sodium valproate had been added to the previous treatment and in the others it had been subsituted for clonazepam (5) primidone (2), carbamazepine (2) ethosuximide (2) and acetazolamide (1).

Haematological and biochemical tests have not so far shown any significant deviation from normal. The PTTK of 2 patients was longer than the control time after one month of treatment but this was attributed to difficult venepuncture.

Comparison with clonazepam

Over the past 3 years we have used clonazepam in the treatment of 70 patients with intractable epilepsy. We have analysed the response of the first 36 patients given clonazepam after they had been followed up for 1-12 months for comparison with the response to sodium valproate. Since some patients were subject to more than one form of seizure, the results for each manifestation have been analysed separately in Table III as they have been for sodium valproate in Table II. A direct comparison was made between the two medications in 15 other patients who had also been treated previously with clonazepam. The comparison was hardly fair to the former drug because the patients' medications were altered only in those whose control was incomplete. In the weeks in which medication was altered, 5 patients had 2 or more major seizures, suggesting that clonazepam had been exerting some measure of control and that sodium valproate was not immediately effective. Of the 15 patients, 5 were not improved by the transfer, 4 patients were marginally better and 6 patients substantially better on sodium valproate during the short follow-up period. One patient

TABLE III
Clonazepam: Follow-up 1-12 Months
(36 Patients)

	% Improvement					
	0	25	50	70	100	Total
grand mal	7	0	1	4	0	12
petit mal	1	1	3	5	3	13
myoclonus	0	2	1	2	1	6
akinetic	2	0	3	1	0	6
T.L.E.	1	1	0	4	1	7
other focal	3	0	0	2	0	5
	14	4	8	18	5	49

with *petit mal* was free of attacks on clonazepam but incapacitated by drowsiness. She is 75% controlled by sodium valproate without feeling tired.

The side-effects of clonazepam were solely related to the nervous system, apart from one patient who was found to have diabetes in the course of the trial, probably unrelated to the medication. One patient died in a fit, but this was unlikely to be linked with her medication since she had been found lying on her face in previous episodes and fears for her life had been expressed. Of the 36 patients, 7 noted drowsiness, 4 giddiness and ataxia and 3 irritability or depression. One became confused and another developed paranoid ideas. Drowsiness and lethargy were more persistent symptoms in patients treated with clonazepam than in those taking sodium valproate.

No firm conclusions can be drawn from relatively small samples but it appears that clonazepam has the greater suppressant effect in *petit mal* and temporal lobe epilepsy and that sodium valproate has a better effect on *grand mal* seizures and myoclonus once its action becomes established after some weeks. A longer follow-up period will help to determine the comparative value of the two medications.

DISCUSSION

Any interpretation of results after such a brief period of observation must be made with extreme caution. Both sodium valproate and clonazepam have been employed in patients who had continued to have seizures under treatment with large doses of other appropriate anticonvulsants so that any success at all indicates that the agent is a useful addition to the therapy of epilepsy. Both agents appear to exert a beneficial effect on *grand mal* and *petit mal*, sodium valproate more on the former and clonazepam on the latter. Both agents are effective in myoclonus, with sodium valproate having a distinct advantage. Clonazepam appears to be more effective in temporal lobe epilepsy .

The side-effects of sodium valproate usually appear only with higher dosage (1200 mg. daily) and are transient, whereas drowsiness presents a problem with some patients taking clonazepam, even in low dosages. One curious and inexplicable effect of sodium valproate was the appearance of unilateral myoclonic jerks in one patient with temporal lobe attacks, in view of the fact that all 4 patients treated for myoclonus responded very well. The addition of clonazepam in this patient abolished myoclonus as well as his remaining temporal lobe attacks, suggesting that the two agents might be synergistic.

Side-effects noted with sodium valproate were much the same as those reported by Jeavons and Clark (1974). These authors also mentioned falling hair as a possible side-effect of sodium valproate. Having encountered falling hair as a side-effect in patients taking placebo as well as active medication in previous trials of preparations for headache, we are inclined to regard it as a natural phenomenon not related to medication.

We remain uncertain as to whether the increased mental alertness reported by many patients on sodium valproate is the result of a direct stimulant action or simply reflects the withdrawal of other more depressant agents. A number of patients commented that they seemed to be improving progressively while taking sodium valproate. This emphasises the importance of a longer follow-up period, which will be the subject of a further report.

SUMMARY

Sodium valproate 400 mg.-1800 mg. daily has been used for 1-4 months in the management of 35 patients with intractable epilepsy. This preliminary report indicates that the agent is a useful addition to anti-convulsant therapy with beneficial effect to the majority of patients with *grand mal, petit mal,* myoclonus and akinetic attacks. Temporal lobe epilepsy and other focal cortical seizures responded less well. There were some minor gastrointestinal and neurological side-effects which subsided with time or the reduction of dosage. The transition period while other anticonvulsants were being withdrawn was accompanied by *grand mal* seizures in 6 patients. It appears that sodium valproate requires 7-10 days to become fully active and that other anticonvulsants should

be withdrawn only after the patient is established on a maintenance dosage. Comparison with clonazepam suggests that the latter is more effective in the control of *petit mal* and temporal lobe epilepsy but has more persistent sedative effects. Most patients transferred from other anticonvulsants to sodium valproate felt more alert and able to concentrate better.

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FLUCTUATIONS OF PLASMA PHENYTOIN LEVELS ON SINGLE DOSE AND TWICE DAILY DOSE REGIMES

F.J.E. VAJDA, J. MERORY and P.F. BLADIN*

Plasma measurements of phenytoin have become accepted as a guide to the effective control of epilepsy (Eadie and Tyrer, 1973; Lund, 1974). Although some patients are managed successfully at low plasma levels of the drug, the majority of epileptics require plasma levels above 10 μg/ml, while at levels in excess of 20 μg/ml toxic symptoms tend to appear. On a constant dose the levels tend to become stable, but the dose required to achieve a stable level varies from patient to patient. The factors influencing plasma levels include the metabolic enzyme capacity for degrading phenytoin, which is an inherited characteristic, the interaction with other drugs, the rate of absorption and protein binding of the drug and renal function.

Phenytoin, like most of the anticonvulsant drugs has a long half-life, ranging from 18 to 50 hours (Van der Kleijn, 1973). Because of this it has been suggested that it may be sufficient to adminster it once daily in order to maintain an adequate plasma concentration. Evidence that the once daily dose is adequate was presented by Wilder, Streiff and Hammer (1972) and subsequently it was reported that this regime was acceptable to a large series of chronic epileptics (Strandjord and Johannessen, 1974).

In order to confirm these reports, it was decided to carry out a crossover study in chronic epileptics, using each patient at his own control. Two questions were studied. The first was whether plasma levels rise excessively when a single large dose is adminstered, and whether this is associated with clincial side effects. The second question was whether there was an excessive fall at the end of 24 hours, to levels below the starting level of plasma phenytoin.

PATIENTS AND METHODS

Details of characteristics and therapy of the patients are shown in Table I. All patients had well documented diagnoses of epilepsy. Eight patients were studied, 5 males and 3 females. They ranged in age from 10 to 49 years, and in weight from 53 Kg to 69 Kg. All have been treated with phenytoin for months or years and during the study their additional drugs were kept constant, both in kind and in dosage. They were admitted to hospital so that their drug intake was supervised and their phenytoin was given twice daily. Plasma samples were taken prior to the morning dose, and then 1, 2, 3, 4, 6, 8, 10 and 12 hours subsequently. For the second part of the study patients were told to take their total daily dose as a single dose prior to admission; plasma samples were taken before the morning dose and subsequent samples were taken 1, 2, 4, 6, 8, 12, 16, 20 and 24 hours later.

Plasma levels of phenytoin were then assayed by a modification of MacGee's method (1970) using gas chromatography. This is a sensitive and specific method. All samples for patients were

* Department of Neurology and Department of Clinical Pharmacology and Therapeutics, Austin Hospital, Heidelberg, Victoria

TABLE 1

Characteristics of patients, diagnoses and therapy

Name	Sex	Age	Wt. (Kg)	Duration of Illness	Clinical Control	Aetiological Diagnosis	E.E.G.	Dose of Phenytoin Mg/Day	Other Drug
J.C.	M	15	56	Years	Good	Lennox-Gastaut Syndrome	Mildly Abnormal Intericta ly	600	Diazepam, Heminevrin
D.S.	F	15	54	Years	Good	Right Frontal Astrocytoma	Mainly Right Frontal Spike Wave Activity	300	Diazepam, Thioridazine, Neogynon
R.R.	M	17	72	Years	Partial Fits	Frontal Lobe Focus	Scattered and Sharp Wave Delta Activity	300	Diazepam, Carbamazepine
J.MCD.	M	49	63	Years	Difficult	Not Ascertained	Spike and Wave Pattern in Bursts	400	Carbamazepine, Clonazepam
G.G.	M	22	70	Years	Fair	Left Frontal Epilepsy with Anterior Encephalocoele	Diffusely Grossly Abnormal Left Frontal Lesions	400	Diazepam, Carbamazepine
D.H.	M	10	69	Years	Fair	Grand Mal and Petit Mal Syndrome	Scattered Theta and Delta Bilaterally: Occasional Sharp Wave Component	300	Primidone, Carbamazepine
A.F.	F	30	53	Years	Fair	Idiopathic, Worsened by Sleep Deprivation	Normal nterictally	400	Carbamazepine, Phenobarbitone
P.Q.	F	19	64	Years	Poor	Mumps Encephalitis, Mental Retardation	Scattered Theta and Delta with Disordered Spike Wave Activity Bifronta v	400	—

run together to eliminate day to day variation in the technique and the results were plotted to compare fluctuations on the two different dose schedules.

Two patients were unsatisfactorily controlled even though their plasma levels were above the upper limit of the therapeutic range, at 25-30 μg/ml; one patient was partially controlled at plasma levels of 6-8μg/ml. All of these patients were severe resistant chronic epileptics and this was the reason for multiple therapy. Only one patient experienced toxic symptoms suspected of being due to phenytoin with a plasma drug concentration of 25 μg/ml, but reduction of the dose resulted in an increased frequency and severity of grand mal episodes.

RESULTS

Table II shows plasma phenytoin levels for individual patients on a twice daily dose schedule. The greatest change in plasma level occurred 2-4 hours after taking the drug, but overall plasma levels were stable and the level at 12 hours closely approximated the starting level, even though the starting level varied from 4.3 to 26.2 μg/ml.

When the mean fluctuation in plasma levels was plotted over 12 hours as a percentage change from the starting level (Fig. 1), there was less than 30% fluctuation in plasma levels. One patient had the study repeated one week later with identical results.

In the 24 hour period following a single dose of drug, plasma levels were comparable to those

seen with twice daily dosage (Table II) and the maximum percentage fluctuation was less than 20%, which represented an improvement over that seen with twice daily dosage (Fig. 2).

TABLE II

Direct comparison of starting peak and final phenytoin plasma levels (in μg/ml) on two dosage schedules

		12 HOUR STUDY			24 HOUR STUDY		
	Patient initials	Starting level	Final level	Peak level (hours	Starting level	Final level	Peak level (hours)
1.	J.C.	25.7	24.2	31.4 (4)	25.7	28.3	30.2 (12)
2.	D.S.	19.7	23.5	26.5 (1)	20.0	25.8	30.0 (8)
3.	R.R.	26.2	21.5	27.8 (4)	17.4	15.4	21.8 (4)
4.	J.McD.	10.7	11.3	13.7 (4)	12.0	8.5	13.0 (8)
5.	G.G.	21.5	23.5	40.0 (4)	25.1	21.5	28.0 (4)
6.	R.H.	19.0	16.0	18.5 (4)	16.5	15.3	19.2 (6)
7.	A.F.	4.3	5.5	8.0 (4)	3.1	2.0	7.8 (2)
8.	P.Q.	19.6	20.5	26.7 (6)	30.0	20.6	26.0 (8)

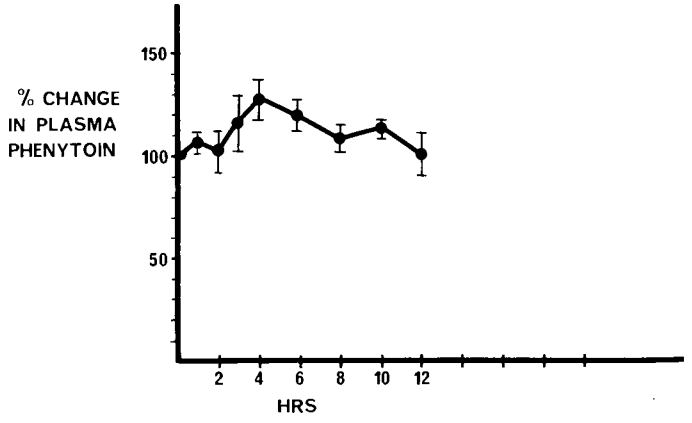

FIG. 1. Change in phenytoin plasma levels (± S.E.M.) expressed as a percentage change from the starting level on twice daily administration of phenytoin.

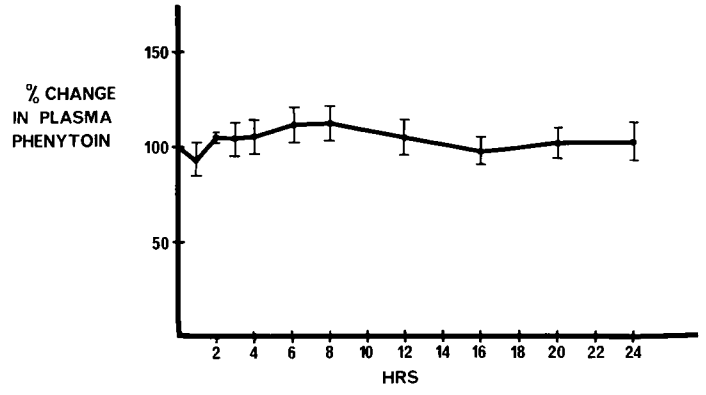

FIG. 2. Change in phenytoin plasma levels (± S.E.M.) expressed as a percentage change from the starting level on single daily dose administration.

DISCUSSION

These results tend to confirm earlier work by Wilder (1972) and Buchanan, Kinkel, Goulet and Smith (1972), that therapeutic levels of phenytoin can be achieved on a once daily dosage. In these studies both twice daily dosage and single daily dosage of phenytoin achieved therapeutic plasma levels which varied less than 30% during the 24 hour study period. It is suggested therefore, that once therapeutic levels of phenytoin are achieved in a particular patient the maintenance treatment can usually be carried out by once daily or twice daily administration of drug. Although some patients may be conditioned to take these drugs in divided doses, most studies indicate greater patient reliability on a once daily or twice daily regime (Gibberd, Dunne, Handley and Hazelman, 1970). Moreover, during the present study patients remained adequately controlled on both drug schedules and there was no evidence of an increased incidence of side effects. In patients with plasma levels below the desirable therapeutic range neither of these regimes succeeded in producing a significant increase in plasma phenytoin levels.

SUMMARY

Eight chronic refractory epileptics were studied with regard to frequency of administration of phenytoin. There were no excessive fluctuations in plasma levels when the total drug dose was given as a single daily dose, and the clinical state of the patients was unchanged from that on twice daily dosage.

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FIBRE FUNCTION AND PERCEPTION DURING CUTANEOUS NERVE BLOCK

R.A. MACKENZIE, D. BURKE, N.F. SKUSE and A.K. LETHLEAN*

The role of individual nerve fibre groups in the appreciation of cutaneous sensation has been the subject of discussion for many years, but difficulties in recording volleys in slowly conducting fibres in intact man have limited the number of studies in which perception has been correlated with evoked neural activity (Collins, Nulsen and Randt, 1960; Hensel and Boman, 1960). One approach has been to block a cutaneous nerve in a manner which is known from animal studies to impair selectively the activity of fibre groups of different sizes, and to correlate these events with changes in perception (Sinclair and Hinshaw, 1950). Such experiments have suggested that touch and cold sensation are mediated by myelinated fibres and pain and warmth by unmyelinated fibres, but the findings have not been fully accepted because of failure to use standardised thermal stimuli (Sinclair and Glasgow, 1960) and also because of uncertainty surrounding the specificity and selectivity of the blocks.

The development of a technique for recording activity from intact nerve fascicles with percutaneous tungsten micro-electrodes (Vallbo and Hagbarth, 1968) allows monitoring of the changes which occur during nerve block in awake human subjects. A recent micro-electrode study (Torebjörk and Hallin, 1973) has confirmed the selectivity of pressure and local anaesthetic block in man and has correlated changes in the evoked neurogram with changes in the perception of electrical stimuli.

In the present study this technique was used to correlate changes in the evoked intrafascicular neurogram during selective blocking procedures with changes in the perception of standardised sensory stimuli.

METHODS

Recording Techniques

The examinations were made on the superficial radial nerve of three healthy adult subjects aged 28, 30 and 47 years. None had any evidence of pre-existing neuropathy or other disease. The surface sensory action potential (S.A.P.) was recorded antidromically using standard neurophysiological techniques. To obtain intrafascicular recordings, insulated tungsten micro-electrodes with a tip diameter of approximately one micron were manually inserted percutaneously into the superficial radial nerve at the wrist. The micro-electrode was guided into a nerve fascicle by stimulating through the bared tip and adjusting its position until a stimulus of less than 0.5V could be perceived. The micro-electrode was then used for recording and the amplified signal was monitored on a

* The Unit of Clinical Neurophysiology and the Department of Medicine, Prince Henry Hospital, Little Bay, Sydney.

loudspeaker, displayed on an oscilloscope, and fed into a fixed programme averaging computer (ND 801 Enhancetron 1024) and a tape recorder (Electrodata Model 6300-2).

The fascicular innervation zone was defined by scraping the skin and listening to the evoked neural activity; needle electrodes were then inserted subcutaneously into the area. The averaged evoked neurogram to single electric shocks delivered through the needle electrodes was assessed and on some occasions the position of the micro-electrode tip within the fascicle was further adjusted to obtain a satisfactory recording from all fibre groups. Supramaximal stimuli were then applied at 1 per sec., or 1 per 3 sec. when studying fibre groups with a conduction velocity below 2 m/sec.

Blocking Techniques

Pressure blocks were produced by screwing a metal plate 1 cm. wide across the distal end of the radius, compressing the superficial radial nerve between stimulating and recording sites. The plate did not interfere with circulation in the distal part of the limb. Local anaesthetic blocks were produced at a similar site by subcutaneous injections of lignocaine or procaine. During a single experimental session the nerve under study was initially subjected to one or more local anaesthetic blocks, and after full recovery a pressure block was applied. A period of at least three weeks elapsed between successive experiments on a particular nerve.

Sensory Stimuli

The subject was prevented from seeing each test stimulus. Pain was tested by deliving single electric shocks to the electrodes inserted in the skin of the fascicular innervation zone at a stimulus intensity which was perceived as a dull painful jab with an after-pain lasting about 1 second. All other stimuli were applied to an area of 1 $cm.^2$ of hairy skin in the fascicular innervation zone which had been selected before the block and marked with Indian Ink. Light touch was tested with a wisp of cotton wool, and a moderately sharp pin held manually was used for pinprick sensation. The extremes of thermal sensation were assessed using a lighted match applied close to the skin for heat and an ice cube placed on a small lead plate for cold. Finer temperature discrimination was tested by applying polished copper tubing through which water circulated at predetermined temperatures. The tubing was bent so that the area of contact was approximately $1cm.^2$. Water bath temperature was thermostatically controlled and monitored with mercury thermometers; it was found to vary by less than 0.25°C. The temperature of the thermal stimulus applied to the skin was taken as the mean of the water bath temperature and that of the returning water, a difference of 0.5°C. When testing thermal sensation, each piece of tubing was applied with moderate pressure for five seconds, then removed. At least ten seconds elapsed between the application of each thermal stimulus.

Room temperature was maintained at 21°C. Skin temperature was monitored with a thermocouple and radiant heat was used when necessary to maintain a range of 31-32°C throughout the experiment.

RESULTS

In 6 experimental sessions the development of 9 pressure blocks and one local anaesthetic block was monitored with surface electrode recordings. In a further 10 separate experimental sessions, continuous micro-neurographic monitoring of 11 pressure blocks and 7 local anaesthetic blocks was performed. Changes in sensory modalities were monitored throughout all blocks and the nerve was allowed to recover fully between each phase of an experiment.

Pressure Block

The earliest change to occur during pressure block was a subjective feeling of dysaesthesia after 20 to 30 minutes in the territory of the nerve being compressed. This was not accompanied by

any change in the size or latency of the S.A.P. recorded with surface electrodes, and there was no detectable change in either the averaged intrafascicular neurogram (Fig. 1a) or the audible response from the loudspeaker to skin scraping.

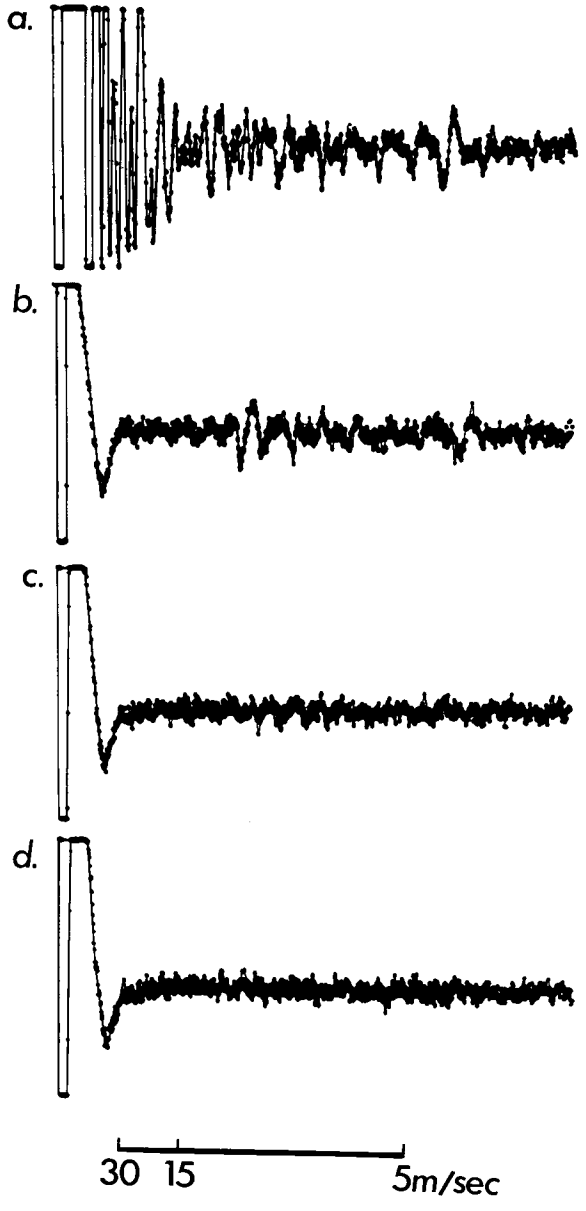

FIG. 1. Changes in myelinated fibre potentials during pressure block. Averaged evoked neurograms to 200 supramaximal shocks delivered at 1/sec.
a. Normal perception, subjective dysaesthesia.
b. Pressure block at 50 minutes. Light touch absent, pinprick and cold discrimination impaired.
c. Pressure block at 55 minutes. Cold and pinprick perception absent.
d. Pressure block at 60 minutes. Warmth and pain perception impaired, other sensations absent.

The first objective sensory change was diminished perception of light touch after 30 to 40 minutes of compression. At this stage there was an increase in the latency and diminution in amplitude of the surface S.A.P. evoked by single shocks. The averaged intrafascicular neurogram showed an abrupt decrease in the complexity of the potentials faster than 30 m/sec. (A-beta-gamma fibres) and within 1-2 minutes these potentials had disappeared (Fig. 1b). These changes were accompanied by complete abolition of light touch sensibility from non-hairy areas, although appreciation of light touch in areas of hairy skin involved by the block remained for several more minutes. The loudspeaker

response to skin scraping in areas devoid of touch sensation was inaudible, and no S.A.P. could be recorded with surface electrodes.

Thermal Sensation

Before each block, the temperatures of the "absolute" thermal stimuli to be applied were adjusted until levels were found which always gave a response of "warm" or "cold" by the subject. Average chosen levels for absolute temperature were 27°C for cold and 36°C for warm. The ability to detect the difference between two successively presented stimuli separated by 1°C was also tested, using 27° and 28°C for cold and 35° and 36°C for warmth discrimination. These pairs were presented a number of times in randomised fashion and the average of correct, incorrect and nondiscriminatory responses was calculated.

The earliest detectable change in thermal perception during pressure block was an increased number of incorrect responses to discrimination of paired cold stimuli, accompanied by subjective diminution in the intensity of the absolute cold stimulus. In all but 3 pressure blocks this change occurred at least 5 minutes before any change in warmth discrimination. In one of the exceptions warmth discrimination was impaired one minute before cold, and in the other two, both were lost together. During the stage of impaired cold discrimination, the averaged intrafascicular neurogram retained fibre potentials of conduction velocity 5-15 m/sec. (A-delta-fibres). However, when compared with the pre-block recordings, these potentials were of lower amplitude and longer latency (Fig. 1b). Fibre potentials with conduction velocity less than 2 m/sec. (C fibres) were not affected; indeed during this stage their amplitude was sometimes increased (Fig. 2b).

Progression from impairment of cold discrimination to loss of cold perception took from 5 to 10 minutes, during which time impairment of warmth discrimination commenced. In all pressure blocks cold perception was lost when myelinated fibre potentials were completely abolished by pressure (Fig. 1c and d) even though unmyelinated fibre potentials remained (Fig. 2c and d). During this stage, an extreme cold stimulus (6°C) was felt as an odd "burning" sensation. When cold perception was absent, A-delta fibres potentials could not longer be seen in the averaged neurogram. A single exception to this general finding is illustrated in Fig. 3. In this instance, an A-delta fibre potential persisted after abolition of perception of all cold stimuli, but was of lower amplitude and longer latency than before. Morever, during this phase, the response to a second shock 20 m.sec. later was abolished (Fig. 3b).

When perception of cold was absent and warmth discrimination was impaired, C fibre potentials were still averaged. However, when compared with the neurogram obtained before the block was effective, the C fibre potentials were reduced in number and their amplitude was less (Fig. 2d).

Other Sensations

The earliest alteration in pinprick sensation was a diminution in the sharpness of the stimulus. This occurred at the same time as impairment of cold discrimination. As the block progressed the pin was felt as a dull stimulus only, without any sensation of sharpness. A-delta fibre potentials were no longer recorded as this stage (Fig. 1c) but unmyelinated fibres were still active (Fig. 2c). The first change in the perceptionof pain during pressure block was a lessening of the jabbing quality of the electrical stimulus, followed by a reduction of the aching interstimulus component. These changes occurred late in the block at the stage when the activity of unmyelinated fibres was reduced (Fig. 2d).

When the block had been in progress for an hour, a spontaneous dull ache began in the territory of the compressed nerve, and continued until the pressure was released. In none of the pressure blocks was unmyelinated fibre activity completely abolished, and some appreciation of pain and heat was always retained.

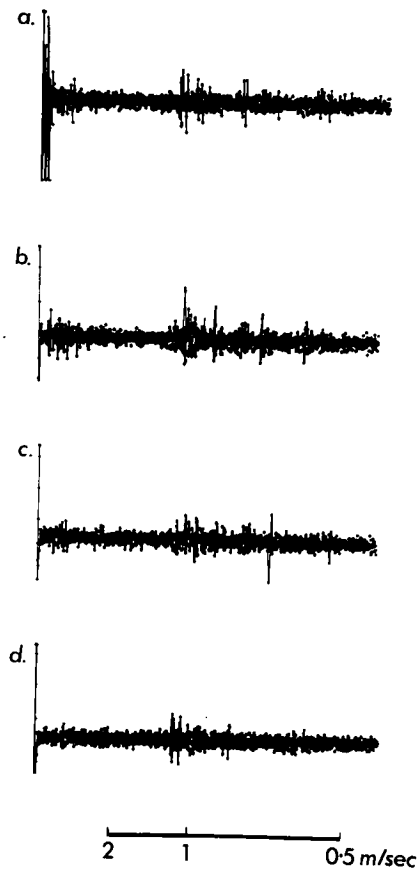

FIG. 2. Changes in unmyelinated fibre potentials during pressure block. Same experiment and similar stages of the block as Fig. 1. Averaged evoked neurograms to 50 supramaximal stimuli delivered at 1 per 3 sec.
a. Normal perception.
b. Fifty minutes. Warmth and pain perception normal.
c. Fifty-five minutes. Warmth discrimination impaired.
d. Sixty minutes. Perception of warmth and dull pain further impaired.

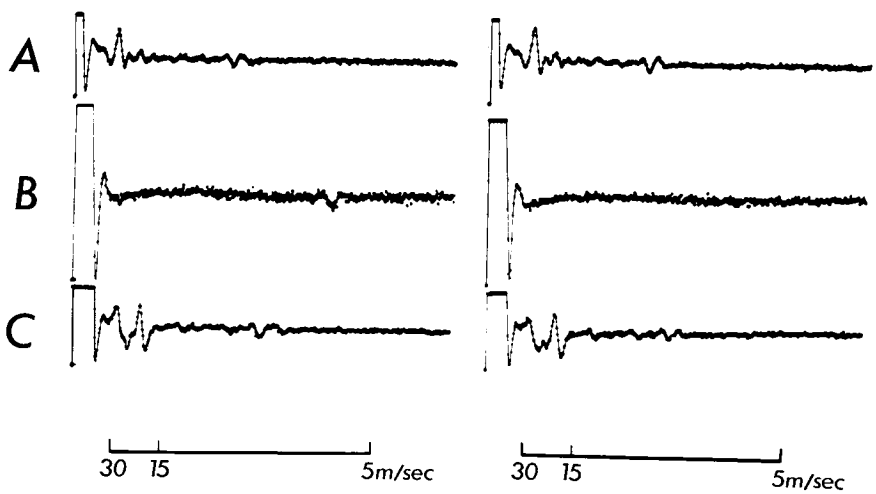

FIG. 3. Pressure block showing persistence of A-delta fibre potential after loss of cold perception. Diagrams on left show average response to 100 single shocks at 1/sec. Diagrams on right shown 100 averaged responses to the second of two supramaximal shocks separated by 20 m.sec. delivered at 1/sec.
a. Pressure block at 30 minutes. Light touch absent, pinprick and cold perception impaired.
b. Pressure block at 50 minutes. Cold perception absent.
c. Pressure block removed. Cold perception normal. Note: Display gain of B was increased to 2.5 times that of A and C.

Recovery

On removal of the pressure clamp, spontaneous pain disappeared within half a minute and appreciation of the painful electrial stimulus returned to normal. Perception of warmth, cold and pinprick recovered within a minute, and both C fibre and A-delta fibre potentials returned within this period. Light touch was the last modality to return, accompanied by recovery of the surface S.A.P. evoked by single shocks.

Local Anaesthetic Block

Concentrations of lignocaine and procaine of 0.25% and 0.50% were found to give quite satisfactory preferential blocks. At higher concentrations changes occurred too quickly to allow progressive measurements. With dilute solutions, the earliest perceptual change was always a hypersensitivity to cold stimuli which was quite striking and lasted several minutes. No change in C fibre potentials evoked by single shocks was seen at this early stage. As the block progressed, the first objective sensory change was impairment of warmth discrimination, followed within one or two minutes by reduced appreciation of the dull aching component of the electrical stimulus. The intrafascicular neurogram contained C fibre potentials of reduced amplitude at this stage, but myelinated fibre potentials were unchanged (Fig. 4).

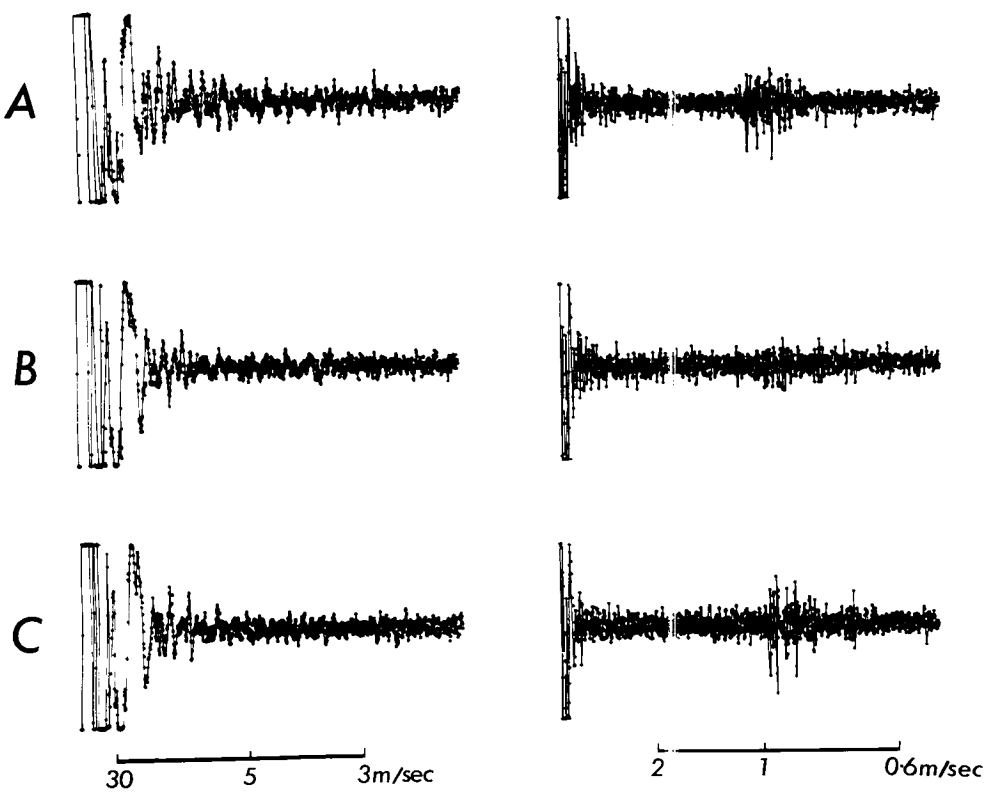

FIG. 4. Changes in myelinated and unmyelinated fibre potentials during block with 0.25% lignocaine. Diagrams on the left show the averaged evoked neurogram to 100 supramaximal shocks at 1/sec. Diagrams on the right show the averaged evoked neurgram to 50 supramaximal stimuli at 1 per 3 sec. Stages of the block are similar in each case.

a. Normal perception.

b. Fifteen minutes after infiltration. Cold hypersensitivity, impairment of warmth discrimination and pain perception.

c. Thirty minutes after infiltration. Recovery of perception. (Pinprick and touch sensation were unaffected during this block.)

When further progression of the block occurred, cold discrimination was the next sensation to be affected together with the appreciation of the sharpness of pinprick. Very soon afterwards, heat and pain perception were abolished and intrafascicular recordings showed decrease in A-delta fibre potentials and absence of C fibre potentials. Light touch was the last modality to be affected. During impairment of light touch perception the surface S.A.P. was reduced in amplitude and the latency was prolonged; when light touch sensibility was abolished, the surface S.A.P. was absent and no intrafascicular activity could be evoked with electrical stimulation or skin scraping.

Recovery from local anaesthetic block was slower than for pressure block, but was always complete, with return of surface S.A.P., intrafascicular neurogram (Fig. 4) and normal perception. There was no clear differentiation of sensory modalities or fibre groups during the process of recovery. No differences were found in the selectivity of fibre blocks induced by lignocaine and procaine.

DISCUSSION

Gasser and Erlanger (1929) recorded changes in the evoked action potentials of animal nerves during the production of pressure and local anaesthetic block, and related these changes to alterations in sensation during similar blocking procedures in man. They concluded that the largest fibres were responsible for touch perception, the medium-sized fibres for temperature, and the smallest fibres for pain. Since then, many studies based on animal nerve block experiments have attributed specific sensory functions to particular fibre groups in man (Heinbecker, Bishop and O'Leary, 1933; Landau and Bishop, 1953). However, both the timing of the block of individual fibre groups and the order of involvement of sensory modalities is variable, casting doubts on the validity of such extrapolations. In the present study, these inherent sources of error have been avoided by the simultaneous recording of fibre activity and changes in perception. The correlations so determined are independent of both the nature of the block and its rate of development. Further, the range of conduction velocity of fibres associated with each sensory modality can be measured.

The perception of light touch in non-hairy areas was dependent on the function of fibres with conduction velocity greater than 30 m/sec. Touch sensibility in hairy areas was probably also carried by fibres of lower conduction velocity, since its appreciation persisted longer in these areas during pressure block. Similar findings have been reported in cats (Zotterman, 1939; Hunt and McIntyre, 1960) and in primates (Darian-Smith, Johnson and Dykes, 1974). Psychophysical studies in man suggested that A-beta fibres serve a purely "tactile" function despite their ability to respond to cold stimuli (Johnson, Darian-Smith and La Motte, 1973). Further, in disease states involving selective decrease in the number of large myelinated fibres, these is a loss of perception of light touch (Dyck and Lambert, 1968).

Dissociation of warmth and cold perception was demonstrated in both pressure and local anaesthetic blocks. The loss of warmth perception many minutes before loss of cold perception in local anaesthetic block has been found by others (Zeng, Fruhstorfer, Holte and Hensel, 1973) and the loss of cold before warmth in pressure block is also in agreement with most studies (Sinclair and Hinshaw, 1950).

In both pressure and local anaesthetic block, cold perception was impaired contemporaneously with change in conductivity of A-delta fibres and was lost with the disappearance of these potentials. In one experiment, after cold perception was completely abolished, a potential in the A-delta fibre range persisted but its conduction time was considerably increased and its amplitude was reduced. This is consistent with the emergence from the blocked area after a time delay of activity in a reduced number of fibres. However these remaining fibres would not transmit two volleys 20 m.sec. apart. The discharge rate at which A-delta fibres in man respond to a cold stimulus is about 50 /sec. (Hensel and Boman, 1960). These partially blocked fibres could not respond at this rate, and it is unlikely that they were capable of conveying reliable information about cold stimuli.

The correlation of perception of warmth and heat with C fibre function is consistent with the findings in primates (Hensel and Iggo, 1971; Darian-Smith *et al.*, 1973) and with recent micro-electrode studies in man by other workers (Torebjörk and Hallin, 1973). An interesting observation during

pressure block when myelinated fibres were inactive was the interpretation of an extremely cold stimulus as "heat". At this stage, only C fibres were capable of afferent transmission and presumably central interpretation of the evoked neural response was in terms of the sensory modality normally carried by these fibres.

Perception of the sharp quality of pinprick correlated with the activity of A-delta fibres, and the dull jabbing pain of electrical stimulation with C fibre activity. In a previous study (Burke, Skuse and Lethlean, 1973), the sharp "pricking" component of the electrical stimulus became apparent with the excitation of A-delta fibres, and further increases in stimulus intensity caused pricking pain without C fibre potentials being recorded. The transmission of pain sensation by C fibres has been inferred from reflex studies in animals (Clarke, Hughes and Gasser, 1935) and has recently been confirmed in man (Torebjörk and Hallin, 1973).

The pin has traditionally been regarded as eliciting two sensations, an early pricking pain abolished by pressure block and a delayed dull pain abolished by local anaesthesia (Lewis and Pochin, 1937). These workers and others (Landau and Bishop, 1953) have suggested that the early response is conducted by A-delta fibres and the later component by C fibres. However, the experience of the "second pain" is variable and its existence as a genuine sensory phenomenon has been questioned (Jones, 1956). In view of these doubts and the confirmation of the present studies that pain can be mediated by both A and C fibres, the role of the pin in neurological diagnosis may be restated. The ability to discriminate a stimulus as "sharp" or "blunt" is dependent on A-delta fibre function, while the appreciation of an adequate stimulus as "painful" can be mediated by A-delta or C fibres. By consideration of both these components, as well as other sensory modalities, peripheral nerve dysfunctions may be definitively characterized in terms of fibre group involvement.

SUMMARY

In awake human subjects, neural responses in cutaneous nerves to electrical stimulation were recorded with intrafascicular tungsten micro-electrodes. Changes in the activity of individual fibre groups during blocking procedures were recorded and correlated with simultaneous alterations in the perception of standardized stimuli. Light touch sensibility in hairy skin was mediated by A-beta-gamma fibres, cold and pinprick by A-delta fibres and warmth and dull pain by C fibres.

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MUSCULAR DYSTROPHY IN YOUNG GIRLS

B.A. KAKULAS, P.E. CULLITY and P. MAGUIRE*

Muscular dystrophy in adult females is not unusual. This type of disorder is usually less drastic in its effects than juvenile muscular dystrophy e.g. dystrophia myotonica, limb girdle dystrophy, and the facio-scapulo-humeral dystrophies. In contrast muscular dystrophy in your girls is unusual and because of this has aroused special comment (Johnston, 1964; Penn, Lisak and Rowland, 1970; Gardner-Medwin, 1971).

Recently many advances in classification of the dystrophies have resulted from more intensive study and the use of sophisticated investigative techniques. Among the more important of these advances is the recognition of proximal muscular atrophy of spinal origin which is of autosomal recessive inheritance. A difficulty in the recognition of this disorder is its frequent association with a moderately elevated serum creatine kinase level (Kugelberg and Welander, 1956).

The records of the Neuropathology Department of the Royal Perth Hospital over the past 10 years contain data on 7 young girls with "muscular dystrophy". Of these three are excluded from the present report for the following reasons. One has been shown due to hypoplasia of type II muscle fibres and was manifested as congenital non-progressive myopathy. This case has been reported previously (Matsuoka, Gubbay and Kakulas, 1974). Another was shown to have spinal muscular atrophy and the third was found to be due to symptomatic hypotonia.

The remaining four cases represent the body of this report. The onset of the disease occurred in each of these patients in early childhood: there was muscle weakness, a myopathic electromyogram, elevation of the serum creatine kinase level and muscle biopsy showed "dystrophic" histopathological features. Each of the four represents a somewhat different entity and is thus instructive. The first case is of a seemingly dystrophic process but the condition has remained relatively non-progressive, but contractures have developed. The second is a girl with two brothers who are also affected. It is noteworthy that this is the only one of the four cases which may be considered to be "Duchenne-like" (Stern, 1972). The third is an unusual dystrophy of limb girdle type with facial involvement. The fourth is distal in type and only slightly progressive.

CASE REPORTS

CASE 1

This girl is now 11 years of age, 149 cms. tall and 26.55 kg. in weight. Her disorder has been characterized by progressive contractures and scoliosis, but there has been little deterioration in her muscle weakness. She is the only member of her family afflicted with any form of muscle disease. Her pedigree is documented for five generations with 52 individuals. She has two sisters and both are normal. Her parents are alive and well.

She was first seen at the age of 3 yrs. 8 mths. with a history of increasing tendency to walk on her toes. She is the

* Department of Neuropathology, Royal Perth Hospital

eldest of three girls. Pregnancy and labour were normal. Foetal movements were normal. She was an "energetic baby" and showed normal early development. She sat at 7 months, crawled at 8 months, walked at 15 months, ran soon afterwards and spoke in sentences at 18 months. However, she was always "clumsy" when walking, with frequent falls, and she never ran fast. Physical examination revealed an increase in lumbar lordosis and contractures of a few degress in both tendo Achilles. There was severe weakness of her neck and of trunk flexion, moderate weakness of proximal muscle groups of upper and lower limbs and weakness of the anterior compartment muscles of the legs. There was no obvious wasting or pseudohypertrophy. There was generalised reduction in muscle tone. Tendon reflexes were all absent except the ankle jerks which were sluggish. Serum creatine kinase (C.K.) activity was 1400 international units (normal < 65 I.U.). Muscle biopsy (B67/1582) showed normal muscle fibre diameter of 40 micra. No abnormal variation in muscle fibre size and no increase in interstitial fat was seen. There were occasional areas where sarcolemmal nuclei were enlarged and vesicular, with prominent nucleoli. As well as these "regenerative" changes there were focal collections of round cells in the vicinity of blood vessels. The changes were considered to be consistent with a "primary" disorder of muscle with degeneration and regeneration, but they were not diagnostic in themselves. Electromyography (E.M.G.) was performed 24/4/67 on the right deltoid and right quadriceps muscles. There was no evidence of spontaneous activity and on maximal voluntary effort the interference pattern in the deltoid muscle was questionably increased, but was normal in the quadriceps. It was concluded that the changes in the right deltoid were consistent with a primary myopathy rather than denervation.

The patient's course has been one of slowly increasing contractures rather than of increasing weakness. At the age of 5 years and 7 months the tendo Achilles were lengthened but the contractures in these tendons have since recurred. At 9 years biceps tenotomy for contracture of the right elbow was undertaken. At the age of 10 years a Milwaukee brace for scoliosis was prescribed. Despite these physical handicaps she has developed some normal skills and plays the piano. She is a popular child who was elected vice-captain of the faction sports despite the fact that the only sport she can play is catch-ball. Her school reports are above average. She is unable to run but manages to climb stairs which have a hand-rail. She rides a large tricycle but tires quickly. She is able to dress herself, needing only a little help.

She was reveiwed in January 1975. She was found to be a bright, thin child with pronounced scoliosis and lordosis. She walked with difficulty in her brace, taking small steps with the heels raised and swaying from side to side with a tendency to invert her feet. All joints except the wrist and knees were severely affected by contractures. These prevented her from raising her head off the pillow or lifting her arms vertically. She was unable to flex her trunk. There was very little subcutaneous fat and muscle bulk was generally reduced. There was no enlargement of any muscle. Normal muscle power was present in the face, hands and wrists, knees and ankles. Abduction of the arms was very weak and there was winging of the scapulae. Other muscles showed moderate weakness. Her range of movement was extremely limited due to the contractures. All tendon reflexes were absent. The plantars were flexor on both sides. There was no sensory loss, fasciculation or myotonia. Serial serum creatine kinase levels were as follows: in 1967 – 1400 units (normal <65); 1970 – 400 units (normal <65); 1973 – 3100 units (normal 25-200); 1975 – 1010 units (normal 20-130). E.C.G. was within normal limits. The E.M.G. was repeated in 1975 and was reported on as follows.

"Both the right biceps and right quadriceps muscles showed a very patchy appearance. In some area there are frank myopathic interference patterns with increased numbers of short duration poly-phasic potentials, whereas in others the appearances were relatively normal; in yet another there was a frank diminution of interference patterns with high amplitude long duration potentials. Nerve conduction and latencies were normal. In conclusion it is considered that the myopathic process is most likely present but there were some areas of apparent denervation."

Thus this patient had a proximal myopathy and presented at the age of 3 years and 8 months. Substantial elevation of creatine kinase was present on several occasions and scoliosis occurred, but with little deterioration of muscle weakness. She was thin and spindly without enlargement of muscles. She remains ambulant and is of high intelligence. Her contractures are probably due to lack of adequate physiotherapy.

CASE 2

This is an 8 year old girl with "Duchenne-like" features and with two affected brothers but no other family history despite a pedigree which documents 72 individuals. The patient is the second of four children. She was born in England in 1966 with an English father and a Mauritian/French mother. The pregnancy and labour were normal and there were no early problems. On direct questioning the mother recalled that when her daughter was an infant her arms felt unusually long and seemed to twist when she was picked up. She sat when supported at 6 months, never crawled on all fours but shuffled at 9 months. She stood at 17 months and walked at 18 months. She ran soon afterwards. The family came to Australia in 1968. She began walking on her toes when 5 years of age. The parents never suspected an abnormality until a school teacher suggested that they should seek medical attention for an older brother (then 8 years) because of his peculiar gait, inability to run and frequent falls. These features had affected the elder brother since he was 12 months of age.

When the patient was 7 years of age she showed the typical waddling, lordotic gait, and had enlargement of the calf muscles and winging of the scapulae. Gowers' sign was positive. Serum C.K. level was found to be 9530 (normal < 110 units). Muscle biopsy of the vastus lateralis (X73/2323) showed great variation in muscle fibre diameter (from 5-35 micra) with an increase in interstitial fat and fibrous tissue. Focal necrosis and regeneration was present. Histochemical methods

revealed a loss of the normal checkerboard pattern with type II fibres predominating. On this basis it was considered that the changes were primarily dystrophic but differed from Duchenne dystrophy because of the focal nature of the lesions and the lack of large rounded fibres which are typical of that condition. E.M.G. (6/11/73) was reported as follows.

"There was no spontaneous activity in the right biceps muscle. On voluntary efforts there was an increased interference pattern. Latency studies and velocity studies gave normal results. It was concluded that a myopatic process existed."

The male siblings both showed very similar features and both had greatly elevated serum C.K. levels (5250 units and 6135 units). The clinically normal sister had normal serum C.K. levels.

In January, 1975, 18 months after she first presented the patient complained of falling a lot. However, she could swim and run but was unable to keep up with normal children and tired easily. She again showed a waddling gait, lordosis, winging of the scapulae, enlargement of the calf muscles and Gowers' sign. She walked on her toes all the time but was able to get her heels to the floor. The facial muscles were unaffected. The hip and pelvic girdle musculature and shoulder girdle musculature were more severely involved than the distal muscles which showed normal power except for dorsi-flexion of the ankle. Tendon jerks were absent. The plantars were down-going. There was no sensory loss and no contractures. Her intelligence quotient was 95 (Binet). Her C.K. level was 5490 units (normal 20-120 units).

CASE 3

This girl is now 23 years old and has facial and limb girdle dystrophy associated with "schizophrenia". She first showed symptoms when she was 12 years old. She is an only child born after 11 years of marriage when her mother was aged 39 years. Her father died at the age of 41 years from coronary artery disease, when the patient was only 14 months old. No details of his family history are known. The mother's pedigree shows no relevant disorder but a maternal aunt has thin shoulders, while a cousin has large calves. There are 25 documented individuals in the pedigree. The patient was born by forceps delivery after a normal pregnancy in which there was a lack of foetal movement. There were feeding problems in infancy. She was never a "lively" baby. She sat at 6 months, crawled at 10 months and walked at 15 months. She never ran. She was slightly deaf and did not speak until she was 4 years old. Her mother noticed winging of her shoulder blades when she was 5 years old. From early childhood the left side of the face had always drooped. She was always shy, withdrawn and uncommunicative. She never joined in other children's games. Her intelligence was rated dull normal. She was in special classes from the age of 9 years. At the age of 12 years increasing weakness of the arms, especially the left, obesity and unusual gait were noted. Psychological and vocational problems were a feature at this stage. At 13 years she began to fall frequently.

In 1966, when she was 14 years of age, she was first seen in our clinic. Her face was myopathic and she was unable to raise her arms above her head; winging of the scapulae was noted. She used her right arm for assistance when asked to arise from the floor. She walked slowly with a waddle and showed lumbar lordosis. There was muscle weakness of the face, neck and shoulders. The hips were much less affected. In the upper limbs there was more severe weakness on the left side than the right. The distal muscles of upper and lower limbs were normal. Tendon jerks were all absent. There was no sensory loss and there was no enlargement of the calves. C.K. level in 1966 was 135 I.U. (normal 3-65 I.U.). Muscle biopsy (B66/1281) of the left deltoid showed enlarged muscle fibres (60-80 micra). There was an increase in interstitial fat and there were several foci of necrosis and regeneration. It was concluded that the biopsy was consistent with a "restricted" myopathy but with some evidence of continuing activity. "Schizophrenia" was "fully developed" at the age of 17 years. She was in mental institutions for many months at that time. She became confined to a wheelchair at this stage. She was withdrawn and apathetic and she became very obese. She was reviewed in January, 1975, and it was found that despite her 94.5 kg. in weight she could still walk a few steps and put her heels on the ground when asked. She was unable to rise from the wheelchair without assistance. She showed weakness of the proximal muscles of the shoulder girdle, and was unable to elevate her extended arms but could put her hands on her head. The pelvic girdle muscles were less involved while the distal musculature of upper and lower limbs was of almost normal power. The face was totally myopathic, i.e. immoble and with a protruding lower lip. There was no myotonia or fasciculations. Tendon reflexes were absent and there was no sensory loss. The C.K. level was now 77 units per litre (normal 22-130 units). On 10th February, 1975, an E.M.G. was performed and it was reported as showing evidence of a "myopathic" process involving the deltoid, biceps and quadriceps muscles on the right side and with normal median motor and sensory conductions. (E.M.G. in 1968 had shown no spontaneous activity but the patient became distressed before the examination was completed.)

CASE 4

This patient shows a very slowly progressive, mainly distal myopathy associated with short stature and hyperhidrosis. She is now 18 years old. She was first seen when she was 9 years old. She was a product of a normal pregnancy induced at 31 weeks because of disproportion. She was delivered by a breech "version" and with forceps. It was said that the baby was "knocked around" soon after birth and she was not seen by her mother for three days. She sucked poorly. She smiled, sat, spoke and became "toilet-trained" at the normal times. She never rolled over by herself. She could stand with support at 19 months and walked at 2 years. She always had difficulty walking and running, and had frequent falls. At about the age of 5 years she began to drag the left foot when she was tired. The pedigree analysis undertaken over five generations and including 119 individuals shows that she was the only member with a myopathic disorder.

When she was first seen at the age of 9 years she could not sit up without using her hands and could not lift her head from the pillow. Her face was long and expressionless. Wasting of the sterno-mastoids was noted. The upper limbs and shoulder girdle muscles showed weakness, especially of the distal muscles where muscle bulk was diminished. In contrast to the atrophy of the distal muscles, proximal muscles of the thigh and shoulders were normal. Both Achilles tendons were shortened. Tendon reflexes were absent except for the knee jerks which were diminished. Sensation was normal. There was no myotonia, tongue fibrillations or fasciculations. C.K. level was 640 I.U. (normal 35-65 I.U.). E.M.G. of the left tibialis anterior in 1966 showed features "consistent with myopathy and with one myotonic discharge". Muscle biopsy of the left gastroncenmius muscle (B66/2860) showed excessive variation of muscle fibre diameter (50-100 micra) with increase in interstitial fat and connective tissue. There was focal necrosis and regeneration. One ring fibre and a short chain of 10 nuclei were noted. These changes were considered to be consistent with a primary myopathy.

Her progress has been unusual. Weakness has remained relatively mild and there has been only slight deterioration. The serum C.K. level has been consistently elevated as follows:

1966	640 units	(Normal: 3- 65)
1969	560 units	(Normal: 3- 65)
1971	400 units	(Normal 0- 70)
1973	520 units	(Normal: 5- 45)
1975 January	2590 units	(Normal: 25-130)
1975 March	2400 units	(Normal: 25-130)

She has required a short caliper on the left foot but managed to play soft ball at school. Tendon lengthening operations have been performed and she now walks well and leads an active life as a clerk in the public service. She drives a car. She can climb stairs, types and has learned the piano. She was last reviewed in January, 1975, at the age of 17 years. She was found to be short (143.5 cm.) with a round-shouldered posture. She complained of excessive sweating with very wet hands and feet, and there was palmar erythema. The distal muscles were weak. Tendon jerks were absent. Sensation was normal. There was no clinical myotonia or muscle enlargement. The findings therefore were the same as in 1966 except for the appearance of slight weakness in the hip girdles. The C.K. was 520 i.u. litre (normal 5-45).

DISCUSSION

In Case 1 the term 'arthrogryposis' has been mentioned by attendants but this is not strictly applicable since contractures were not present at birth. The contractures in this case, as in others with muscular dystrophy, are most probably due to lack of adequate physiotherapy. This patient has a proximal myopathy, static or only very slightly progressive, with typical laboratory findings of dystrophy. Case 2 shows features of Duchenne-like dystrophy. However, in the strict sense this term should only be used for x-linked muscular dystrophy. The occurrence of a similar syndrome in a female is, therefore, better referred to as pseudohypertrophic muscular dystrophy of autosomal inheritance. Such a condition is well recognised (Dubowitz, 1960; Jackson and Carey, 1961; Stern, 1972). This patient can certainly be considered to show autosomal recessive inheritance as she has two brothers with the disorder and her parents are normal. Her clinical features do closely resemble x-linked (Duchenne) dystrophy although they are somewhat milder in their manifestations — a feature reported by Walton (1955) in the original discussion of this subject. Case 3 presents unusual features of asymmetric limb girdle dystrophy with facial involvement and psychosis. Limb girdle and facial dystrophy are described by Stevenson (1953). Case 4 is also unique, showing a distal myopathy with short statue, hyperhidrosis and palmar erythema. This girl, now 17 years of age, began to show signs of illness at the age of 5 years. An interesting point is the lack of certain progression. She is gainfully employed, is able to drive a car and is ambulant within reasonable limits, despite laboratory evidence of a truly dystrophic process. Distal dystrophies are known in infancy (van der Does de Willebois, Bethlem, Meyer and Simons, 1968; Magee and DeJong, 1965) but cases of this present type are rare.

Notwithstanding this report, x-linked muscular dystrophy can be expected in females in certain theoretical situations. One of these would be the XO or Turner's Syndrome. In fact a typical case of Duchenne-type dystrophy has been described in Turner's Syndrome (Ferrier, Bamatter and Klein, 1965). Clinical weakness is known to occur in female carriers of muscular dystrophy in the heterozygote state but this is never very severe (Emery, 1963). Other theoretical situations are a mutation occurring in the x chromosome of a father, married to a carrier female, or the mating of a male patient with the x-linked disease with a carrier female. The actual occurrence of these possibilities is not known to exist.

SUMMARY

Muscular dystrophy occurred in four girls. In only one of these was the syndrome both proximal and with pseudo-hypertrophy, thus clinically resembling the x-linked Duchenne type of the disease. The evidence for a primary dystrophic process existing in the four individuals is based on the laboratory findings of very high serum creatine kinase levels, myopathic E.M.G. appearances and muscle biopsies. However, each case is clinically different (one is proximal with contractures, another limb girdle with facial involvement and the fourth is distal) and worthy of documentation.

The recent demonstration of a neurogenic basis for several myopathies previously considered to be dystrophic in nature has not caused us to revise our view that true muscular dystrophy does occur in girls but that the "Duchenne-like" type is rare.

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AUTONOMIC DISTURBANCES PRODUCED BY LUNG CANCER: A REPORT OF TWO UNUSUAL CASES.

J.C. WALSH, P.A. LOW, and J.L. ALLSOP*

Lung cancer is a common malignancy which may present with various, and often unusual, clinical symptoms and signs (Joseph, 1965). Considerable attention has been given to the remote effects of lung cancer on the central and peripheral nervous system, but the more common type of involvement is either by metastasis to the brain or spinal column, or by direct invasion of the brachial plexus or of nerves within the thorax.

Direct neural invasion may produce impairment of autonomic function in the region; for example, apical lung tumours may produce Horner's syndrome (Pancoast, 1932), but in most other situations impaired function is not obvious either to the patient or to the examiner. Localised autonomic hyperactivity has not been previously reported, and for this reason the two following clinical cases are presented.

CASE HISTORIES

CASE 1

A 40 year old Frenchman was referred from New Caledonia with a history of pain below the left shoulder-blade spreading around the trunk on the left to just above the umbilicus. There had been no rash or other symptoms. The pain was relieved slightly by lying with the legs up and by exercise. Over the past few months his weight had decreased by 10 Kg.

On examination, there was a band on the left side of the trunk which extended from the T8 spine to the L1 spine in the mid-line posteriorly, and to the xiphoid and umbilicus anteriorly (Fig. 1); within this band the skin was pale and cold, and piloerection was present (Fig. 2). Beads of sweat exuded from the skin. Pain appreciation was mildly impaired in this region. Apart from a mild thoracic scoliosis convex to the right there was no other abnormality.

On admission to hospital the intensity of the pallor, piloerection and sweating varied from time to time but could be increased by rubbing the affected area. This would also produce a burning pain in the mid-line anteriorly.

Plain X-rays of the thoracic and lumbar spine were normal: the hemoglobin, white cell count, biochemistry screen and spinal fluid were normal, and the blood WR and Mantoux test were negative. There was a minimal opacity in the left costo-phrenic angle on the chest X-ray. The ESR was 27 mm/hour (Westergren). A myelogram was normal. Intradermal histamine was injected bilaterally, and there was no response in the abnormal area, suggesting that the lesion was distal to the dorsal root ganglia. Considerable pain relief was obtained by Xylocaine injection of the left dorsal sympathetic trunk at the T7 and T8 levels and for this reason a surgical sympathectomy was planned.

A left thoracotomy was performed and the pleura in the paravertebral region was found to be thick and indurated, and several firm lumps were palpated. The autonomic trunk could not be identified in this tissue which was anaplastic large cell carcinoma of pulmonary origin. Following radiotherapy he was free from pain, and there was no abnormal autonomic activity. Ten months later there was a recurrence of mild pain in the same area which responded to a second course of radiotherapy.

* Department of Neurology Royal Prince Alfred Hospital, Sydney

FIG. 1. Case 1:
The region of reduced sensation and spontaneous sweat secretion is indicated by the marked area.

FIG. 2. Case 1: The lumbar area, illustrating unilateral pilo-erection.

CASE 2

A 61 year old butcher presented with a history of dull but constant pain in the right shoulder for 15 months. There was no weakness, wasting or sensory deficit, and the reflexes were symmetrical. Marked spontaneous sweating was present over the right side of the face and neck, right hand and right cubital fossa (Fig. 3). The external jugular vein was distended on the right side, and the presence of an apical lung lesion was demonstrated by X-ray examination.

Electromyography was performed on the right deltoid, triceps, forearm extensors, abductor pollicis brevis and abductor digiti minimi and no significant abnormality was demonstrated. Motor conduction velocity in the forearm segment of the median and ulnar nerves was 56 M/sec in both nerves with terminal latencies of 3.6 m.sec. and 2.7 m.sec. respectively. On stimulating the index and little fingers sensory action potentials of latency to peak 2.8 m.sec. and 2.5 m.sec. were recorded from the right median and ulnar nerves respectively at the wrist via surface electrodes. The amplitudes were each 17 μV.

He was treated with radiotherapy but the pain did not remit. An exploratory operation was performed, and the tumour was found to be invading the proximal ends of ribs 2 and 3, and also the sympathetic trunk. These involved structures, and the upper lobe were removed. The patient is now free from symptoms.

DISCUSSION

Direct invasion of the peripheral nervous system by malignant tissue is a common occurrence, but consequent overactivity of the autonomic nervous system has not been reported previously. Both cases in the present report were characterized by profuse spontaneous sweating in the territory of nerves directly infiltrated by lung cancer; in the first case several intercostal nerves were involved, and in the second case the sympathetic trunk was involved. In both cases dull, constant pain was present.

The infiltrating malignant tissue could produce both pain and excessive sweating by directly stimulating the sensory afferent fibres; the central projection of the stimuli would produce pain, and convergence of these impulses with the sympathetic efferent outflow could produce excessive sweating. In addition, it is well known that nerve injury will on rare occasions produce causalgia, a condition characterised by excruciating, persistent, unrelenting and demoralising pain. Although

FIG. 3. Case 2: Spontaneous sweating over the right hand, face and cubital fossa is demarcated by the application of Alizarin Red.

the pain experienced in these two cases bears no similarity to causalgia, the autonomic overactivity could be due to a similar mechanism. Doupe, Cullen and Chance (1944) suggested that fibre-fibre interaction, or an artificial synapse, may occur at the site of a nerve injury, and the experimental studies of Granit, Leksell and Skoglund, (1944) give support to this theory. It has been suggested that the constant flow of sympathetic efferent impluses stimulates sensory afferent fibres at the site of injury, producing the pain characteristic of causalgia. It is possible that in the present two cases sensory afferent impulses are producing cross stimulation of sympathetic efferent fibres, with excessive spontaneous sweat secretion. It was noted that brisk rubbing of the affected area in Case 1 produced both increased sweat secretion and a dull, burning painful sensation, a phenomenon which could be due to cross stimulation between sensory and autonomic fibres in the intercostal nerves. By contrast the unusual distribution of increased sweating in Case 2 suggests that the site of the lesion is within the sympathetic trunk with cross stimulation produced by afferent fibres from the viscera.

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SUMMARY

Two cases of malignant infiltration of nerve are presented in whom a major feature was excessive spontaneous sweat secretion. The possible mechanisms for the production of this unusual symptom are discussed.

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ENTERIC COATED LEVO-DOPA IN CLINICAL PRACTICE

E.P. HICKS and M.W. O'HALLORAN*

In November 1973 the results of treatment of 90 Parkinsonian patients collected over the previous four years were reviewed. It was observed that at least 12% of these patients failed to benefit. Most of the failures were due to the intolerable side effects of standard Levo-dopa. Peripheral dopa decarboxylase inhibitor drugs could not be obtained for any of these patients. In spite of the highly unpleasant gastric side-effects most of these patients preferred to continue with Levo-dopa therapy although the quality of their life was miserable in the extreme. Enteric coated Levo-dopa became available July 1973 and during the course of the clinical trial, which commenced on the 13th August, 1973, twelve of these patients formed the nuclear group for the evaluation of the new formulation. The enteric coating was designed to resist digestion in the stomach and to release its active drug in the alkaline medium of the duodenum. It was postulated that this would increase bio-availability by avoiding decarboxylation in the stomach. Preliminary absorption studies confirmed this concept (Hinterberger, H., and Anthony, M., *in press*).

MATERIAL AND METHODS

The protocol for this study was similar to that used in the evaluation of standard Levo-dopa (Hicks and Rischbieth, 1971). The grading of disability was similar to that proposed by Hoehn and Yahr (1967). Nineteen patients were included in the trial. Eleven were females, and of these, nine were poor responders to standard Levo-dopa. In addition, one of these also suffered from post-stabilization regression with the "on-off" phenomenon. One female was included because of severe postural hypotension on standard Levo-dopa; the other was an ordinary uncomplicated new case. Of the eight male cases, two were included because of post-stabilization regression, having previously responded well to standard Levo-dopa; three were new cases with extreme rigidity, one was a post-gastrectomy case, and two were ordinary uncomplicated cases of idiopathic Parkinson's disease. All patients, with the exception of Case 3, (Table V), were admitted to hospital for stabilization. The dosage schedule commenced at 200 mg. of the enteric coated Levo-Dopa daily, with increments of 200 mg. at three day intervals, to achieve a daily dose of 1.6 grams by the end of the third week. The total daily dose was divided into eight portions given at two-hourly intervals. The response in the initial cases was so good that a rapid method of stabilization was substituted, but following the occurrence of a toxic reaction in one individual, this was modified to an intermediate rate. However, one further toxic reaction persuaded us to revert to the original method which has continued to give uniformly good results. No attempt was made to regulate the times of medication to coincide with the intake of food.

Since the daily dosage level achieved for each patient was based on clinical assessment, differences between time intervals for the same Levo-dopa preparation and between Levo-dopa preparations were statistically analysed using the non-parametric Mann-Whitney U test (Siegel, 1956).

* Queen Elizabeth Hospital, Adelaide

RESULTS

The overall assessment of the results is shown in Table I. Good and very good responses were obtained in 63% of the group and a fair response in a further 21%. Case 13 has been recorded as a failure because of initial temporary regression and failure to control her pre-existing postural hypotension, but both features improved soon after the official closure of the trial on the 1st August, 1974. The other notable failure, Case 4, a post-gastrectomy subject, was included in the trial in the belief that gastric irritation would be avoided. He proved to be psychologically unsuitable and suffered distressing side-effects, probably from excessive absorption of ordinary doses, and he was withdrawn from the trial. He has now re-entered the continuing trial and is responding well to smaller doses.

TABLE I

Results of treatment with enteric coated Levo-dopa 13/8/73 to 1/8/74. 19 patients. Age Range 44-80 years

	Very good	Good	Fair	Temporary Regression	Failed
8 Males	4	1	2	–	1
11 Females	6	1	2	2	–

TABLE II

Duration of therapy with enteric coated Levo-dopa

	Males	Females	Total
3 Months	1	1	2
3-6 Months	3	6	9
6-9 Months	2	2	4
10 Months	1	1	2
11 Months	1	–	1
11½ Months	–	1	1
Total	8	11	19

TABLE III

Range of enteric coated Levo-dopa dosage

		Gram per day
Smallest effective dose	100 mgm 6 times daily	0.6
Average therapeutic dose	200 mgm/2 hourly/8 times daily	1.6
Largest dose without side effects	600 mgm/2 hourly/7 times daily plus 800 mgm once daily	5.0

Three of the new patients presented with extreme rigidity, and all gained rapid relief.

The range of duration of therapy is shown in Table II and the range of daily dosage is shown in Table III. The commonest initial stabilizing dose was found to be 1.6 grams daily. The exceptionally high dose of 5.0 grams daily was well tolerated without side-effects by a 48 years old male, Case 17, in an attempt to control his post-stabilization regression syndrome. Mild anorexia appeared when 5.2 grams daily was used, but this disappeared on returning to the 5.0 gram daily dose.

An analysis of the side effects is shown in Table IV. It is interesting to note that 60% of the patients have been completely free from side-effects. A further 20% have had easily reversible, mild, or transient side-effects, and there has been no evidence of bio-chemical, haematological

TABLE IV

Side Effects

		Males	Females	Total
None		5	7	12
Transient nausea		–	1	1
Anorexia		–	1	1
Nausea & weight loss relieved by reduction of dose		1	–	1
Increase of postural hypotension (pre-existing)		–	1	1
Mild dyskinesia of facial muscles		1	–	1
Internal tremor Vertigo Insomnia Pressure in Head	Acute toxicity	1*	1*	2
				19

* Both patients on rapid stabilisation: easily relieved – good result.

TABLE V

Analysis of daily dosages of enteric coated Levo-dopa in grams during 1973-74

Case No.	Age	Sex	Weight (Kg.)	Months of Treatment 3	6	9	12
1	69	F	56	1.6	1.6	1.6	1.6
2	66	M	80	2.0	2.4	2.4	2.4
* 3	66	F	71	0.15	0.3	0.6	0.6
4	68	M	66	0.8			
5	71	M	73	1.6			
6	51	M	65	1.6	1.6	1.6	1.6
7	72	M	73	1.6	2.4	3.2	
8	74	F	52	0.4	0.5	1.6	1.5
9	65	F	54	0.8	0.7	1.2	
10	44	M	69	1.6	2.0		
+ 11 (3)	72	F	46	1.6			
12	75	F	69	1.6	1.6		
13	69	F	53	1.6	2.2	0.2 #	
14	75	M	84	1.6	1.6	1.6	1.6
15	80	F	70	1.2	0.6		
16	77	F	53	1.6	1.6	1.6	
+ 17 (15)	48	M	93	4.0	4.8	5.0	
18	71	F	44	1.2	1.2		
19	53	F	67	1.2			
Sex Ratio F/M	11/8						
Mean	66.7		67	1.46	1.67	1.87	1.55
Mode				1.6	1.6	1.6	1.6
Standard deviation				0.77	1.09	1.31	0.57
Coefficient of variation				56.2 %	65.5 %	69.7 %	36.9 %
Probability **					0.5	0.4	0.7
Probability ***				0.001	0.03	0.2	0.2

* Also receiving 2.5 gm daily of standard Levo-dopa at each recorded interval.

** Compared with treatment dose at 3 months using Mann Whitney U test corrected for ties.

*** Compared with control patients on standard Levo-dopa (Table VI) using Mann Whitney U test corrected for ties.

+ Number in parenthesis is the case number in the control series (Table VI)

\# Temporary accidental omission of full regular dose.

or electrocardiographic abnormalities. Two patients developed toxic reactions during the early stages of the trial when rapid stabilization methods were being tentatively explored. The reaction in each case was identical and was characterised by sensations of "internal" tremor, vertigo, insomnia, and a feeling of high pressure within the head. In both cases the symptoms were promptly dispersed by reducing the size of the dose and the rate of its administration. Both patients achieved an excellent overall improvement in the final assessment. Strict adherence to the slow method of stabilization has abolished this unpleasant reaction in subsequent cases.

Comparison was made of the dose required for initial stabilization and maintenance on enteric coated Levo-dopa with a control series of the first 19 cases treated with standard Levo-dopa in the 1970 and 1971 series. These series were roughly comparable with respect to age, weight and severity of disease (Tables V and VI). With twelve severely disabled patients as the nucleus of the test group it was deemed cruelly unethical to attempt any form of cross-over evaluation. However, a comparison is currently being made retrospectively with the last nineteen patients to receive standard Levo-dopa, in order to assess the bias created by the increased experience of the authors in handling new drugs. The changeover of Case 3 in Table V to full enteric-coated therapy has now been completed with excellent results in average dosage (1.6 grams). In the arbitrary selection of the 19 control patients it was apparent that Cases 11 and 17 were duplicated, but it was not thought that this would introduce an unfair bias into the results after an interval of three years. It was also impossible to allow the twelve nuclear cases to act as their own controls when comparing standard Levo-dopa with enteric coated Levo-dopa because they had all had to be poor responders.

TABLE VI

Control patients on standard Levo-dopa in 1970-71. Daily dosage in grams.

				Months of Treatment			
Case No.	Age	Sex	Weight (Kg)	3		9	12
1	52	F	52	4.0	4.	4.0	3.0
2	44	M	68	5.25	6.	2.25	2.25
* 3 (11)	72	F	46	2.0	2.	1.5	1.75
4	74	F	63	4.75			
5	50	F	76	0.6	0.	0.5	0.5
6	55	M	82	2.25			
7	58	F	61	0.6	0.	0.5	0.5
8	75	M	56	2.75	2.75	1.75	1.5
9	61	M	70	1.5	3.	3.0	3.0
10	66	M	68	5.25	4.75	3.5	3.5
11	66	M	76	3.0	1.	0.75	0.75
12	64	F	37	2.5	2.	2.5	2.5
13	60	F	40	0.6	0.	0.6	0.6
14	81	F	72	4.0	3.	3.0	
*15 (17)	48	M	93	5.25	5.75	5.25	6.25
16	71	M	76	5.25	4.	4.0	4.0
17	61	M	110	5.25	5.75	5.25	4.5
18	55	M	62	2.5	4.	3.75	3.75
19	70	F	47	2.0	2.		
Sex Ratio F/M	9/10						
Mean	62.3		66	3.12	3.70	2.63	2.56
Median				2.62	2.87	2.5	2.37
Standard deviation				1.71	1.79	1.61	1.68
Coefficient of variation				54.8 %	59.7 %	61.1 %	65.8 %
Probability **					0.	0.4	0.3

* Number in parenthesis is Case number in Prodopa group. Table V.

** Compared with treatment dose at 3 months using Mann Whitney U test corrected for ties.

or highly intolerant to standard Levo-dopa in order to qualify for admission to this study.

In the opinion of the authors, the most meaningful analysis of the results is made when full initial stabilization has been completed and the early phase of the maintenance plateau has commenced. This occurs at approximately three months in the case of enteric coated Levo-dopa and at approximately six months in the case of standard Levo-dopa. The difference is not statistically significant.

Statistical analysis of the data in Tables V and VI has shown that the daily dosage of enteric coated Levo-dopa and of standard Levo-dopa did not vary significantly during the twelve months over which the data were collected, although, as can be seen from the Tables, individual patients did require some adjustment. Comparison of the mean daily dosages required with the two types of Levo-dopa used in this study show very considerable differences which are highly significant at the third and sixth month of the trial (Table V). Whereas the enteric coated Levo-dopa achieved effective clinical levels with 1.5 grams daily, the standard Levo-dopa achieved effective levels with a dose of 3.1 grams after the first three months ($P<.001$); the differences between the two forms of Levo-dopa were maintained throughout the study. However due to incomplete data at the ninth and twelfth period these latter differences did not achieve statistically significant levels. Furthermore, in the case of enteric coated Levo-dopa, the daily dosage required was far less variable (S.D. = 0.776 gm. per day at three months), than for the standard Levo-dopa (S.D. = 1.712 gm. per day at three months).

In the case of enteric coated Levo-dopa, after three months a satisfactory dosage range of between 0.8 and 2 grams daily had been achieved in 90% of patients, whereas 90% of the patients in the group on standard Levo-dopa required dosages between 0.6 and 5.25 grams a day.

Two deaths have occurred during the course of the trial (Table VII). Both patients were in the terminal stages of their disease when they entered the trial and both had pre-existing cerebral arteriosclerosis. Both received substantial benefit from the enteric coated Levo-dopa during the three months in which this treatment was given. No obvious causal relationship coud be established between the therapy and the factors responsible for death.

TABLE VII

Deaths During The Trial

	Case No. 11	Case No. 15
Age	72	77
Sex	Female	Male
Duration of disease	19 years	Many years
Disablement at commencement	Very severe	Very severe
P.S.R.S. & intractable nausea	Yes	Not previously treated
Duration of enteric coated Levo-dopa therapy	3 months	3 months
Associated features	Thalamotomy	Double hemiplegia
Result	Good	Good – return of speech
Side effects	Nil – nausea relieved	Nil
Comment		Easier nursing
Mode of death	Diarrhoea, coma, pneumonia	? C.V.A.
Cause of death	? Septicaemia, no brain pathology	No autopsy
Relationship of death to therapy	None	None

(P.S.R.S. = post stabilisation regression syndrome)
(C.V.A. = cerebral vascular accident)

A study of the post stabilization regression syndrome showed some interesting results. Two males entered the trial because of this syndrome. The younger, Case 10, had previously maintained a good control on standard Levo-dopa for two years, and the older male, Case 17, had been successfully maintained for three years before slipping from control. The younger man was completely relieved

by changing to enteric coated Levo-dopa in average dosage, but Case 17, although greatly improved, has, at the time of writing, failed to revert to the original state in spite of brief responses to each increment of the dose of enteric coated Levo-dopa which has now reached 5.0 grams daily. He continues to have trouble with intermittent shuffling of gait, although he is well controlled in every other respect. The recent addition of a 6 a.m. dose has brought an encouraging improvement in the gait.

Two females have also been observed with this syndrome. Case 11 almost certainly had the syndrome when she transferred from inadequate doses of standard Levo-dopa, but the increase in the severity of the symptoms made it difficult to decide whether this was a changeover phenomenon. However, the syndrome was completely reversed as the enteric coated Levo-dopa dosage increased and she gained substantial benefit in all respects during the three months prior to her death from other causes.

The other female, Case 18, was also elderly and had been transferred to enteric coated Levo-dopa as a result of inadequate dosage due to intolerable nausea on the standard preparation. At the time of writing she has achieved a fair degree of relief of her Parkinsonism without nausea and the "on-off" phenomenon is barely perceptible. In this case, the syndrome developed during the changeover period from the standard to the enteric coated form of the drug, and reversal occurred steadily as re-stabilization proceeded. Reversal was complete when pyridoxine was rigorously excluded from her diet. Therefore the overall degree of apparent relief of this post stabilization regression syndrome is assessed as occurring in at least 50% of the cases, and, depending on the definition of this disorder, may be as high as 75%.

DISCUSSION

The theoretical concept of improved bio-availability with an enteric coated preparation of Levo-dopa appears to have been fully vindicated by the results of this trial. There is a significant reduction of the dose required for stabilization and maintenance on the therapeutic plateau. The average stabilization time of three weeks is a significant reduction compared with the usual minimum of three months for standard Levo-dopa. Side effects have not presented any serious problems. The mean lowering of the dose is 53%, but this is not considered necessarily disadvantageous when compared with the much greater reductions in dosage claimed for combined therapy of standard Levo-dopa with peripheral dopa-decarboxylase inhibitor drugs (Barbeau 1973; Andrews and Somerville, 1974), since it appears that there is a high risk of abnormal involuntary movements developing with the combined therapy. For the same reason the additional one or two weeks required for the stabilization of the average case with enteric coated Levo-dopa is not regarded as a disadvantage since only one of our subjects has exhibited mild dyskinesia as a transient reversible side-effect. This study has shown that certain individuals may tolerate very large doses of enteric coated Levo-dopa without side-effects, and it has also been shown that some individuals can be introduced to the therapy much more quickly if urgency exists and careful supervision is maintained. The virtual absence of nausea with enteric coated Levo-dopa appears to give some support to the theory that part of this side-effect is due to local gastric irritation. Doses which are slightly in excess of the therapeutic optimum will produce effortless vomiting without much preceding nausea, and this is thought to be the result of brain stem stimulation. However, it seems that if excessively high doses are given, the vomiting centre is inhibited because emesis is not a part of the acute toxicity complex. In the experience of the authors the characteristic symptom complex of acute toxicity has not previously been encountered and may represent a new phenomenon. There are strong reasons for believing that pyridoxine is an effective antagonist of enteric coated Levo-dopa. Case 18 showed marked improvement when stopped from taking six cups of a chocolate vitamin tonic every day. Other cases have inexplicably relapsed after returning home from hospital and again responded to treatment on readmission. In several of these instances the family has been found to be obsessed with the virtues of vitamins. During the course of this trial no adverse interactions have been encountered with anti-cholinergic drugs, amantadine, tricyclic anti-depressants, or the benzodiazapines. In many new cases these adjuvants have proved to be superfluous.

It is greatly regretted that a study of blood levels of dopa and its metabolites has not been possible. It is hoped that the clinical thesis that much of the "on-off" phenomenon is related to low blood levels of circulating dopa may be put to the test by workers with the facilities for these investigations. On present clinical indications it would appear that the number of non or poor responders to L-dopa therapy will be reduced to a very low level, but a minimum of three years will be required before the necessary facts can be extracted. At this point in time, enteric coated Levo-dopa is seen as the most useful preparation currently available for the routine management of Parkinsonism, and although it is slightly more expensive than its progenitor, in our experience it is proving much less wasteful in the long term.

SUMMARY

The results of a clinical trial of enteric coated Levo-dopa are described for nineteen patients with Parkinsonism. Twelve cases comprise the nuclear group and all were intolerant to therapeutic doses of standard Levo-dopa. Seven cases were receiving Levo-dopa for the first time. Treatment periods ranged from three to twelve months. Of the whole group, 84% have improved. Of the poor responders to standard Levo-dopa 58% have improved markedly and the remaining 42% have improved to a moderate degree using clinical criteria. The mean stabilization dose was 1.5 grams daily and using the Mann-Whitney U test the difference is highly significant when comparison is made with the stabilization dose of 3.0 grams for standard Levo-dopa ($P<.001$) The method of stabilization is described; the commonest initial stabilization period is three weeks. Side-effects are dose-related. No side-effects have appeared in 60% of the patients and only mild or transient side-effects have appeared in 20%. A characteristic toxic reaction is described.

This enteric-coated preparation of the drug appears to control the "on-off" phenomenon in at least 50% of cases with this problem. The preparation is suitable for routine use in outpatients but added care is required to ensure that vitamin tonics are rigorously avoided. Two deaths are recorded during the trial, but analysis shows them to be unrelated causally to the therapy. Enteric coated Levo-dopa is recommended as the primary treatment in all new cases where Levo-dopa therapy is indicated. No adverse interactions have occurred with other commonly used anti-Parkinsonian drugs.

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FRONTAL AGRAPHIA, (INCLUDING A CASE REPORT)

J.J. VERNEA* and J. MERORY+

The rarity of cases of frontal agraphia, as first described by Exner (1881) casts doubts as to the very existence of this entity. However, even though such cases are now well documented, their pathogenesis is far from clear. Agraphia arising from lesions of the dominant prefrontal region is generally considered to be either of aphasic or of apraxic nature (Botez, 1974). The following observations are presented not only because cases of front agraphia are very rare, but also because they evinces the role of prefrontal disorder in the genesis of agraphia.

CASE REPORT

P.D., a 57 year old male clerk, had a history of adenocarcinoma of the sigmoid colon, only partially removed at operation in September 1972, when the lesion was found to be adherent to and invading the bladder and the mesenteric nodes. He presented in August 1974 with the gradual onset over two weeks, of mild headache, feeling of heaviness but not true weakness in the right arm and difficulty with writing. On neurological examination, the stretch reflexes were slightly increased on the right, and the right plantar reflex was not responsive, whereas the left was flexor. There was a pronation reaction on the right, but no arm drop. Dynamometric examination of the hands however showed no right-left difference, and no clear weakness could be detected in the legs. There was mild facial asymmetry suggesting right facial weakness. Abnormal reflexes such as the grasp reflex, tonic extensor reflex of the fingers (Vernea and Botez, 1965), tonic reflex of the palm (Botez, 1957) and traction response (Rushworth, 1969) were absent. There was mild bilteral papilloedema, but the rest of the neurological examination was normal.

General examination revealed no further abnormalities. Chest radiograph (8.8.1974) showed a rounded nodule (approx. 1.5 cm. in diameter) in the apical segment of the lower lobe, probably a metastatic deposit.

The left carotid angiogram (8.8.1974) showed lateral displacement of the middle cerebral artery, stretching and attenuation of the small branch arteries in the frontoparietal area, and some displacement of the midline structure to the right (Figs. 1 and 2). The E.E.G. showed slow waves (theta and some delta) in the left anterior quadrant, but no clearcut focus. The 99mTc Brain Scan showed an area of increased uptake about 3.5 cm. in its greatest diameter situated in the left prefrontal region, relatively superficially (Figs. 3 and 4).

Neuro-Psychological Examination

The patient was right-handed with no family history of left-handedness. He had completed 7 years of schooling and his occupation was that of a clerk. He was perfectly orientated in time and place, and was cooperative.

The neuro-psychological examination (13.8.74 – Dr. K. Walsh) showed a deficit in the Benton Verbal Fluency test and frontal signs on the Weigl colour form sorting test. There was also a deficit in the performance of the Milan Token Test. The Porteus Maze test was at an average (IQ = 100) level. Memory quotient of 87 was depressed by his inability to perform the paired associated learning test. The Boston aphasia test (Goodglass and Kaplam, 1972) showed a deficit in fluency in controlled association (animal naming), a mild reduction in oral non-verbal and verbal agility and a slightly slowed verbal output. Visual confrontation naming as well as body-part naming were normal, and only naming of very uncommon objects (e.g. stethoscope, sphygmomanometer) was delayed. All the other tests for expressive and receptive aphasia were

* Neuro-Psychiatric Centre, Mont Park, Victoria and Austin Hospital, Heidelberg, Victoria.
+ Austin Hospital, Heidelberg, Victoria.

FIG. 1. Lateral view of left carotid angiogram, consistent with a left prefrontal space occupying lesion.

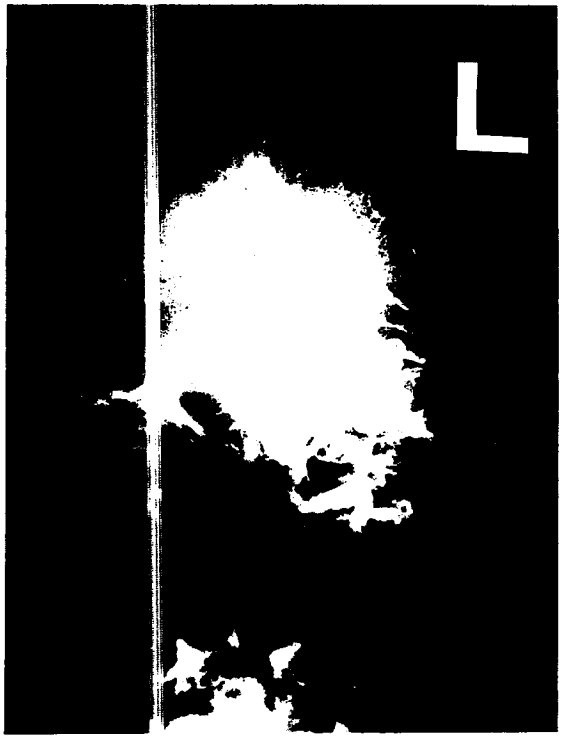

FIG. 2. Antero-posterior view of left carotid angiogram, consistent with a left prefrontal space occupying lesion.

FIG. 3. Lateral view of brain scan, showing an area of increased uptake in the left prefrontal region.

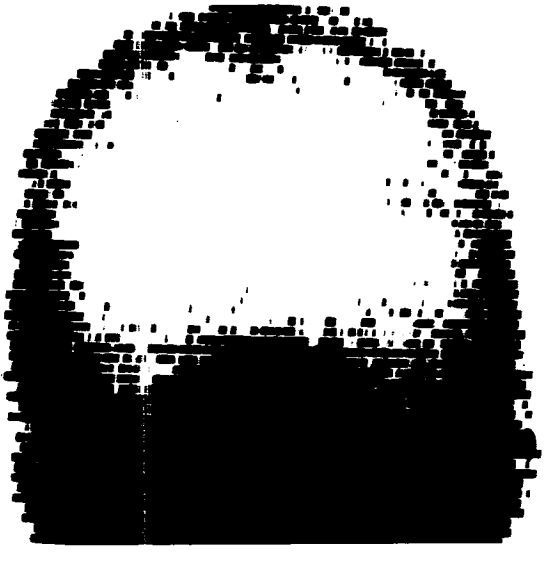

FIG. 4. Antero-posterior view of brain scan, showing an area of increased uptake in the left prefrontal region.

normal and so was the intonational pattern. There was no apraxia, agnosia or alexia of any kind and his rhythm sense and oral mathematical performance were normal.

The scheme of examination for agraphia was as follows:

Automatic and semi-automatic writing: signature, name and address, "Dear Sir".

Serial writing: alphabet, days of the week, months.

Verbal-graphic performance:

Dictation: single letters, words (short, long) sentences.

Copying: identical ("slavish") reproduction, transliteration.

Writing from letters and words written on his skin.

Nonverbal – graphic performance: writing names of objects or gestures, (actions) presented through the visual, auditory, tactile, taste and olfactory channels.

Narrative writing: discussion of pictures, answer to questions, e.g. how he became ill.

Oral spelling of given words.

Writing of words and sentences with cardboard letters.

Writing of logatoms (meaningless words).

The examination of written mathematical abilities: figures, numbers, calculations, problem solving. (The patient was requested to perform these tests with the right hand as well as with the left hand.)

The following disorders were detected:

The shape of letters was not impaired, whether they were single letters on dictation, alphabet letters, or letters included in non-verbal-graphic, verbal-graphic, or narrative writing. However, occasionally the appearance of some letters was changed by the fact that the patient superimposed them on wrong letters.

Words displayed fairly frequent spelling mistakes only of literal paragraphic type. Generally the paragraphias were of the type in which there is substitution of wrong letters (e.g. bady for baby, chark for chalk); rarely there was omission of letters (sealing for stealing) and even more rarely addition of a group of letters (e.g. cooking for cookies). There was no significant difference between the performances on dictation and on narrative writing.

The performance on copying depended on the method used by the patient: if he read the words and wrote them down, the mistakes were similar to those mentioned above. On the contrary, if the patient concentrated on each letter, such as in transliteration (slavish copying) or transcoding (e.g. from handwriting to printing or vice versa) the performance was almost perfect. A good performance was also obtained on copying logatoms or writing with cardboard letters, for the same reasons. Automatic and semi-automatic writing was without mistakes, but the serial writing showed some mistakes, and there were even mistakes in the alphabet (wrong letters), corrected subsequently – Fig. 5. The patient was almost always aware of his mistakes after he made them, but sometimes he knew beforehand that he was going to make a mistake. He explained that the wrong letter came to his mind just before he was going to write it and this was how he accounted for his slowness in writing. In fact, the patient was able to correct spontaneously all his mistakes after reading what he wrote. Very often he left a word unfinished, after he had made a mistake, and started it again, which gave the impression of perseveration. However, no true perseveration was noted, either literal or verbal. The oral spelling of words, even long and complex ones, was very good, though very often he spelled a word correctly and wrote it incorrectly immediately afterwards. There was great variation in the spelling mistakes; when asked to write the same sentence more than once, he always made mistakes, but never in the same words (Fig. 5). His performance was similar when the patient used his left hand. One could also notice great variation in the frequency of mistakes from sentence to sentence (variability of performance) as well as a certain degree of fatigability. Sometimes, difficulty in initiation of the sentence was evident.

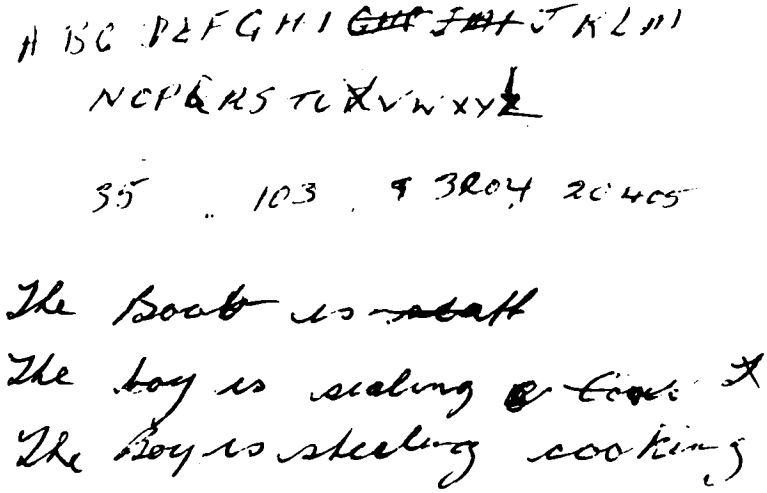

FIG. 5. Performance on writing of the alphabet, dictated numbers and dictation of a short sentence.

An attempt was made to establish some qualitative indices of this word (verbal) dysgraphia (Dubois, Hecan and Marcie, 1969). The following were calculated:

the number of the letters spelled correctly (in comparison with the model, and expressed in percentages).

the total number of the letters written by the patient (in comparison with the model and also expressed in percentages).

the percentage of errors for the first, second, third, etc. letter of the words.

The great variation in performance would make respective figures useless. One can only say that, in general, the total number of letters rarely exceeded that of the model, which is consistent with the absence of perseveration. However, if one takes into consideration the words crossed out by the patient, the total number of letters exceeds that of the model, which shows the patient's capacity to correct himself. As for the number of errors regarding the position of the letter in the word, one can see that there were occasional paragraphias involving the first letter, which was not seen in the cases described by Assal, Capuis and Zander, 1970).

The written mathematical performances were very good, e.g. writing of dictated numbers (Fig. 5), as were the written calculations for the four elementary operations.

The structure of sentences was impaired. On verbal-graphic tests (dictation, copying, etc.) there were no disorders other than literal paragraphies and lack of punctuation. Narrative writing showed the most striking abnormality. The grammatical disorder was characterized by the omission of the auxiliaries and relational words ("telegram style") as in Fig. 6. This corresponds with the agrammatism described in expressive aphasia, though here there was no spoken agrammation. There were also paragrammatisms, i.e. errors of syntax, e.g. "sink washing dishing". Another feature was the poverty of written words.

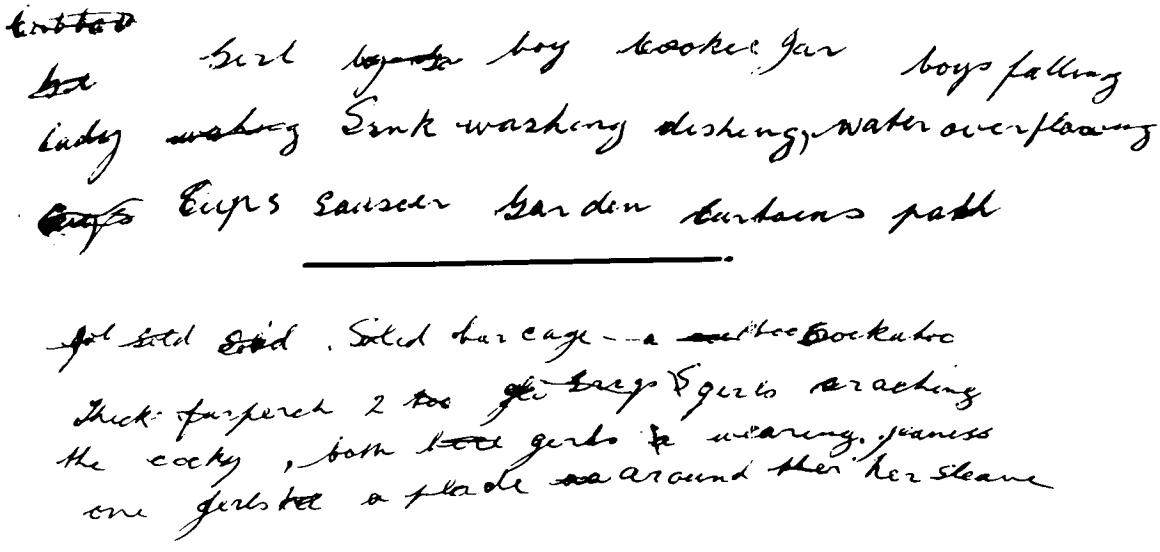

FIG. 6. Two examples of "narrative writing" (interpretation of two pictures).

DISCUSSION

As can be seen from the examination of speech, there was an obvious discrepancy between patient's mild dysphasia (involving especially fluency) and his marked agraphia. The written account resembles expressive aphasia, though there are no corresponding verbal disorders. This shows conclusively that the agraphia cannot be caused in this case by aphasia. Neither is it possible to ascribe it to apraxia, which was not present. In spite of the mild papilloedema there was no impairment of the state of consciousness so that a pseudo-agraphia caused by this condition (Chedru, 1972; Heilman, Coyle, Gonyea and Geschwind, 1973) cannot be taken into consideration. Since other manifestations such as weakness, sensory deficit, ataxia, apraxia and spatial perception disorder were absent, the writing disorder is consistent with so called pure agraphia, in spite of the presence of a mild prefrontal syndrome (detectable by tests only).

Although most of the cases of agraphia are considered to be of aphasic or apraxic origin, pure agraphia, in spite of being documented only in a few cases, is a recognised entity (Hecaen, Angeler-

gues and Douzenis, 1963; De Jong, 1969; Leischner, 1969). However, this condition can be caused not only by frontal lesions, but also by left parietal, parieto-temporal, temporo-occipital lesions (Critchley, 1953; Dubois *et al.,* 1969) as well as right frontal (non dominant for speech) and parietal lesions (Hacaen and Angelergues, 1965). Cases of pure agraphia are also seen in left-handers with right-sided frontal lesions (Ectors, 1945) and this has been attributed in some instances to the presence of the speech area on the left whereas the writing area was situated on the right (Heilman *et al.,* 1973). Pure agraphia has also been described in lesions of the subthalamic area under the left centrum medianum after steroencephalotomy (Sugishita, 1973).

After Exner (1881) localised the "writing" centre in the second left frontal gyrus, similar cases were described by Gordinier (1899), Rosenblath (1907), Bychowski (1909), MacConnel (1905), Kroll (1911), Campbell (1911), Mills and Martin (1912), Dufour and Legras (1914), Sinicco (1926), Hermann and Poetzl (1926), Morselli (1930), Rawak (1933), Marcus (1937), Mahoudeau (1950; 1951), Penfield and Roberts (1959), Hecaen *et al.* (1963), Hecaen and Angelergues (1966), Dubois *et al.* (1969). Henschen (1922) and Nielsen (1946) considered the frontal localization as relevant to their theories on agraphia, whereas Dejerine (1891), Kleist (1934), Golstein (1948) and Leishchner (1957) denied the special importance of this localization. On the other hand, it must be pointed out that not all cases of prefrontal agraphia display pure agraphia; many of them show aphasia and/or apraxia.

There are few explanations of frontal agraphia. Henschen (1922) considered the frontal area (F2) as the "motor centre" of writing and he localised the "sensory centre" in the angular gyrus. Nielsen (1946) put forward the hypothesis that the frontal writing centre is activated by the gyrus angularis; and in frontal agraphia either the connection between the two centres is broken or the frontal centre is damaged. According to Brain (1967) the written expression of language is achieved by the evocation of "graphic letter-schemas dependent upon the left angular gyrus, and these in turn must arouse the graphic motor schemas organized in the neighbourhood of the hand area of the left precentral convolution". The process of writing makes it necessary to effect a preliminary auditory analysis, to single out the phonematic composition of the words, to recode the phonemes into graphemes and to preserve the order of the sound and letter elements (Luria *et al.,* 1970). The present authors' hypothesis is that basic disorders produced by prefrontal lobe damage play an important part in the causation of frontal agraphia. We have no knowledge of previous theories relating the frontal agraphia to prefrontal disorders. One disruptive factor is the deficiency in the regulatory role of speech (Luria and Homs Kaya, 1964). This, as Pribram (1969) points out, implies a lack of temporal correspondence between the verbal and written code. Discrepancy between the verbal signal and action is confirmed by Milner (1964). In other words, though speech is preserved and consequently the oral spelling is not impaired, the patient cannot write the correct grapheme (letter) because speech has lost its regulatory role on writing. Another contributing factor is the frontal lobe disorder characterized by a derangement of behavioural programming (Nauta, 1971). In frontal agraphia, the recording of phonemes into graphemes is disturbed, and though auditory analysis is possible, the corresponding grapheme cannot be written.

The slowing of information processing in the visual system (Spinelli and Pribram, 1967) as well as the deficit of visual scanning (Smith, 1974) present in prefrontal lobe lesions may also contribute to the deficit of feed-back which impairs writing. We are here referring to the almost instantaneous process, which normally prevents the writing of wrong letters and which is not operating in such cases of agraphia. This is not contradicted by the fact that the present patient was able to make subsequent corrections of his writing errors, as this is a different, slower process. Moreover, the visual perception deficit of prefrontal origin does not cause alexia.

Deficits of interest ("incentive"), initiative, and drive also play a part in the genesis of frontal agraphia. This is seen particularly in the deficiency of initiation of the writing of words and in the tendency of the patient not to complete the task, unless he is prompted. Of course, these considerations do not provide a full explanation of frontal agraphia, and the question why this particular frontal localisation can cause a pure agraphia cannot be answered, although the proximity of the lesion to the cortical representation of the hand may be a factor.

SUMMARY

Frontal agraphia has always been a subject of interest, although very few documented case reports have been published. A 57 year old male clerk, suffering from adenocarcinoma of the signoid colon, presented with mild headache and difficulty in writing. Minor features of dysphasia could be detected, but there were no alexia, agnosia or apraxia. Brain scan and angiography confirmed a metastasis in the posterior part of the left prefrontal region. The patient was able to write single letters, and had no difficulty with automatic writing or copying. The writing of words and of sentences was more affected. After a brief review of the literature and discussion, the authors concluded that frontal agraphia is related to frontal lobe diorders, especially the inability to translate verbal signals into motor behaviour (i.e. writing).

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THE SURGICAL MANAGEMENT OF EXTRACRANIAL CEREBROVASCULAR OCCLUSIVE DISEASE: A REVIEW OF 200 CONSECUTIVE SURGICAL CASES

D.A. HORTON, R.D. FINE and R.G. HICKS*

The occurrence of occlusive disease of the extracranial portion of the arteries supplying the brain and its relationship to strokes was first recognised by Todd in 1844, but it was almost one hundred years later that the first reconstructive procedures on these vessels were performed. The first report of successful surgery for internal carotid stenosis was made by Eastcott, Pickering and Rob in 1954. Subsequently, reports on the surgical treatment of lesions of the great vessels and the vertebral artery appeared in the literature.

Angiographic studies of patients with cerebral arterial insufficiency indicate that in about 50 percent of the cases the occlusive lesion or lesions causing this disturbance are located in the thoracic and cervical portions of the cerebral vessels and are thus surgically approachable.

ANATOMICAL AND PATHOLOGICAL LESIONS:

Occlusive lesions are found in certain characteristic locations e.g. around the bifurcation of the common carotid artery, extending into the origins of the internal and external carotid arteries, the vertebral artery near its origin from the subclavian artery, and the origins of the common carotid, innominate and subclavian arteries. The vast majority of occlusive abnormalities in the extra-cranial cerebrovascular system are atheromatous in nature; lesions at the carotid bifurcation in particular are frequently ulcerated and display mural thrombus which may embolise. Lesions at the origin of the vertebral artery most commonly consist of an encroachment on the vertebral orifice by arteriosclerotic disease in the subclavian artery in the region.

It is noteworthy that stenosis or occlusion of the subclavian artery, proximal to the origin of the vertebral artery, may either reduce perfusion through the vertebral artery or may actually cause a reversal of ipsilateral vertebral flow. Subclavian stenosis promotes flow through the vertebro-basilar system into the low-pressure segment of the subclavian artery distal to the stenosis, thus effectively stealing blood from the brain. Stenosis or occlusion of the innominate artery may have the same effect.

CLINICAL MANIFESTATIONS:

In clinical practice neurological symptoms vary considerably both in type and severity and do not correlate well with the location of the lesion. The classical feature of symptoms caused by extracranial cerebrovascular disease is that they are frequently transient in nature. Frequently, these transient ischaemic attacks are a prelude to a complete stroke and although figures vary, it is

* Sydney

generally conceded that about 50 percent of patients with transient ischaemic attacks, particularly those due to carotid lesions, may progress to a complete stroke within three to four years.

THE ROLE OF SURGERY IN EXTRACRANIAL CEREBROVASCULAR OCCLUSIVE DISEASE:

Essentially, the role of surgery is to eliminate transient ischaemic attacks and to prevent the occurrence of a stroke.

INVESTIGATIONS:

Every patient who is considered for surgery must undergo arteriography. High quality four vessel arteriograms provide the vital information on which the decision of whether and where to operate is based.

SELECTION OF PATIENTS FOR OPERATION:

Patients are selected for operation on a basis of symptoms and signs and on arteriographic findings. In general, all symptomatic patients with extracranial cerebrovascular occlusive disease, without complete obstruction, are suitable cases for reconstructive surgery. In addition, surgical treatment is also recommended for patients with completely obstructive lesions of the great vessels, these lesions usually being segmental in nature, the distal portion of the vessel or the branches of the vessel maintaining patency via collateral circulation.

Completely obstructive lesions of the internal carotid and vertebral arteries are a different proposition. Complete obstruction of the internal carotid artery, at its origin, is associated with cephalad thrombosis of that artery at least as far as its next major branch which is the ophthalmic artery. Such an event may produce a disastrous neurological deficit or, in fact, may not produce any symptoms at all. In either event, surgical intervention is non-contributory. The same principle applies to the vertebral artery where the next point of significant vascular communication is, of course, at the origin of the basilar artery.

When evaluating arteriographic findings, one must bear in mind the clinical signs and symptoms of the particular case and relate these to known pathology. The tightly stenosing lesion produces its symptoms by critical reduction in blood flow, but in about 50 percent of cases, the symptomatology of extracranial cerebrovascular disease is produced by recurrent embolisation of thrombus from the surface of an ulcerated plaque, classically situated at the bifurcation of the common carotid artery. Such lesions should be removed just as surely as a stenotic lesion providing there is strong clinical evidence to incriminate them as the source of symptoms.

The most suitable candidate for operation is the patient who has suffered transient attacks of cerebral arterial insufficiency and who is without neurological deficit. Patients with increasing neurological deficit over a period of several hours should not be subjected to surgery because early operation can cause haemorrhage into areas of cerebral softening following restoration of full carotid flow.

Patients who have stable neurological deficits not amounting to total loss of function, may also be offered operation, provided the lesions are not total and not progressive; there is no rigid rule as to the most favourable time to operate. In regard to acute stroke, there is no place for surgery at all, at any stage, in the patient who has a deficit amounting to total loss of function.

OPERATIVE TECHNIQUES:

The basic techniques are those of arterial grafting, endarterectomy and angioplasty. During all procedures involving internal carotid clamping, we employ intra-operative E.E.G. monitoring to assess the adequacy of cerebral flow during internal carotid occlusion.

Surgery of the common carotid bifurcation and the internal carotid artery:

Arteriosclerotic lesions of the carotid bifurication are treated by endarterectomy, with, if indicated,

patch graft angioplasty. A temporary internal shunt is employed if there are untoward changes in the E.E.G. The shunt is not used routinely because it is unnecessary and it carries the hazard of intimal damage in the internal carotid artery. In addition, there is a possibility of air embolism and there is no doubt that endarterectomy is made more difficult by the presence of a shunt, particularly in the internal carotid artery towards the upper end of the arteriotomy.

Obstructing kinks in the internal carotid artery are treated by resection and end-to-end anastomosis. The surgical treatment of fibro-muscular hyperplasia of the internal carotid artery consists of gradual internal dilation of the vessel, sometimes combined with patch graft angioplasty or resection of a particularly pathological portion of the vessel.

Surgery of the vertebral artery:

This essentially consists of patch graft angioplasty.

Surgery of the great vessels:

As previously described, both partially and completely occlusive lesions of the great vessels are amenable to surgery. Lesions of the innominate artery or lesions of both the subclavian and carotid vessels on the same side are treated by Dacron bypass graft from the ascending aorta. Lesions of the common carotid and subclavian arteries on the same side require the insertion of a bifurcation graft from the aorta with distal anastomosis to each vessel at the appropriate level.

Lesions of the common carotid vessels associated with normal subclavian vessels on the same side, can be effectively treated by inserting a Dacron graft between the subclavian artery and the common carotid artery, distal to the lesion. A similar technique applies to lesions of the subclavian arteries associated with normal common carotid arteries. Not infrequently, a lesion in one of the great vessels can be treated by endarterectomy.

RESULTS OF SURGERY:

We wish to report our experience in the surgical management of extracranial cerebrovascular disease. We have now performed 200 operations for this condition, 152 on the region of the common carotid bifurcation, 14 for lesions of the great vessels and 34 for lesions of the vertebral artery. All these operations have been performed at the Prince Henry Hospital since April, 1970. The overall hospital mortality is 2.5%.

OPERATIONS ON THE GREAT VESSELS:

The details of these operations were as follows:—
Aorto-subclavian bypass – 2; Aorto-carotid bypass – 2; Subclavian endarterectomy – 5; Subclavian carotid bypass – 1; Carotid subclavian bypass – 4;
Operative morbidity – 9; Operative Mortality – 0; Recurrence of symptoms – 1; Re-operation – 1; Late death – 0.

OPERATIONS ON THE VERTEBRAL ARTERY:

Vertebral endarterectomy and patch graft angioplasty – 1; Vertebral patch graft angioplasty or angioplasty – 3;
Operative morbidity – 2; Operative mortality – 0; Persistence of symptoms – 3; Re-operation – 0; Late deaths from myocardial infarction – 1.

OPERATIONS ON THE CAROTID BIFURCATION:

Number of operations – 152, seven patients having undergone bilateral procedures.

Operative mortality – 5, Operative morbidity – 7. This group of seven patients is a group in which there was a prolonged neurological deficit post-operatively. In three cases this deficit was an exaggeration of a pre-operative deficit and in two out of these three cases recovery after three weeks had occurred to a level considerably above the pre-operative status.

Six patients have had a recurrence of symptoms. In two of these further angiographic studies were undertaken and re-operation performed. Both the recurrence of symptoms and the second procedures took place after about twelve months. One of these patients who is now again asymptomatic had in fact developed quite a large plaque immediately below the level of the previous endarterectomy, i.e. in the common carotid artery, and this plaque was removed at the second procedure. The other patient who underwent re-operation had redeveloped disease at his bifurcation and, over a period of twelve months, proceeded to complete occlusion of his internal carotid on the other side, this having been normal twelve months before. This is most unusual in our experience and will be the subject of a separate paper. Overall, there have been three late deaths in this group of 145 patients.

Details of the actual procedures performed were:–

Carotid endarterectomy – 139; Carotid endarterectomy and patch graft angioplasty – 5; Carotid endarterectomy and carotid dilation (for a combination of arteriosclerosis and fibromuscular hyperplasia) – 1; Resection of internal carotid artery and end-to-end anastomosis – 5; Exploration of the carotid bifurcation – 2, both cases being a type of acute arteritis with virtual complete occlusion of the internal carotid artery. Recognition of this particular lesion in future should prevent us from performing operations on these people.

The details of the operative deaths were as follows:–

Two of the patients were operated on in a state of semi-coma and hemiplegia following an acute stroke. Neither patient demonstrated any neurological recovery and one died on the third post-operative day from an intra-cerebral haemorrhage into a cerebral infarct and the other patient died from a gastro-intestinal haemorrhage about two weeks post-operatively. One patient had an unsuspected cerebral metastasis from a carcinoma of the lung and died following haemorrhage into the cerebral lesion. This haemorrhage probably occurred during operation and presumably during the time of heparinisation because the patient did not wake from her anaesthetic. The other two deaths occurred in two patients with significant pre-operative neurological deficits and severe bilateral disease. One of these patients obviously had incurred some brain stem damage and found swallowing and coughing very difficult post-operatively. In spite of tracheostomy, this 78 year old patient eventually died from pulmonary infection about four weeks post-operatively. The other patient in this category had a dense hemiplegia from a completely occluded internal carotid artery and tight stenosis of the contralateral internal carotid. The contralateral carotid was operated upon but 24 hours post-operatively the patient became comatose and developed a dense hemiplegia on the other side. It is thought that thrombosis occurred at the operative site because of the advanced disease in the vessels.

It is interesting to note that the 143 patients who underwent reconstructive procedures of the carotid bifurcation, 129 had no significant pre-operative neurological deficit. In this group of 129 patients, the operative mortality was 1 and that was the patient who had an unsuspected cerebral secondary deposit. The operative morbidity was 4 cases, the term morbidity referring to patients who had prolonged neurological deficit post-operatively which was not present pre-operatively. Of these four patients, two have made a complete recovery: another six weeks after operation still had a slight loss of co-ordination in his left hand resulting from a cerebellar infarct while the fourth is making a gradual but satisfactory recovery from a stroke which occurred suddenly 24 hours post-operatively. The patient who incurred the cerebellar infarct post-operatively has severe bilateral disease and although the patient had a shunt during his carotid endarterectomy and the E.E.G. recording from the hemisphere was satisfactory during the procedure, there was obviously a critical reduction in blood flow to the cerebellum about which of course the E.E.G. does not give any information.

SUMMARY

The role of surgery in the treatment of extracranial cerebrovascular disease is essentially a prophylactic one but it should be borne in mind that apart from preventing stroke, such procedures will or should eliminate symptoms.

The authors believe that every patient suffering from cerebrovascular insufficiency should be thoroughly evaluated for extracranial cerebrovascular occlusive disease and that arteriograms should be performed on all patients who could be expected to be candidates for surgery.

The various indications for surgery have been discussed. The authors believe that people who have severe bilateral disease and who are of an advanced age are probably in a higher risk group. They also believe that surgery should not be offered to people who have a complete stroke and who are in semi-coma or coma, no matter how rapidly they may be transferred to the operating theatre.

The authors firmly believe that intra-operative E.E.G. monitoring is an important adjunct to the safe surgical treatment of lesions of the carotid bifurcation, not only to indicate when shunting is necessary but also to indicate how well that shunt is functioning.

In spite of the frequent presence of associated heart disease, hypertension and other vascular lesions, operation can be offered with confidence to suitable candidates. Elimination of symptoms can be expected in over 90% of cases. Only one patient has suffered a stroke since leaving hospital and this occurred because of occlusion in his internal carotid artery which was not operated on.

Apart from patient selection, the factors which have contributed to the authors' low morbidity and mortality have been the use of intra-operative E.E.G. monitoring, intra-operative heparinisation and the availability of excellent angiographic studies.

ACKNOWLEDGEMENT

The authors wish to pay a tribute to the high quality of the operative assistants and theatre staff who are available at the Prince Henry Hospital, Sydney.

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REVERSIBLE CORTICOSPINAL ABNORMALITY IN THE ALCOHOLIC

C.Y. HUANG, G.A. BROE, and P.G. PROCOPIS*

Except for Marchiafava-Bignami syndrome, which remains poorly recognised in English speaking countries, the various neurological complications of alcoholism, (e.g. the Wernicke-Korsakoff syndrome, peripheral neuropathy, cerebellar degeneration, myopathy, head injury, delirium tremens and withdrawal fits) are all readily diagnosed clinically. Central pontine myelinolysis has remained, however, a pathological diagnosis with only two cases having been recognized in life (Boudin, Labet, Lyon and Brunet, 1963; Paguirigan and Lefken, 1969). Most other cases are noted retrospectively to have had mental confusion, hypotension, reflex changes and weakness, mainly in the lower limbs (Goebel and Zur, 1972).

Recently we have seen five alcoholic patients who had corticospinal distribution weakness, with generalised hyperreflexia, which was reversed by thiamine therapy. It is felt that these may have been cases of central pontine myelinolysis which have responded to therapy.

CASE REPORTS

CASE 1

SH, a 42 year old female Caucasian, known to be an alcoholic, had been depressed, and suffered from anorexia and vomiting for approximately seven months prior to her admission. She had stopped eating and had continuous vomiting in the five days before admission. She was admitted drowsy with a blood pressure of 100/50, and a serum sodium of 117 meq/l., a potassium of 2.0 meq/l., and a chloride of 63 meq/l. Her mental state improved with correction of the electrolyte disturbance, but two days later she developed an agitated state. This confusion was controlled with chlormethiazole. Thiamine, however, was not administered and five days after admission she was found to be quite ataxic with spasticity in all limbs. When seen by the Neurology Service nine days after admission she was found to have occasional confabulation and poor recent memory. Her face was expressionless and her speech dysarthric. There was marked dysphagia and inappropriate crying; eye movements were full and pupils normally reactive; fundi were normal; the gag reflex was poor with a positive glabellar tap; the snout reflex and jaw jerk were brisk (3+); gross action tremor was seen in all limbs; tone was generally increased but no weakness was demonstrable; pathologically brisk reflexes were present with plantars equivocal. Glove and stocking sensory loss to pain was noted with normal proprioception and there was marked gait ataxia. She was treated with large dose of thiamine. The following investigations were carried out: Haemoglobin 10.4g/100ml, with burr cells, anisocytosis and poikilocytosis, W.B.C. 4,700; E.S.R. 60mm/hr, normal blood urea, creatinine, calcium, bilirubin, alkaline phosphatase and thyroid function; C.S.F. normal; E.E.G. and brain scan normal. The patient gradually improved but still had bilateral spasticity, hyperreflexia and minimal heel-toe incoordination four months later. However, at follow-up one year later she had become neurologically normal apart from mildly impaired recent memory.

* Department of Neurology, Lidcombe Hospital, Sydney

CASE 2

MH, a 45 year old female Caucasian, had been a barmaid with a long history of chronic alcoholism. She had been noticed to have recent memory loss and personality changes in the previous six months with intermittent parasthesia in the lower limbs and poor balance on walking. She had been found at home with anorexia and abdominal pain and in obvious poor health.

On admission, she had B.P. of 120/80, evidence of chronic obstructive airways disease and hepatomegaly, bilateral horizontal nystagmus on lateral gaze, Korsakoff psychosis and slightly dysarthric speech; power was normal in her upper limbs but weak in her hip flexors and knee flexors with normal hip and knee extension; tone was normal; upper limb reflexes and ankle jerks were pathologically brisk (3+); however, knee jerks were reduced, the plantars were flexor; the snout reflex was negative but the jaw jerk was pathologically brisk (3+). There was some mild distal sensory loss and truncal ataxia. Nerve conduction studies confirmed a widespread peripheral neuropathy with a severe lesion of the femoral nerve. Routine hemogram, serum creatinine, calcium, immunoglobulins, glucose tolerance test and E.C.G. were normal. Serum bilirubin and alkaline phosphatase were elevated with decreased levels of plasma protein and albumin. She had a serum sodium of 123 meq/l., a potassium of 2.3 meq/l., and a chloride of 100 meq/l. on admission.

She improved on thiamine and when seen four months afterwards had lost the hyperreflexia and weakness with only the features of her peripheral neuropathy remaining.

CASE 3

JB, a 46 year old male Caucasian with a long history of alcoholism, cerebellar ataxia, epilepsy treated with phenytoin 300mg. daily and past episode of peripheral neuropathy, had loss of appetite and ate very little for a week prior to admission.

On admission he was mentally alert and orientated with bilateral horizontal nystagmus, reduced power in both hip flexors, gross incoordination of lower limbs and truncal ataxia. Reflexes were generally brisk (2+ to 3+) with extensor plantar responses bilaterally. The ankle jerks, however, were absent. He was treated with large dose of thiamine and within two days had lost his abnormal plantar responses and became much stronger in his hip flexion.

Routine hemogram, liver function tests, and serum electrolytes were normal. C.P.K., L.D.H., S.G.O.T., S.G.P.T. were all within normal levels on repeated estimation. Nerve conduction studies were normal.

CASE 4

JM, a 52 year old male Caucasian with a long history of chronic alcoholism and poor nutrition, was admitted with hepatomegaly, confusion, disorientation and ataxia. He was treated with Intravite. He was seen by the Neurology Service five days after admission and found to have vertical and horizontal nystagmus, Korsakoff psychosis, action tremor and mildly increased tone in his upper limbs. There was marked weakness of shoulder abduction and elbow extension and marked flexor weakness in the lower limbs, particularly involving the hip flexors. There was a clinical glove and stocking neuropathy to pain and touch with normal proprioception and a spastic-ataxic gait. The jaw jerk was 2+ and snout reflex 3+. All tendon reflexes were pathologically brisk (3+). Plantars were down-going. Biochemical investigation (serum electrolytes, calcium, liver function tests) and brain scan showed no significant abnormalities. An. E.M.G. showed mild peripheral neuropathy with myopathic changes in upper and lower limbs.

At review after two months there was no nystagmus, the gait remained spastic-ataxic and all tendon reflexes were pathologically brisk. The jaw jerk and snout reflex were, however, normal and there was only slight residual corticospinal weakness in upper and lower limbs.

CASE 5

DA, a 50 year old male Caucasian, known to be an alcoholic, and living alone in poor circumstances, was admitted with confusion, diplopia, bilateral horizontal and vertical nystagmus and cerebellar ataxia. He was treated with chlormethiazole and Intravite and was seen by the Neurology Service seven days after admission. On examination he had bilateral horizontal nystagmus on lateral gaze and vertical nystagmus on attempted upward gaze. There was paresis of voluntary upward and downward gaze. Korsakoff psychosis was present. Tone was normal. The jaw jerk was increased (+). There was moderate weakness of shoulder abduction and wrist extension and more marked weakness of flexors of the hips and knees. Reflexes in the upper limbs were patholigically brisk (3+) with normal knee jerks and reduced ankle jerks. Plantars were downgoing and gait was spastic-ataxic. On review after one month there was only slight improvement in gait with no change in the other signs.

Biochemical investigations (serum electrolytes, liver function tests) and brain scan showed no significant abnormality. Nerve conduction studies showed a peripheral neuropathy with a marked femoral nerve lesion.

DISCUSSION

The five patients had in common pathologically brisk reflexes. In four a corticospinal pattern

of weakness was demonstratable and the other had bilateral spasticity. In all five cases the abnormality diminished with intensive thiamine therapy. In addition all five patients had evidence of central nervous system involvement – Wernicke-Korsakoff syndrome, nystagmus and truncal ataxia. They all had a prolonged period of malnutrition previous to admission and, in two cases, there was marked dilutional hyponatremia and hypokalemia.

Two other cases in the literature are of interest. Sheremata and Sherwin (1972) reported a 43 year old alcoholic who presented with urinary retention and was found to have mild weakness of the extensors of the wrist and abductors of fingers and marked weakness of the flexors and abductors of the lower limbs. Reflexes were hyperactive and plantars extensor bilaterally. The abnormality subsided on vitamin therapy. The case was interpreted by the authors as an instance of alcoholic myelopathy becase of the presence of a spastic bladder.

Khurana, Post and Kalyanaraman (1974) reported a 46 year old alcoholic man who was presented with severe electrolyte disturbance, hyponatremia, hypokalemia and hypochloremia. He was found to have marked dysarthria, fine nystagmus in all directions, dysphagia with poor gag reflex and difficulty protruding his tongue. There was bilateral spasticity and quadriparesis; his jaw jerk was absent but his snout response prominent. All reflexes were brisk bilaterally with extensor plantar responses. He also improved after hospitalisation and had only bilaterally brisk reflexes and a right ulnar neuropathy eighteen months later. The authors suggested that this man may have been a case of central pontine myelinolysis.

The exact locus of injury to the pyramidal system in these two cases and our five cases is purely conjectual. It is striking, however, how similar the cases are (Table I).

TABLE I

A comparison of various features of the present cases, and the cases of Khurana *et al.* (1974) and Sheremata and Sherwin (1972).

	Present Series	Khurana *et al*	Sheremata & Sherwin
Tone Abnormality	2/5	Spastic	Spastic
Corticospinal Weakness	4/5	+	+
Jaw Jerk Increased	4/5	N	?
Snout Reflex	3/5	+	–
Hyperreflexia	5/5	+ + +	+ + +
Extensor Plantar Response	1/5	+	+
Pseudobulbar Palsy/Bulbar	1/5	+	–
Electrolyte Disturbance	2/5	+	–
Wernicke Korsakoff's Syndrome	5/5	+	–
Cerebellar Ataxia	5/	–	–
Peripheral Neuropathy	4/5	R. Ulnar	–
Myopathy	1/3	?	?

Generalised hypertonia with extensor plantar responses is seen in Marchiafava-Bignami syndrome. However, in this complication of alcoholism there is usually coma and epileptic seizures in the acute form and progressive dementia in the chronic form (Castaigne, Buge, Cambier, Escourelle and Rancurel, 1971). Pathologically, there are lesions in the white matter as well as the corpus callosum. In the absence of pathology we cannot exclude the possibility that our cases were due to hemispheric white matter lesions. However, although our cases presented acutely they were not comatose, nor did they have fits. Therefore they were dissimilar to the acute forms of Marchiafava-Bignami syndrome.

Central pontine myelinolysis is seen clinically in severe malnutrition and alcoholism. There is a frequent association with liver disease, severe electrolyte disturbance, infection and disorders of impaired immunological response. Wernicke encephalopathy is often present. Most cases of central pontine myelinolysis have been diagnosed only at post mortem and therefore clinical details of the patients are incomplete and unreliable. In reviewing the previous literature, however, Darke and Kakulas (1973) reported that spastic quadriparesis and pseudobulbar palsy were recognised

in 17% of cases. Only two cases have previously been diagnosed in life and subsequently proven at autopsy. The case of Paguirigan and Lefken (1969) was a 47 year old alcoholic with electrolyte disturbance, who had mutism, quadriplegia, generalised hyperreflexia with brisk jaw jerk and extensor plantar responses, but normal sensation. Boudin *et al.*, (1963) described a case of quadriplegia with intact sensation, aphonia, trouble swallowing and moving the tongue. Eye movement was full with nystagmus.

Both peripheral neuropathy and myopathy are frequent complications of alcoholism and were present in many of our cases. Both myopathy and neuropathy will cause weakness; hip flexor weakness can result from femoral neuropathy and this was indeed present in two of our cases. However, weakness should not be in a selective pattern of corticospinal type in the other antigravity muscles. Further, diminished reflexes might be expected, whereas in the material presented above pathologically brisk reflexes were present in all cases despite the presence of myopathy in one and peripheral neuropathy in four.

In one of our cases, extensor plantar responses were present. It may be expected that if the peripheral neuropathy was severe enough, cases of central pontine myelinolysis might show diminished reflexes. This was, in fact, so with the cases of Goebel and Zur (1972). Their cases unfortunately were based on retrospective clinical notes.

Large bilateral subdural hematomes have been reasonably excluded by the negative brain scans. Closed head injury may cause damage to corticospinal tracts bilaterally but the symmetry of the abnormality in the present cases makes subdural haemotoma unlikely. The possibility of myelopathy was raised by Sheremata and Sherwin (1972) but this complication only occurs in the presence of hepatic disease with portal-systemic shunts, and is, in these cases, irreversible. Only one of our patients showed abnormal liver function.

Thus our five cases, as well as the other two in the literature, suggest the presence of a reversible corticospinal defect in alcoholics. This usually appears in the company of cerebellar ataxia and the Wernicke-Korsakoff's syndrome, as well as other neurological complications of alcoholism and is frequently associated with severe malnutrition or electrolyte disturbance. Without tissue examinations we cannot ascertain the pathological basis of the corticospinal abnormality in these patients. However, our first case (SH) and the case of Khurana, Post and Kalyanaraman (1974) had all the recognised features of central pontine myelinolysis. Our other four cases of corticospinal abnormality may similarly be mild forms of central pontine myelinolysis which have recovered with intensive thiamine therapy.

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INTERACTIONS BETWEEN ANTICONVULSANTS

C.M. LANDER, M.J. EADIE and J.H. TYRER*†

Approximately one in every 200 members of the adult population suffers from epilepsy (Lennox and Lennox, 1960). Almost all of these persons will require anticonvulsant therapy for long periods of time. Many will receive more than one anticonvulsant preparation at the same time to control their seizures. It is therefore important to know if one anticonvulsant drug will alter the effects of another when they are taken together. Naturally, interactions may occur between any drugs which a patient is taking. However, the present paper is restricted to discussion of possible interactions between anticonvulsants.

DRUG INTERACTIONS

An interaction between two drugs is said to occur when the effects of one drug are altered by the presence of another drug. Thus the biological effect of two drugs given simultaneously is not necessarily the sum of the effect of each drug given alone; the overall biological response may be greater or less than the sum of the usual responses to the individual drugs.

Drug interactions may occur as a result of modification of many of the processes by which drugs enter the body, are distributed through it and are eliminated from it, or by which they combine with receptors to produce drug actions. Pre-receptor interactions all feature a change of plasma drug level whereas receptor interactions do not alter plasma drug concentration.

Pre-Receptor Interactions

There are several different mechanisms of pre-receptor interaction.

(i) Modification of the absorption of a drug may occur due to changes in pH produced by another drug within the upper gastrointestinal tract, or because of competition for transport systems within the mucosal cells of the alimentary tract. Two drugs, or a drug and an excipient compound, may form complexes within a combined preparation; two drugs, given separately, may interact within the gastrointestinal tract. The formation of a complex between a drug and its excipient was shown to be the cause of the outbreak of phenytoin intoxication in Australia in 1968-69 (Bochner, Hooper, Tyrer and Eadie, 1972). Investigations showed this to be related to a change of the excipient from one containing calcium sulphate to one containing lactose in one brand of phenytoin capsule. It appeared that the initial excipient had rendered part of the phenytoin unabsorbable. The new excipient did not have this effect, and consequently more drug was absorbed from each dose and this resulted in phenytoin intoxication.

* Department of Medicine, University of Queensland
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(ii) A drug may bind to plasma proteins, fat, or connective tissues. If another drug is given simultaneously, it may act directly by competing with the former drug for its specific binding site. Another possibility is that the second drug may act indirectly by displacing the first drug from plasma protein or tissue binding sites. This process increases the amount of the first drug that is free in plasma water, and some of this extra free drug is able to bind to its specific receptors. Its action may thus be increased although the total amount of this drug within the body may remain unaltered. Phenytoin is a strongly protein bound drug in plasma, approximately 80-90% being bound at body temperature (Hooper, Sutherland, Bochner, Tyrer and Eadie, 1973). Sulthiame has been shown to displace phenytoin from its plasma protein binding sites (Hooper *et al.*, 1973). These authors stated that, at therapeutic concentrations, it is unlikely that ethosuximide or carbamazepine would compete with phenytoin for protein binding sites.

(iii) Biotransformation of drugs usually occurs in the hepatic endoplasmic reticulum. It usually results in the production of more polar compounds which are more readily excreted than the parent molecules. The enzyme systems responsible for biotransformation of one drug may be inhibited or induced by another drug, or a combination of these two effects may occur. Phenobarbitone is a well known inducer of the hepatic drug metabolizing enzyme (Conney, 1967).

(iv) Excretion of drugs may be altered by several mechanisms, e.g. changes in the urinary pH as a result of the administration of other compounds. Phenobarbitone is known to be more rapidly excreted in alkaline urine.

Receptor Interactions

The receptor is that part of the cell directly involved with drug action. Drug interactions at receptor sites can occur by several mechanisms, e.g. competitive inhibition, non-competitive inhibition, non-equilibrium inhibition.

Determining the exact mechanisms of drug interactions can be exceedingly difficult. Many interactions are complex processes and may involve more than one mechanism.

THE PRESENT STUDY

METHODS

As a screening procedure to detect interactions between anticonvulsants, a series of multiple linear regression analyses were performed on plasma anticonvulsant level data collected at Royal Brisbane Hospital. In each analysis, plasma levels of one anticonvulsant drug were correlated with the dose of that drug, and with the doses of up to three other anticonvulsants that might be given simultaneously. Data from populations of up to 400 patients treated for epilepsy were studied. Since the study was based on plasma drug levels, it could detect pre-receptor interactions only.

For each pair of drugs in any particular regression equation, a partial correlation co-efficient (r) was calculated and its probability (P) determined. In addition, a potential interaction between phenytoin and sulthiame was investigated by examining the relation between plasma phenytoin level and dose in patients taking, or not taking, the potential interacting drug. Also, a number of apparent interactions between anticonvulsants were documented by serial plasma drug level measurement in three patients.

RESULTS

The various multiple linear regression analyses are shown in Table I. Statistically significant correlations between plasma drug levels and doses of various drugs are indicated. As might be expected, plasma levels of drug (or in the case of methylphenobarbitone and primidone, the drug

TABLE I

The relation between plasma anticonvulsant concentration and doses of the various drugs, as expressed in the equation:–

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

where y = plasma level of anticonvulsant as specified, expressed in μg/ml.

x_1, x_2, x_3, x_4 = daily dose of drug in mg. per Kg.

The table shows the a, b, c, d and e values for the fittings of the equation when x_1, x_2, x_3 and x_4 correspond to the drugs, as indicated, reading from left to right across the Table

Plasma Drug Level 'y'	'a'	Phenytoin	Phenobarbitone	Carbamazepine	Sulthiame	Methylphenobarbitone	Primidone
Phenytoin	+1.16	+1.67**	+1.42	+0.04+	+0.20		
Phenytoin	+1.01	+1.61**	+1.83+			+0.20	+0.05
Phenobarbitone	+3.48	+0.56	+3.93**	+0.04	+ .00		
Phenobarbitone	+4.12	+0.66		+0.41	-0.05	+0.87*	
Phenobarbitone	-3.59	+0.51		-0.35	+ .00		+2.27**
Carbamazepine	+5.63	-0.46**	-0.41	+0.18**	-0.04		

** $P<.01$
* $P<.05$
+ $.05<P<.1$

metabolite viz. phenobarbitone) varied with dose of drug for the drugs studied. The only interactions, or potential interactions detected, were as follows:

(i) Carbamazepine tended to raise plasma phenytoin levels, but the interaction was not quite significant at the 5% level of confidence, and quantitatively would have been of insignificant magnitude with therapeutic doses of carbamazepine.

(ii) Phenobarbitone dosage tended to raise plasma phenytoin levels. This interaction was almost significant at the 5% level. At therapeutic doses, phenobarbitone would tend to increase phenytoin levels.

(iii) Phenytoin dosage had a statistically significant effect in decreasing plasma carbamazepine levels, and the effect was of appreciable magnitude, the mean plasma carbamezepine level tending to fall by 0.9 μg/ml for each 2 mg/kg of phenytoin taken each day.

When the multiple linear regression analysis failed to provide evidence of an interaction between phenytoin and sulthiame, plasma phenytoin concentrations were correlated with phenytoin dose in patients taking this anticonvulsant alone, and in patients taking phenytoin together with sulthiame. An analysis of covariance showed that the two regressions did not differ to a statistically significant degree in either slope or elevation. Thus the second method of study also failed to provide evidence of an effect of sulthiame on phenytoin.

Studies in individual patients suggested the possibility of interaction between certain anticonvulsants, namely, carbamazepine and phenytoin, ethosuximide and phenytoin, and clonazepam, phenytoin and carbamazepine (Figs. 1,2,3).

DISCUSSION

The multiple linear regression approach used in the present study is basically a method of screening for interactions. It should be appreciated that this method may fail to detect interactions between drugs, including interactions which involve two mechanisms, one raising and one lowering the plasma level of a drug. Such mechanisms may be dose dependent, and in different patients taking different drug doses, the levels of one drug might be appreciably increased or decreased by another. Yet

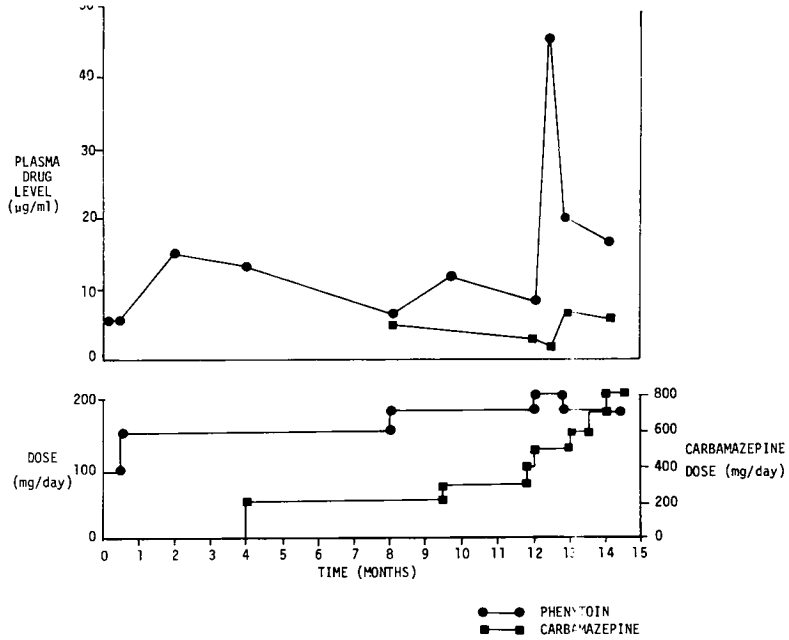

FIG. 1. The commencement of carbamazepine therapy at 4 months and the increased carbamazepine dose at 9½ months were followed by falls in plasma phenytoin concentration. At 12 months, despite increasing carbamazepine dose, the increased phenytoin dose resulted in a fall in plasma carbamazepine concentration.

The peak phenytoin level at 12 months followed a dose increment from 180 mg to 200 mg per day. (Plasma level changes of such a magnitude are not unusual if phenytoin metabolism is near to saturation.)

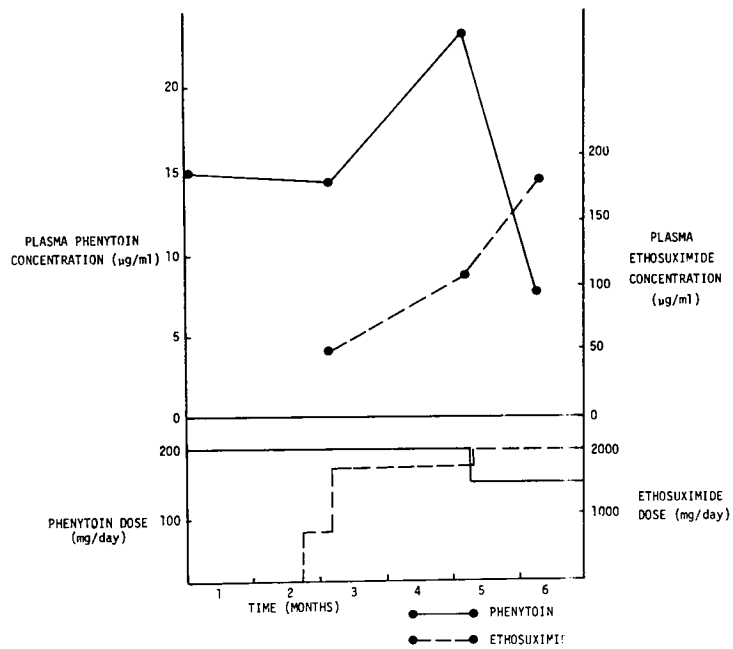

FIG. 2. The addition of ethosuximide at 2 months was followed by higher plasma phenytoin levels, although the daily dose of phenytoin remained unaltered.

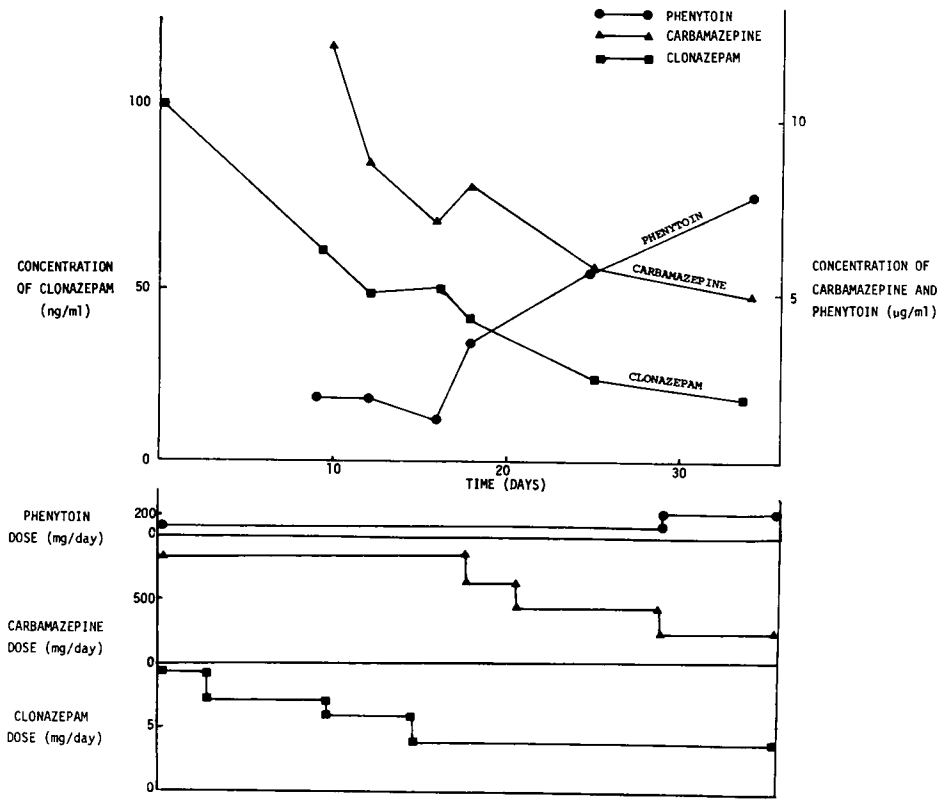

FIG. 3. During the period Day 1 to Day 18, decreasing clonazepam dose was associated with a decrease in plasma carbamazepine level, although the dose of the latter drug remained unaltered. Clonazepam dosage was unaltered after Day 15, but its level continued to fall as carbamazepine dose was decreased. The plasma phenytoin concentration increased during the period when clonazepam and carbamazepine doses were decreased, and phenytoin dose remained constant.

these effects may cancel out in a population, members of which are taking different drug doses. These considerations may explain failure to detect the often mentioned phenytoin-sulthiame interaction, but also suggest that the mechanism of this alleged interaction might be worth study in detail.

The tendency for phenytoin administration to decrease plasma carbamazepine levels is statistically significant. This is in agreement with work done by Christiansen and Dam (1973) who suggested that one possible mechanism for this decrease of plasma carbamazepine level was increased carbamazepine metabolism. Phenytoin and phenobarbitone both stimulate the hepatic microsomal enzyme systems which are responsible for drug metabolism (Conney, 1967).

The findings of the present study suggest the possibility (not quite significant at the 5% level of confidence) that carbamazepine administration may result in higher phenytoin levels. This is in contra-distinction to previous reports (Hansen, Siersboek-Neilson and Skovsted, 1971; Cereghino, Van Meter, Brock, Penry, Smith and White, 1973; Hooper, Dubetz, Eadie and Tyrer, 1974).

The interactions between the barbiturate group of anticonvulsants and phenytoin have been analysed. There is some evidence, statistically significant at the 10% level but not at the 5% level of confidence, that phenobarbitone tends to cause increased plasma phenytoin levels. The subject of phenobarbitone and phenytoin interaction has been well discussed by Kutt, Haynes, Verebely and McDowell (1969). These authors found that plasma phenytoin levels in patients on phenytoin and phenobarbitone were sometimes higher, sometimes lower and sometimes unchanged when compared to the plasma phenytoin levels in patients on phenytoin alone. It was suggested that

the effect of usual therapeutic doses of phenobarbitone on plasma phenytoin levels was of small magnitude and of little consequence in an individual patient. Methylphenobarbitone and primidone are transformed to phenobarbitone in the body and might therefore be expected to have similar effects to phenobarbitone. In the present study, no effects of these anticonvulsants were detected on plasma phenytoin concentration.

The present paper should be taken only as a preliminary attempt to define the clinically frequent interactions between anticonvulsants. It is intended to serve as an indication of those interactions in man which might be worthy of detailed study as to mechanism.

SUMMARY

Anticonvulsant drug interactions have been investigated using multiple linear regression analyses. The one statistically significant interaction found was that in which phenytoin dosage decreased plasma carbamazepine concentrations. There was a suggestion that carbamazepine and phenobarb dosage tended to increase phenytoin levels. No interaction was detected between phenytoin and sulthiame.

Studies in individuals suggested that ethosuximide may increase plasma phenytoin concentration and that clonazepam tends to decrease carbamazepine and phenytoin concentrations.

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REMYELINATION AFTER TRANSIENT COMPRESSION OF THE SPINAL CORD

B.M. HARRISON,* R.F. GLEDHILL,† and W.I. McDONALD†

A little more than ten years ago, it was demonstrated for the first time that the central nervous system (C.N.S.) is capable of repairing myelin damage. Bunge, Bunge and Ris (1961) showed that new myelin sheaths are formed around demyelinated axons in an experimentally produced lesion in the cat spinal cord. Since then similar observations have been reported in other experimentally produced central demyelinating lesions (Bubis and Luse, 1964; Lampert, 1965, 1967; Hirano, Levine and Zimmerman, 1968; Prineas, Raine and Wisniewski, 1969 and Blakemore, 1972, amongst many others) and it is now established beyond any reasonable doubt that remyelination occurs in the C.N.S. Despite this many fundamental questions about the way in which myelin sheaths are organised during remyelination in the C.N.S. remain unanswered. For instance, it is not known whether the myelin is laid down in segments which are bounded by nodes and, if they are, whether the internodal length is appropriate to the diameter of the enclosed axon.

It was to answer these and other questions about the process of remyelination in the C.N.S. that we undertook a light and electron microscope study of a lesion produced in the cat by transient compression of the spinal cord. The morphological changes in central nerve fibres during the early stages of the evolution of this lesion have already been described (Gledhill, Harrison and McDonald, 1973). It was shown that, providing the degree of compression is mild, demyelination followed by remyelination is the predominant pathological feature.

MATERIAL AND METHODS

For the present series of experiments four adult cats were examined and five normal animals were used as histological controls.

The method used for producing the compression lesion has been described in detail elsewhere (Gledhill *et al.*, 1973). In short, a laminectomy at L1 was performed under pentobarbitone anaesthesia. The exposed spinal cord was compressed by means of a brass screw which was firmly supported so that only its smooth tip rested on the surface of the unopened dura over the mid-line of the posterior columns. Compression was increased every 20 minutes by turning the screw through 180°, producing an advance of 0.5mm. The duration of compression was no longer than 3 hours.

The animals were killed under pentobarbitone anaesthesia by the perfusion of fixative solutions through the abdominal aorta 1 month, 6 months, 13 months and 18 months respectively after compressing the cord. The perfusion method using buffered glutaraldehyde and chrome-osmium fixatives has been described previously (Harrison, McDonald and Ochoa, 1972,a). After perfusion the laminectomy site was exposed. The spinal cord was removed from the site of compression and prepared for examination by light and electron microscopy.

* Department of Medicine, University of Sydney
† National Hospital, Queen Square, London

EXPERIMENTAL RESULTS

There were many abnormal nerve fibres in the central part of the lesion at one month. Only a small proportion of these fibres was completely denuded by myelin; the majority of fibres in the middle of the lesion had abnormally thin myelin sheaths surrounding axons of normal appearance. Fig. 1 shows such a thinly myelinated fibre. Close examination of the structure of the myelin sheath around this fibre shows that it resembles those myelin sheaths undergoing myelination during development. The myelin lamellae are arranged around the fibre in a continuous spiral and in one region the lamellae are incompletely compacted. These appearances suggest remyelination is occuring. This suggestion is further supported by the fact that fibres with these features are not seen in earlier lesions and with the passage of time they become more and more common in later lesions.

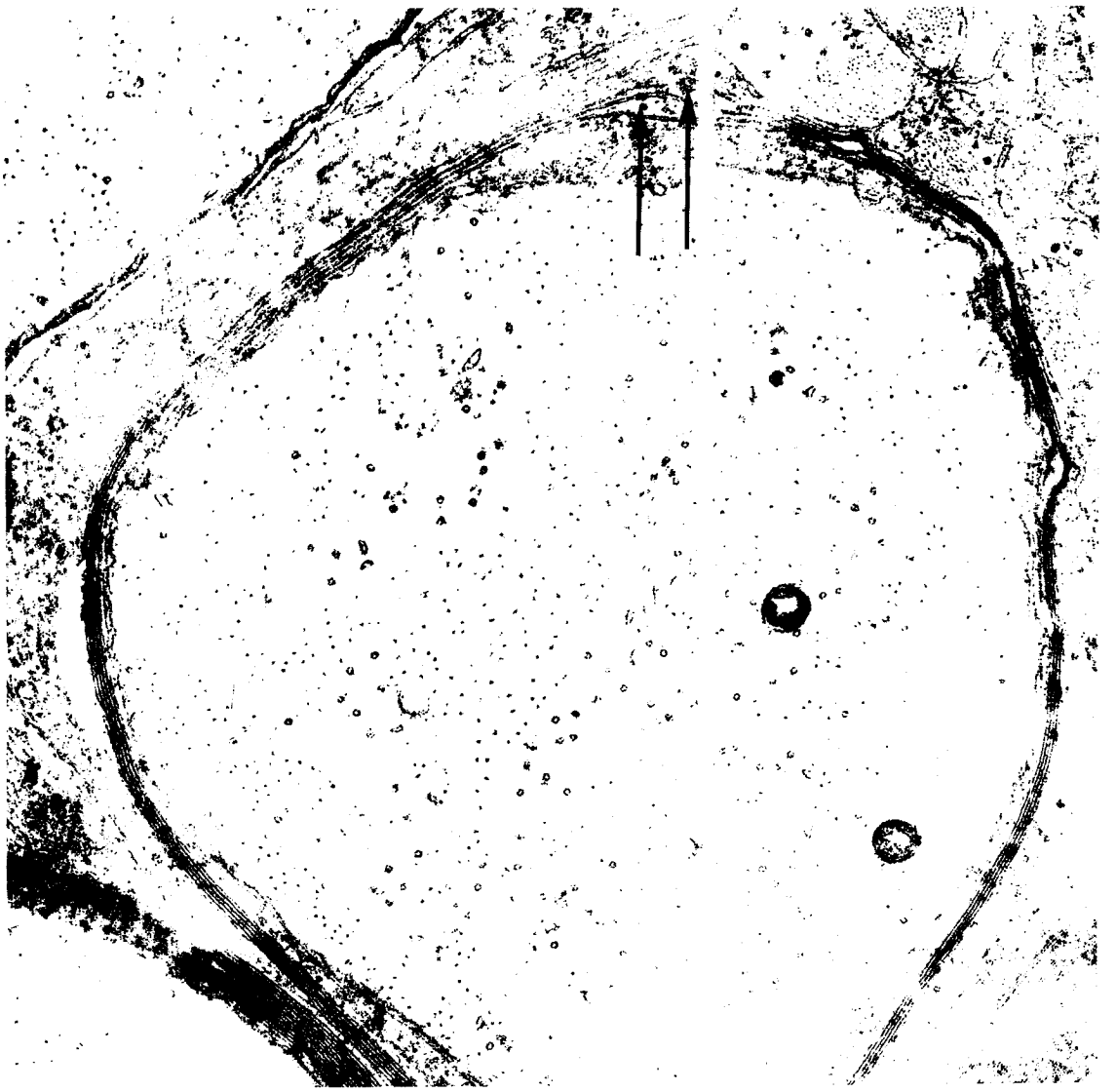

FIG. 1. Remyelinated fibre. An axon 5μm in diameter is surrounded by a thin myelin sheath. The lamellae are arranged in a continuous spiral. In one region of the sheath (arrows) cytoplasm is still retained between the lamellae.

By 6 months only occasional demyelinated axons were present in the lesion; the vast majority of fibres had at least a thin covering of myelin. The thin myelin sheaths appeared to be thicker in the 13 months lesion and thicker still at 18 months, but even at this very late stage they were still noticeably thin for the axon diameter.

Longitudinal sections through the lesions regularly showed that the newly formed myelin sheaths were arranged in segments. Fig. 2 shows a longitudinal section from a 1 month compression lesion in the posterior columns. An axon approximately 5μm in diameter is covered by an abnormally thin myelin sheath which is of uniform thickness along a total length of 165μm. The continuity of the myelin is interrupted by a number of gaps (marked by arrows) which separate the fibre into 2 consecutive segments each approximately 75μm long. Examination of the gap regions under higher power shows that they have the characteristics of central nodes. Fig. 3 shows that the myelin lamellae terminate in cytoplasm filled loops, most of which are attached to the axon by transverse bands. Fig. 3 also shows that there is a layer of granular material beneath the bare stretch of axon. It was therefore concluded that after demyelination produced by spinal cord compression complete thought short myelin internodes are formed with a true node at each end.

FIG. 2. 1 month compression lesion. Longitudinal section through the posterior columns. Details discussed in text.

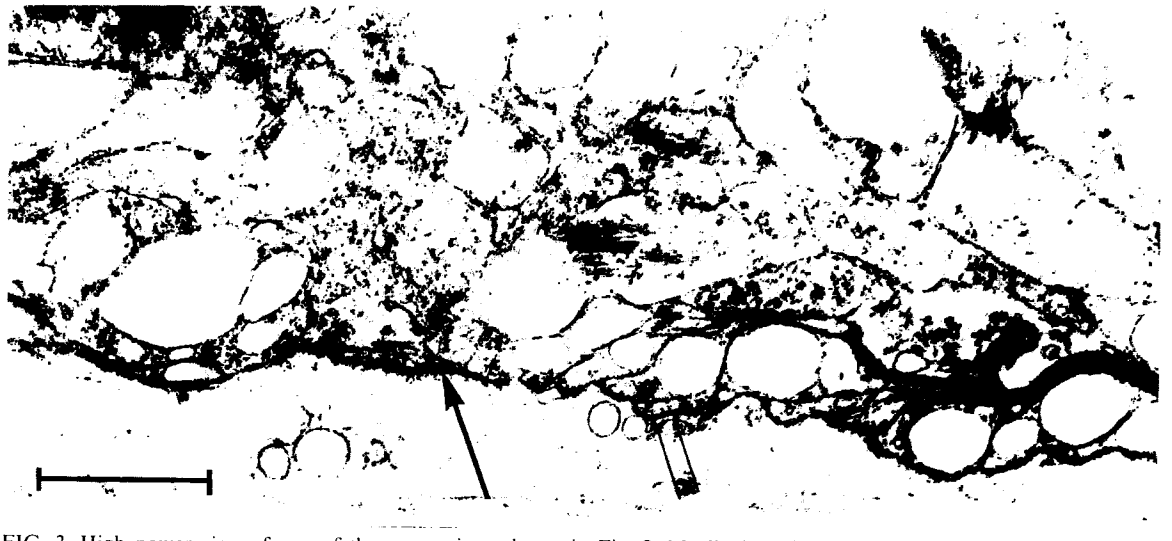

FIG. 3. High power view of one of the gap regions shown in Fig. 2. Myelin lamellae terminate in cytoplasm filled loops which are attached to the axolemma by transverse bands (small arrows). To the left of this region there is a bare stretch of axon which has a layer of granular material beneath the axolemma (large arrow). Bar 1μm.

What is the nature of the remyelinating cell in this lesion? In the peripheral nervous system the Schwann cell is responsible for the formation of myelin sheaths whilst in the C.N.S. myelin is made by oligodendrocytes. The two types of cell produce myelin sheaths which are easily distinguishable by electron microscopy. In this series of experiments the remyelinated fibres have all the features of central nerve fibres undergoing myelination during development and we are thus confident that in this situation remyelination is effected by oligodendorcytes (Gledhill *et al.*, 1973).

FIG. 4. 3 month severe compression lesion. Longitudinal section through the posterior columns. A complete myelin internode formed by a Schwann cell. The nodes are marked by arrows the distance between which is 65μm. A Schwann cell nucleus is seen in the centre of the field.

However, in another series of experiments we examined lesions in the cat spinal cord produced by more severe compression and noted that remyelinated fibres of quite a different appearance were seen. There was evidence in these lesions that Schwann cells formed short remyelinated internodes around demyelinated central axons in damaged parts of the posterior columns. Fig. 4 shows a complete internode of myelin. The nodes at each end of the segment are marked by arrows the distance between which is 65μm. There are several features of this short internode which show that the myelin is made by a Schwann cell and distinguish it from other short remyelinated internodes formed by oligodendrocytes. Firstly, there is a cell nucleus which is placed in the middle of the internode lying close to the myelin sheath and secondly, the whole internode including the nucleus is surrounded by a basal lamina. The latter feature is more clearly seen in Fig. 5 which is a high power view of one of the nodal regions in Fig. 4. Fig. 5 shows that the basal lamina ends abruptly at the node and does not carry on to cover the myelin of the next internode. The structure of the myelin sheath in the adjacent paranode appears quite different. It has neither a layer of cytoplasm above the myelin nor an outer basal lamina; these findings indicate that it is central nervous system-type myelin made by an oligodendrocyte.

DISCUSSION

The question of the origin of the cells which give rise to peripheral nervous system-type myelin in the C.N.S. has been thoroughly discussed by Hirano, Zimmerman and Levine, (1969). They concluded that the balance of evidence was firmly in favour of the myelin being formed by a cell which entered the C.N.S. after the lesion occurred, and that the most likely candidate was the Schwann cell. Lampert and Cressman (1964) have shown that axonal sprouts from peripheral nerve fibres in the dorsal roots invade the spinal cord after transection of the dorsal columns. These sprouts are associated with Schwann cells and appear similar to the fibres which are surrounded by peripheral type myelin in the severe transient compression lesion. However, since we have shown that the myelin on either side of the Schwann cell internode has the features of C.N.S. type myelin made by oligodendrocytes, this fibre is most likely to be an original central nerve fibre and not an axonal sprout from the peripheral nervous system. Furthermore, the axon around which the invading Schwann cell formed a myelin sheath was of large diameter. A fibre of such large calibre must be a mature central nerve fibre which has demyelinated; invading axonal sprouts do not attain such a large diameter (Lampert and Cressman, 1964). It can therefore be concluded that Schwann cells are capable of forming complete new internodes of myelin around demyelinated central nerve fibres.

We are at present interested in the factors which govern the entry of Schwann cells into the spinal cord. Two such factors have so far emerged. Firstly, the migration of Schwann cells into the spinal cord appears to depend on the presence of fibres undergoing Wallerian degeneration

FIG. 5. High power view of one of the nodal regions shown in Fig. 4. A basal lamina (arrow) which surrounds the myelin of the paranode on the left ends abruptly at the node. The myelin sheath of the adjacent paranode on the right appears quite different. There is no collar of cytoplasm above the myelin and a basal lamina is absent.

in the lesion. Schwann cells were not seen in the compression lesions in which demyelination with the preservation of axon continuity was the predominant feature but were present in the lesions produced by more severe compression in which complete degeneration of nerve fibres was extensive. The second factor appears to be the proximity of the lesion to the root entry zones. In the compression lesions (Harrison, Gledhill and McDonald, in preparation) and also in the lesion produced by the direct micro-injection of diphtheria toxin into the spinal cord (Harrison, McDonald and Ochoa, 1972,b) the first central demyelinated fibres to be remyelinated by Schwann cells are situated on the side of the lesion closest to the dorsal root entry zone.

Finally, it is interesting to enquire whether remyelination might restore transmission to fibres with conduction block due to demyelination since we have shown that the new myelin sheaths are laid down in segments which have many of the morphological pre-requisites for saltatory conduction. However, there remain at least two morphological differences between the structure of myelin sheaths in normal and remyelinated fibres (McDonald, 1974,a). The first difference is that the myelin sheath of remyelinated fibres remains abnormally thin. The question therefore is whether such a thin covering of myelin is adequate to insulate the fibre and restore conduction. Results from other studies might provide an answer to this question. A computer simulation of

conduction in the peripheral fibres devised by Koles and Rasminsky (1972) has shown that conduction might still be possible with only 3% of the normal myelin thickness. If, as seems reasonable, the computer prediction applies to central nerve fibres as well as peripheral fibres (McDonald, 1974,b) it is possible that even limited remyelination, say 2 or 3 lamellae, might be sufficient to restore conduction. The second important difference between normal and remyelinated nerve fibres is the distance between successive nodal gaps. It is possible that the leakage of current through the numerous gaps in chains of very short internodes might be sufficient to block saltatory conduction; but conduction might occur if the majority of the gaps were fully-functional nodes. There is at present no evidence about this possibility and the question of whether remyelination of central demyelinated fibres is an important event contributing to the recovery of lost functions remains open.

SUMMARY

Transient mild compression of the spinal cord produces a lesion in which demyelination with preservation of axon continuity is the predominant nerve fibre change. This damage is repaired by oligodendrocytes which produce complete though abnormally thin and short internodes of myelin along demyelinated stretches of axons. When compression is more severe, this damage is also repaired by Schwann cells which migrate into the spinal cord from nearby root entry zones and form complete segments of peripheral nervous system-type myelin around demyelinated central axons.

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THE BIOAVAILABILITY OF CARBAMAZEPINE

L.M. COTTER, G. SMITH, W.D. HOOPER, J.H. TYRER and M.J. EADIE*+

Although carbamazepine ("Tegretol") has been in use for over a decade it is only recently that studies on its pharmacokinetics have become available. Evidence is now appearing which raises the possibility of a bioavailability problem with the drug, i.e. an unsatisfactory rate and extent of its entry into the systemic circulation when it is given by mouth.

PLASMA CARBAMAZEPINE LEVELS IN RELATION TO DOSE

Several workers have found a relatively poor correlation between plasma carbamazepine concentrations and drug doses in patients taking carbamazepine (Reynolds, 1973). In a personal series of 145 patients taking carbamazepine regularly, the regression for plasma drug level on oral dose was as shown in Fig. 1. A wide scatter of individual points can be inferred from the 95% fiducial

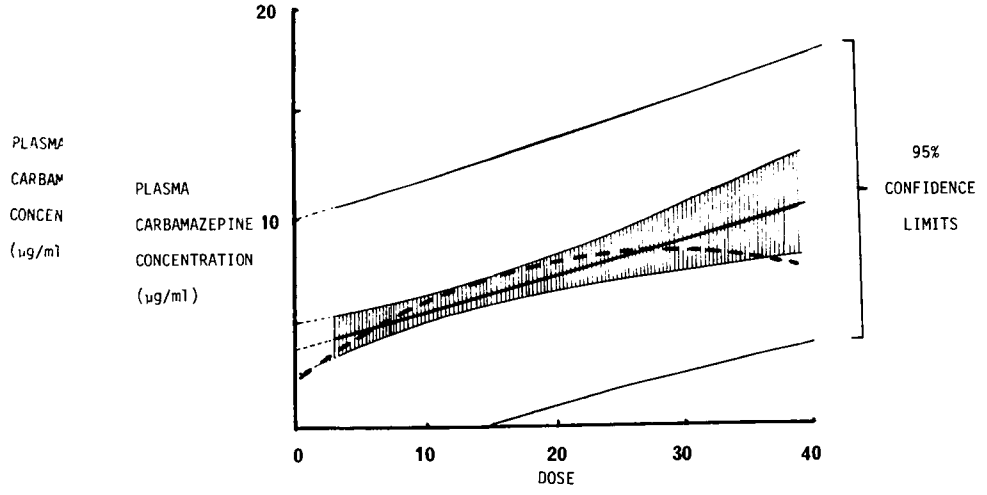

FIG. 1. The regression for plasma carbamazepine level on drug dose in 145 patients. The linear regression line is shown with its 95% fiducial limits shaded, while the outermost pair of lines enclose the 95% fiducial limits for predicting plasma drug level from dose. The parabolic regression of best fit is shown as a broken line.

* Department of Medicine, University of Queensland
+ Supported by a grant from the National Health and Medical Research Council of Australia.

limits for predicting plasma drug level from dose. The 95% fiducial limits of the regression line itself make it extremely unlikely that the extrapolated regression will pass through zero, yet clearly the true regression for plasma drug level on dose must pass through zero when no drug is taken. There are a number of possible explanations for this discrepancy. The relation between plasma carbamazepine level and drug dose might not be linear; the method for measuring plasma carbamazeine levels might be inaccurate; or the nominal drug dose might not bear a close relation to the amount of drug actually entering the body. When various forms of curvilinear regression were fitted to the data, a parabolic regression did fit marginally better than the linear regression, but still intercepted the y axis well above zero. The method for measuring plasma carbamazepine levels, that of Friel and Green (1973), has proved accurate and reliable in our hands, and its confidence limits have been published elsewhere (Eadie, 1974) Therefore one might suspect that there is a poor correlation between the nominal oral carbamazepine dose and the amount of the drug that is actually absorbed in man.

In the series of 145 patients referred to above, there were only three who were taking carbamazepine alone and who had their steady state plasma carbamazepine levels measured while receiving two different doses of the drug. In all three the rate of rise in plasma carbamazepine level decreased as drug dose increased (Fig. 2). It should be indicated that this relation does not apply when

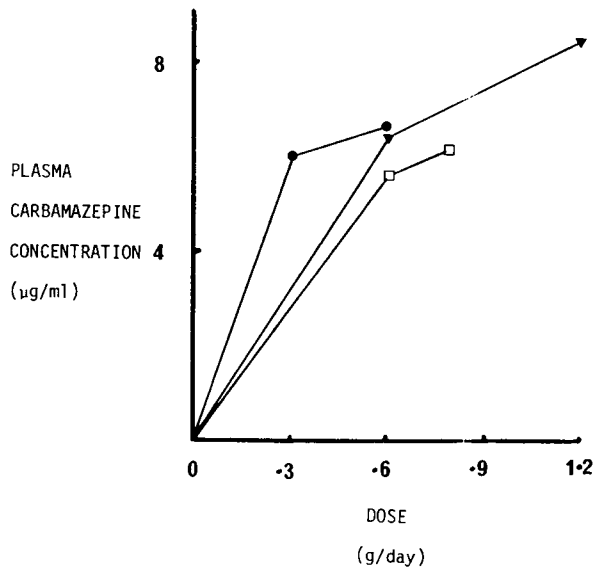

FIG. 2. The effect of carbamazepine dose increase on plasma carbamazepine level in three patients taking no other therapy.

carbamazepine dose is increased in patients taking the drug together with diphenylhydantoin (Hooper, Dubetz, Eadie and Tyrer, 1974). However it is known that concurrent diphenylhydantoin therapy alters plasma carbamazepine levels (Christiansen and Dam, 1973). There are several possible explanations for the decreasing rate of rise in plasma carbamazepine levels with increasing drug dose in patients taking the drug alone. For instance the absorption of the drug could decrease as its dose increased. Other possibilities e.g. an increase in the volume of distribution of the drug in the body as more drug accumulated, or an increase in its rate of biotransformation, cannot entirely be discounted, though in terms of existing knowledge they seem less likely.

Thus there are two lines of evidence raising the possibility that carbamazepine may be incompletely and variably absorbed from the alimentary tract of man. With this possibility in mind the absorption of carbamazepine was investigated as part of a study of the pharmacokinetics of the drug.

CARBAMAZEPINE PHARMACOKINETICS

Materials and Methods

Plasma carbamazepine levels after single oral doses of the drug were measured at intervals over 4 or 5 day periods in 6 healthy volunteers receiving no other therapy. Every two or three weeks each volunteer, while fasting, took a dose of the drug in the form of commercially available tablets, till each had taken doses of, respectively, 200, 400, 500, 600, 700, 800, 900 and sometimes 1,000mg. The time-courses of the plasma carbamazepine level curves were plotted, and the area under each curve was determined by the technique of cutting out and weighing. The time at which peak drug concentrations occurred was read from the graphs, and the data were analysed for absorption and elimination kinetics in terms of a one-compartment model with first order absorption and elimination (Portmann, 1970). This analysis was carried out with the aid of a programmable desk calculator. Because of the limited numbers of venepunctures that could reasonably be carried out in a subject, and the need to have a sufficient number of points during the elimination phase, often there were not sufficient data for accurate determination of carbamazepine absorption parameters.

Results

The study of the elimination kinetics of carbamazepine tended to exclude two alternatives to the proposition that the absorption of the drug might be defective. The mean elimination half-lives of carbamazepine in the six subjects proved to be, respectively, 28, 30, 30, 35, 35 and 39 hours. There was no consistent relation between elimination half-life and drug dose, a point which argues against increased biotransformation of the drug occurring as its dose increased. (The possibility of increased biotransformation was raised earlier in this paper as an explanation for the decreasing rate of rise of plasma carbamazepine level with increasing drug dose in the individual.) Another possibility raised to explain this effect, an increase in volume of distribution was increasing drug dose, was ruled out by the finding that the calculated volumes of distribution, assuming complete drug absorption, tended to fall as drug doses increased in the volunteers.

Where there were sufficient data for their calculation, the absorption rate constants for carbamazepine, and the corresponding absorption half-time, are set out for each subject in Table I. The relation between absorption half-time and drug dose is shown in Fig. 3. There is a tendency

TABLE I

Carbamazepine Absorption Kinetic Data. Absorption rate constants, expressed as $^{-1}$, are shown with the corresponding T½ in hours in brackets beside them.

Dose (mg.)	Subject I	II	III	IV	V	VI
200	.252 (2.7)	.838 (0.8)	.356 (1.9)	–	–	.047 (14.6)
400	.099 (7.0)	.088 (7.9)	.089 (7.8)	.607 (1.1)	.080 (8.6)	.306 (2.3)
500	.109 (6.3)	.065 (10.6)	–	.093 (7.5)	.083 (8.3)	–
600	–	–	–	–	.076 (9.2)	.057 (12.1)
900	–	.091 (7.7)	.066 (10.6)	–	–	–
1000	–	–	–	–	.065 (10.7)	.066 (10.5)

for absorption half-time to increase, i.e. for absorption to slow, as carbamazepine dose increases. Assuming a first order process, absorption of 95% of a drug dose should occupy 4 times the absorption half-time of a drug. For carbamazepine doses in excess of 400 mg. the half-times were never below 6 hours, and even with doses of 400 mg. four of six subjects had absorption half-times of over 6 hours. If these subjects passed one bowel movement each 24 hours it is unlikely that they would absorb the full amount of a single 400 mg., or greater, carbamazepine dose.

In an individual, the area under the plasma level curve is a measure of the amount of a drug dose absorbed. The mean area under the curve for the subjects has been plotted on the ordinate

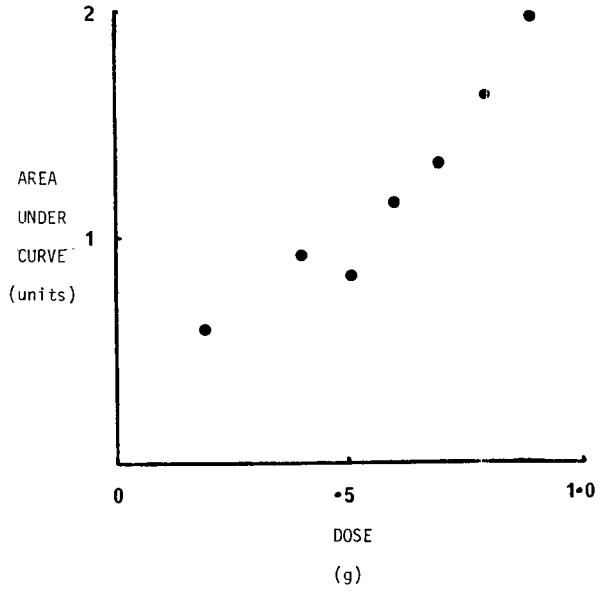

FIG. 3. The regression of carbamazepine absorption half-time on drug dose. Absorption half-time tends to increase as drug dose increases.

against drug dose in Fig. 4. The relation between the two changes as dose increases. In proportion to carbamazepine dose, area under the curve tends to be smaller at higher (greater than 0.5G) than at lower doses of the drug.

Thus study of the pharmacokinetics of carbamazepine provided evidence of slow, and probably incomplete, absorption of the drug from the alimentary tract of man. Absorption is likely to worsen

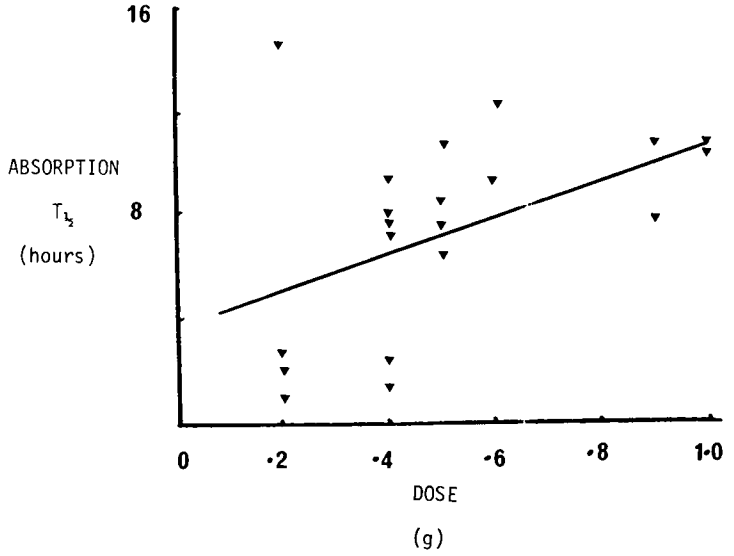

FIG. 4. Relation between mean area under plasma drug level curve and carbamazepine dose in 6 subjects. The curve of best fit is shown. The points corresponding to doses below 0.5G would appear to lie along a straight line (passing close to the origin) which differs from the straight line which passes through the points corresponding to doses above 0.5G.

as drug dose is increased. This leads to an interesting situation. The elimination kinetic profile of carbamazepine in man suggests that the drug plasma levels would be adequately maintained if the drug were taken regularly once a day, i.e. more often than once each elimination half-life. Yet if a divided daily drug dosage that had produced satisfactory plasma carbamazepine levels were changed to a once-daily regime, it is possible that the total drug dose might have to be increased to maintain the plasma drug levels, because of reduced absorption of the larger single dose.

The question remains as to whether the indifferent absorption of carbamazepine is an inherent property of the drug molecule itself, or whether it is a consequence of the pharmaceutical formulation in which carbamazepine is delivered to the body.

THE RELATIVE BIOAVAILABILITY OF CARBAMAZEPINE TABLETS

In an attempt to answer the question posed above, five of the six subjects ingested 400 mg. of carbamazepine in a specially prepared solution in ethanol and glycerol. The carbamazepine content of this solution was verified analytically. Plasma carbamazepine levels were followed as in the previous studies, with the intention of comparing the derived pharmacokinetic parameters with those which had applied when the same subjects took 400 mg. of carbamazepine as commercially available tablets.

Unfortunately blood sampling times which had seemed appropriate for derivation of absorption kinetic parameters on the basis of experience with the tablets proved quite unsuitable when the solution was taken. In all subjects absorption of drug from the solution was complete, or nearly complete, before any blood was taken. The times to achieve peak plasma drug levels, and the areas under the curves, when subjects took 400 mg. carbamazepine as tablets and in solution are shown in Table II, and the plasma level curves for one subject are shown in Fig. 5. Peak plasma

TABLE II

Comparisons of Carbamazepine Tablets and Solution

Subject	Time to reach peak level (hours)		Area under curve (arbitrary units)	
	Tablets	Solution	Tablets	Solution
I	14-24	<2	0.66	1.01
II	16-27	<3	0.72	0.86
III	18-22	<2	0.57	0.83
IV	8-25	<5	1.51	1.35
V	4-7	<3	1.10	1.21

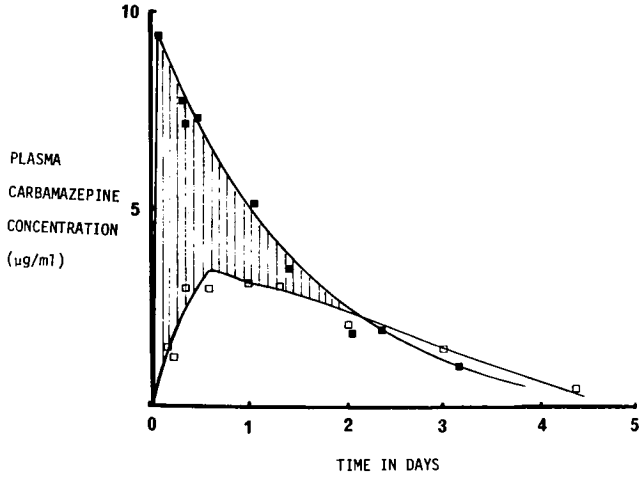

FIG. 5. Time courses of plasma carbamazepine levels after one subject took 400 mg. of the drug as tablets (open squares) and as a solution (solid squares). The increase in area under the curve when the drug was taken in solution is shaded.

levels occurred very much earlier in all subjects when the drug was taken as a solution rather than as tablets, and in four of five subjects the area under the curve was greater. Thus the drug tended to be absorbed faster and more completely from solution than from tablets. Hence it is the pharmaceutical formulation of carbamazepine which limits its bioavailability, rather than the intrinsic properties of the drug itself.

CONCLUSIONS

There have been intimations from overseas that there may be a bioavailability problem with carbamazepine preparations (Kauko and Tammisto, 1974) and it appears that a similar difficulty applies in Australia. At first sight it might appear desirable that the manufacturers of carbamazepine should introduce a preparation of carbamazepine with improved bioavailability as soon as possible. However, there is no clinical difficulty in the use of the currently available carbamazepine preparation in Australia, and if its bioavailability is enhanced many epileptics may need readjustment of their anticonvulsant dosages. If this happens before facilities for measuring plasma carbamazepine levels are generally available, and before more is known about the pharmacokinetics and interactions of carbamazepine, the endeavour to produce a pharmaceutically more satisfactory preparation may lead to a therapeutically less satisfactory situation, at least temporarily. Those who treat epilepsy will need to be prepared for the day when the bioavailability of carbamazepine is improved.

SUMMARY

Two aspects of the correlation of plasma carbamazepine level with drug dose in patients taking carbamazepine tablets indicated the possibility that the drug may be incompletely and variably absorbed from the alimentary tract of man.

To investigate this possibility, pharmacokinetic studies were undertaken in six volunteers, who were given increasing single doses of carbamazepine in tablet form at appropriate intervals. These studies gave evidence of slow, and probably incomplete, absorption of carbamazepine. After administration of carbamazepine in a specially-prepared solution to 5 of the subjects, rapid absorption of the drug occurred, and in 4 subjects more drug was absorbed than when the same normal dose was given as tablets.

It was concluded that the pharmaceutical formulation of carbamazepine tablets limits the bioavailability of the drug, and that problems may arise if the bioavailability of the drug is to be increased.

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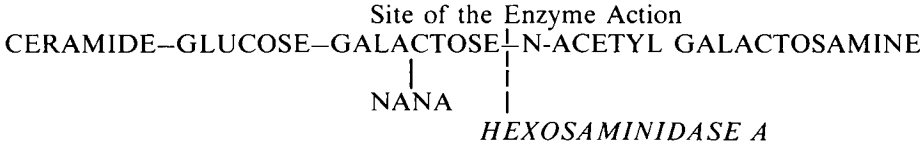
TAY SACHS DISEASE IN A CHILD AND MANAGEMENT OF A SUBSEQUENT PREGNANCY

D.B. APPLETON, T.J. GAFFNEY, H. McGEARY and N.J. NICOLAIDES*

Accurate diagnosis of the known lipid storage diseases is now possible from their clinical features and biochemistry. As a result, reliable procedures for the identification of heterozygous carriers and prenatal detection of affected foetuses have been established (Brady, Johnson and Uhlendorf, 1971).

Tay-Sachs disease results from the accumulation of GM_2 ganglioside in neural tissues. This material is normally degraded by the enzyme hexosaminidase A which is lacking in brain, blood and viscera in the majority of affected patients (Okada and O'Brien, 1969).



Total hexosaminidase is normal in the disorder but the B component is not actively hydrolytic.

The condition is transmitted in autosomal recessive fashion with a gene frequency of 1 in 40 people of Jewish extraction and 1 in 380 in non-Jews in the United States of America (Menkes, 1974). The incidence of cases in Australia is therefore predicted to be low.

CASE REPORT

The first pregnancy of a 34 year old mother was complicated at 3 months' gestation by a coelic crisis which responded to a gluten-free diet. The father was a widower whose first marriage produced three normal children. A male child was born and appeared normal in all respects until four months of age when his mother suspected he was more hypotonic than normal and noticed that he was not beginning to roll. Little further motor development occurred and he was first seen for assessment at 10 months of age. There was then considerable head lag. The upper limbs were hypotonic while the lower limbs were hypertonic. Tendon reflexes were pathologically brisk with bilateral ankle clonus and extensor plantar responses. A typical cherry red spot was present at the macula of each eye; no visceral enlargement was found. His head circumference was 48 cms. at the 90th percentile for age. Hexosaminidase A was absent from a leucocyte preparation subjected to electrophoresis (Friedland, Schenck, Jaifer, Pourfar and Volk, 1970; Singer, Nankervis and Schafer, 1972).

A full thickness rectal biopsy was carried out. The biopsy material was divided into three separate portions. Fresh material was kept for frozen section and lipid stains. One portion was fixed in 10% formal saline, dehydrated in alcohols and embedded in paraffin for routine histology and special stains. The third portion was fixed in glutaraldehyde in phosphate buffer for electron microscopy.

Sections of the rectal wall were examined by light microsopy. The only abnormality detected was the presence of abnormal ganglion cells. The ganglion cells tended to be enlarged and were readily seen. Their cytoplasm tended to be foamy and

* The Royal Children's Hospital, and the Royal Brisbane Hospital, Brisbane.

reticulated in appearance and showed slight basophilia in haematoxylin and eosin staining (Fig. 1). The normal acidophilic staining reaction appeared to be lacking. The nuclei were sometimes centrally placed but in some cases were eccentrically situated. Special stains, viz. P.A.S., oil red O, toluidine blue,were performed in an attempt to categorize the material distending the ganglion cells. P.A.S. positivity was faint only and the cytoplasm stained in a faint finely granular fashion. The oil red O stain also gave a faintly positive reaction. The material did not stain in a metachromatic fashion with toluidine blue.

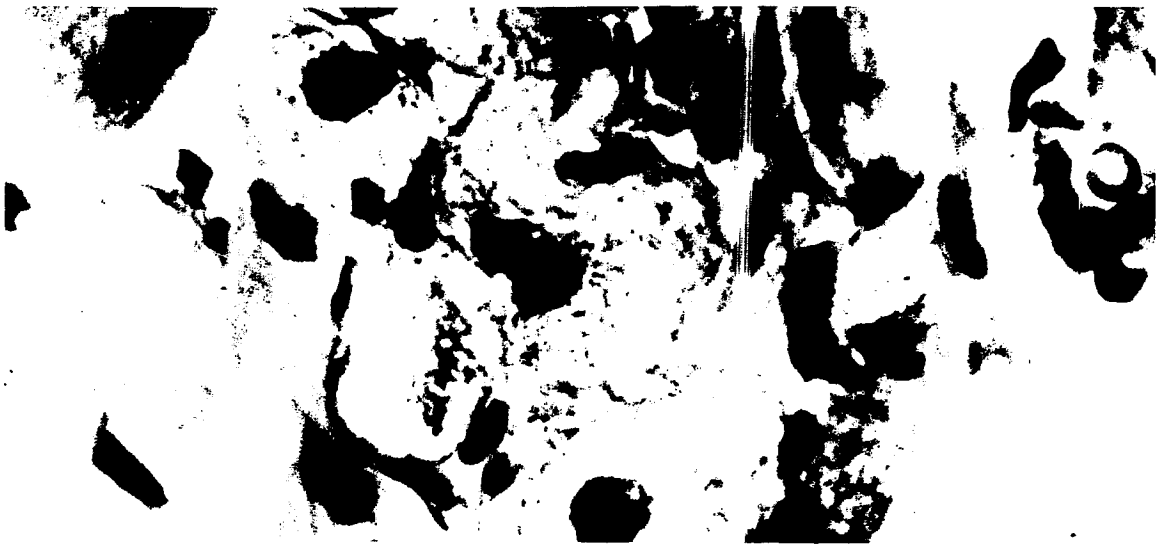


FIG. 1. Neurones with foamy reticulated cytoplasm. Magnification x 1000 approximately.

Fresh tissue taken at the time of rectal biopsy was fixed in 5% glutaraldehyde in phosphate buffer and post fixed in 1.5% osmium tetroxide in S-collidine buffer. Following dehydration in ethanol, the tissues were embedded in EPON 812. Thin sections were cut with an LKB ultrotome and stained with uranyl acetate and lead citrate and examined in a Hitachi HS7S electron microscope. The neurones examined were striking in their appearance. Much or most of the cytoplasm was occupied by a great number of abnormal round or oval membranous cytoplasmic bodies. The neuronal nucleus was essentially normal in appearance with normal nucleolus, nucleoplasm and nuclear membrane (Figs. 2 and 3). Cytoplasmic

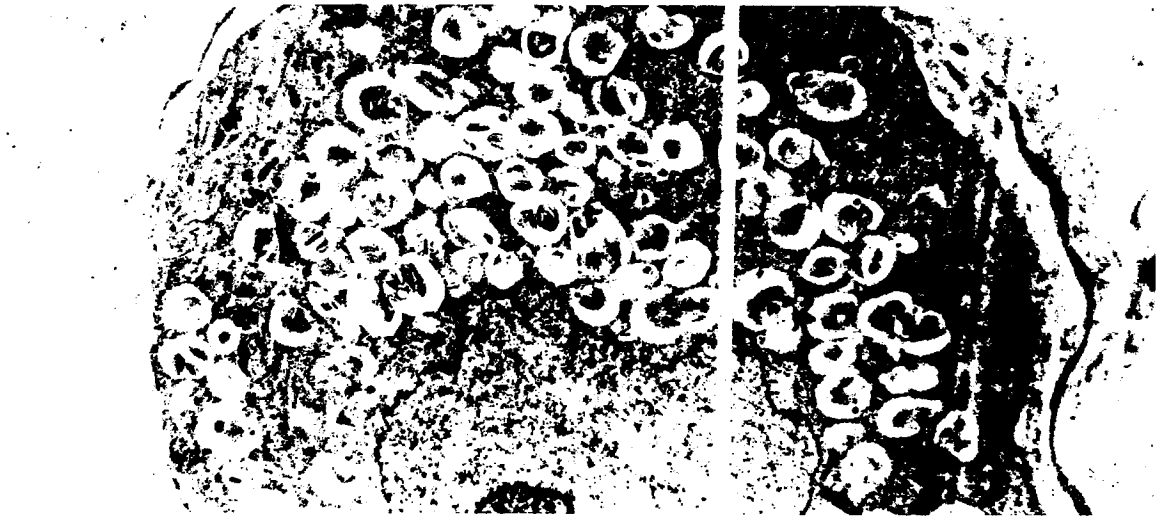


FIG. 2. Neurone: normal nucleus and nucleolus.
Cytoplasm: filled with membranous cytoplasmic bodies; reduced proportion of normal cytoplasmic organelles (mitochondria, etc.). Magnification x 5280 approximately.

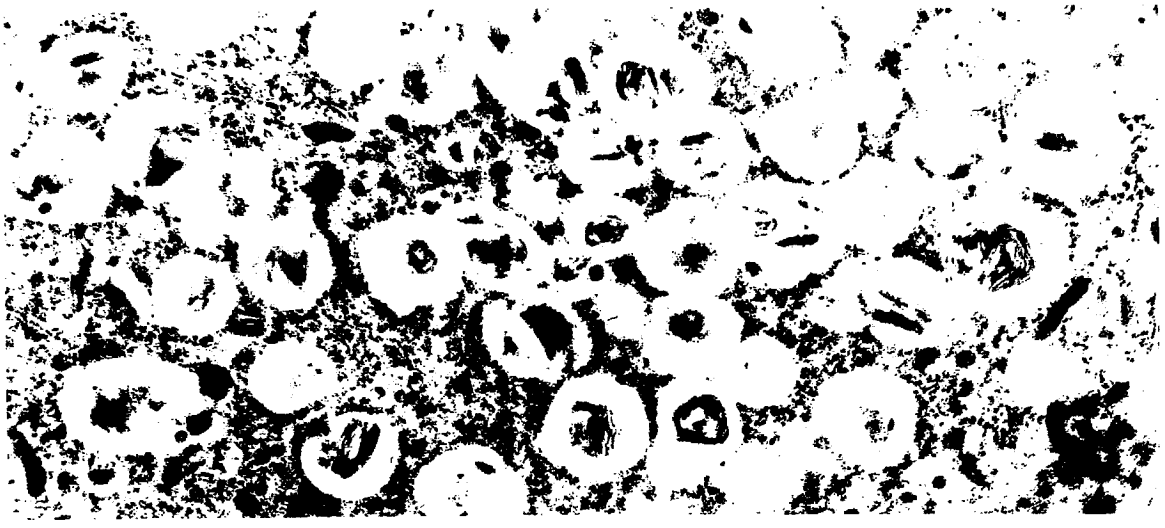


FIG. 3. Showing membranous cytoplasmic bodies exhibiting different patterns of arrangement of membranes. Mitochondria and ribosomes also are visible. Magnification x 10.100 approximately.

organelles were present but markedly reduced in proportion to the quantity of abnormal cytoplasmic organelles. Ribosomes were present throughout the neuronal cytoplasm. The inclusions tended to vary in size but mostly ranged from 0.5 μ to 1.0 μ in greatest diameter. They presented a distinctive appearances in that they were composed of closely packed electron dense membranes frequently arranged in a regular fashion. Some showed a concentric arrangement whilst in others the membranes showed gentle curves or flat layers. Some varied in appearance with a mixed pattern of concentric and curved or flat membranes. Some contained a small homogeneous or finely granular zone (Figs. 4 and 5). The membranes appeared to possess a lamellated structure composed of varying numbers of dense lines bordered by pale lines (Fig. 6). Occasional lines were seen to undergo fusion (Fig. 7). The outer layers in general were essentially similar to the inner layers.

The histological findings and histochemical findings resemble those described in Tay Sachs disease (infantile form). The electron microscopic findings are quite distinctive and strongly support the clinical diagnosis.

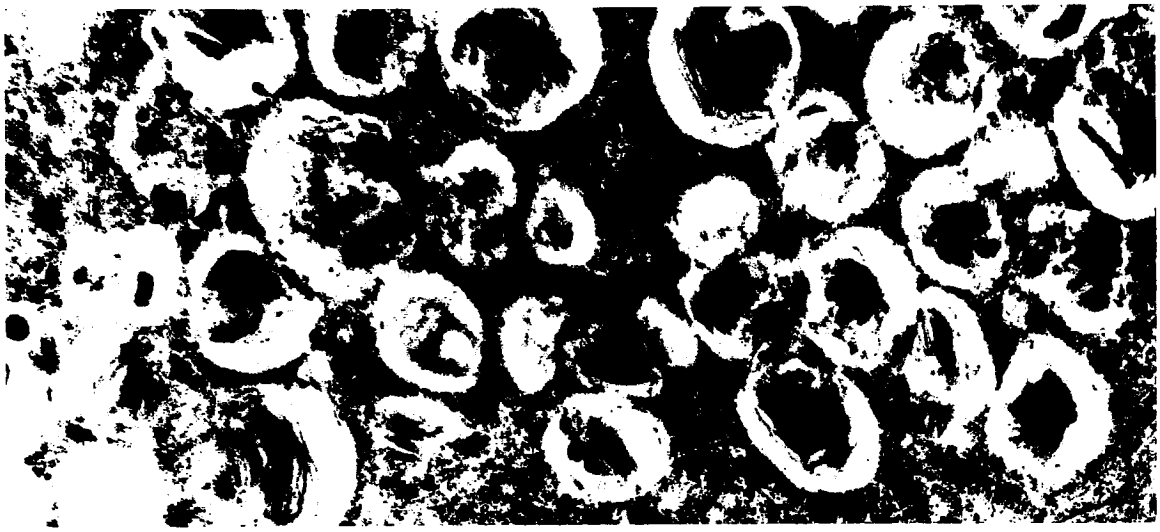


FIG. 4. Cytoplasmic bodies in finer detail, showing flat layers with homogeneous or granular zones. Magnification x 16.500 approximately.

FIG. 5. Cytoplasmic bodies exhibiting membranes and granular zone. Magnification x 36,300 approximately.

The mother had missed a period at the time of her first attendance with the patient. It was confirmed that she was pregnant. The parents understood the possible outcome of the pregnancy and an amniocentesis was performed after discussion of the difficulties involved in the procedure (O'Brien, Okoda, Ho, Fillerup, Veith and Adams, 1971).

Cultured fibroblasts from mother, father, control, patient and embryo were used as an enzyme source and the substrate was 4 methyl umbelliferyl-N acetyl glucosamine. (Rattazzi and Davidson, 1972). The following results were obtained:

Hexosaminidase A (% of total activity)	
Baby (affected)	5
Mother	44
Father	52
Control	70
Embryo	73

A normal female child was subsequently born and has made good progress. The affected male child is now aged 22 months and is very rigid with frequent myoclonic seizures and marked hyperacusis. Severe respiratory infections occur frequently.

FIG. 6. Membranous bodies showing dense homogeneous zones and lamellated structures. Magnification x 46,200 approximately.

FIG. 7. Detail of membranes indicating lamellated structure with dense lines and pale lines. Fusion of lines is visible. Inner dense lines are bordered by pale lines. Magnification x 80,000 approximately.

DISCUSSION

Tay described the ocular changes of the disease in 1881 and Sachs the neurologic features in 1887. Development of artificial substrates and radioactive labels has allowed the biochemical basis of this and other lipid storage diseases to be determined. Application of these methods allows identification of the carrier state and makes pre-natal diagnosis possible. Pitfalls exist where the culture medium introduces exogenous hemosaminidase A. Falsely high levels of the enzyme can then be reported (Michael, Hahnel, Hockey and Wysock, 1974) so that an affected embryo is not detected.

Rectal biopsy will provide adequate neural tissue for a histological diagnosis, obviating the need for brain biopsy if enzyme assays are not available. The cytoplasmic bodies shown by electron microscopy are round or oval and characteristic of the disease. They consist of aggregates of lipid (90%) and protein (10%), one third to one half of the lipid being ganglioside (Menkes, 1974).

SUMMARY

A case is reported illustrating the typical features of Tay-Sachs disease, the light microscopy and ultrastructure of the stored material in the condition, and the feasibility of prenatal diagnosis of the disorder.

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THE ACTION OF THALIDOMIDE ON THE PERIPHERAL NERVOUS SYSTEM OF THE EMBRYO

J. McCREDIE*

The mode of action of thalidomide in producing congenital deformities is unknown. Most research over the last decade has assumed that its action is on mesoderm, to account for the wide variety of malformations of both skeletal and visceral structures.

In 1971-2, the radiographs of some Australian thalidomide children claiming compensation were reviewed. After analysing these, and radiographs of eighty similar cases in Britain, the conclusion was reached that thalidomide was acting on the sensory neurons of the embryo (McCredie, 1973; McCredie and McBride, 1973). The drug action appeared to be primarily on ectoderm with secondary effects on mesodermal structures.

An absent radius with absent, hypoplastic or tri-phalangeal thumb, was the most frequent single defect, with an incidence of 63% in the British series. This peculiar distribution of disease demanded explanation. Radiologically, such a disease distribution did not conform to the usual pattern of bone or cartilage disease. The distribution was not that of a bone dysplasia, which is typically epiphyseal, metaphyseal or diaphyseal in site. It was not the distribution of a generalised bone disease, because neighbouring bones appeared normal. Not was it a disease of random distribution, because the frequent occurrence of a particular pattern of defect in two series was not a random phenomenon. It strongly suggested an underlying organisation of pathology on a segmental basis such as that of segmental sensory nerves. Theoretically, by eliminating the C_{11} dermatome from the arm, together with its underlying muscle and bone, radial aplasia might result.

In addition, the bizarre malformations of bones and joints made no sense unless interpreted as congenital neuropathic bones and congenital Charcot's joints (McCredie, 1973). Comparison was made with radiographs of adults showing the trophic skeletal effects of prolonged sensory peripheral neuropathy due to tabes dorsalis, syringomyelia, diabetes and leprosy. From the comparison, an analogy was evident. In both conditions, bones were absent, short, deformed, tapered or fused. In both conditions, joints were absent, incomplete, dislocated or fused. In both, the skin was affected, either being anaesthetic with trophic ulceration in the adult, or reduced in surface area due to failure of formation in the child. The basic pathological process in both age groups could be regarded as derangement of organised growth: failure of organised primary growth in the embryo, and failure of organised repair, or maintenance growth, in the adult. The site of the lesion in the adult is the sensory neuron. This should also be the site of pathology in the embryo, because the radiographs suggest that the embryo, like the adult, has suffered a sensory peripheral neuropathy.

MATERIALS AND METHODS

In order to test this hypothesis, dorsal root ganglia of thalidomide-deformed animals were examined. Female laboratory-bred rabbits were given thalidomide 400 to 550 mgms. daily in their drinking water from day 7 to day 14 after artificial insemination. Deformities resulted in treated litters at a rate of 20%. There were no deformities in control litters. Control and deformed newborn rabbits were killed within 24 hours of birth, photographed, X-rayed and fixed.

* Royal Prince Alfred Hospital, Sydney

Two animals with bilateral radial aplasia (Fig. 1), two litter mates without deformities, and two untreated controls were fixed in formalin. The cervical dorsal root ganglia were exposed, and each ganglion was excised and individually embedded in paraffin, longitudinally sectioned and stained with cresyl violet.

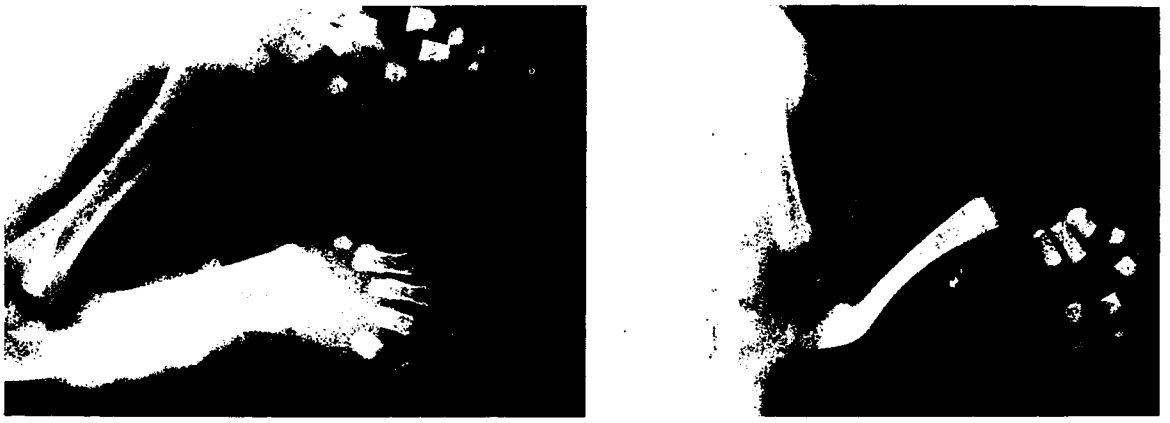

FIG. 1. Left: Normal forelimb radiograph of control newborn rabbit.
Right: Thalidomide-induced radial aplasia with absent first digit.

Six rabbits were born with hindlimb deformities. These, with controls, constituted a second series. Fig. 2 illustrates the typical reduction deformities of hind legs, with absent and vestigial toes. Fig. 3 shows a unilateral deformity, with absence of the fibula and one ray of bones in the foot. All rabbits in this series were perfused with glutaraldehyde within 24 hours of birth, and their lumbar and sacral ganglia were dissected, separately fixed in glutaraldehyde and embedded in araldite. Each ganglion was sectioned transversely at three levels, first at the equator, then at 50μ and 100μ distant from this. After staining with toludine blue, one section at each level was photographed, enlarged 250 times, and its cell population was analysed on a Zeiss particle size analyser.

FIG. 2. Left: Control newborn rabbit. Straight hindlegs with four toes.
Right: Thalidomide deformity. Short legs, three toes, vestigial fourth toe on the left foot.

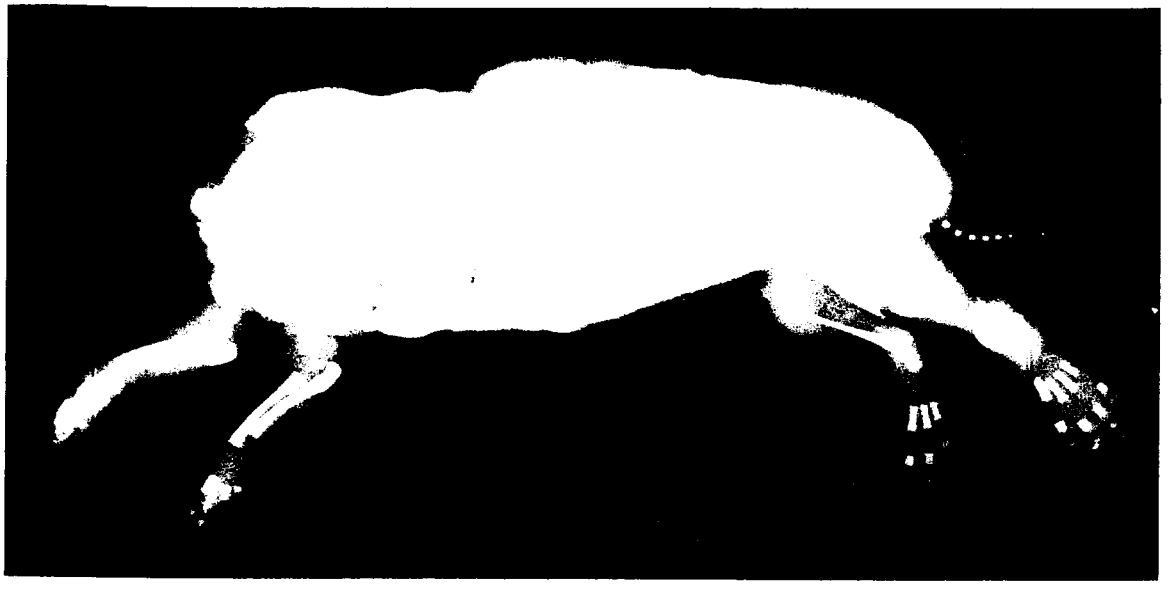

FIG. 3. Radiograph of unilateral hindlimb deformity. The abnormal leg has absent fibula and lacks one ray of bones in the foot.

RESULTS

The dorsal root ganglia of control rabbits showed mature histology at birth. The dominant cells were large neurons of adult type, separately encapsulated, with a large volume of pale cytoplasm and a small nucelus. Multiple nucleoli were infrequent.

In dorsal root ganglia related to limb deformities in thalidomide-treated rabbits, these mature neurons were scanty. There was a population of predominantly smaller, dark cells, with relatively large nuclei and infrequent multiple nucleoli. These characteristics are typical of immature or embryonic ganglion cells (Tennyson, 1965), and are an abnormal finding at birth (Warrington and Griffith, 1904).

To compare the maturity of controls with deformed animals and their non-deformed litter-mates, maximum cell size was chosen as an index. The series of rabbits with forelimb deformities was surveyed from C_2 to C_8. The twenty largest cells in multiple sections of each ganglion were measured and recorded. The mean diameter of large neurons at C_5 and C_6 in the three groups is shown in Fig. 4. The differential maturity throughout the cervical chain is demonstrated in Fig. 5. Control rabbits had large mature neurons throughout. Deformed rabbits, with absent radius and thumb, had smaller cells at all cervical levels, especially at C_1, C_5 and C_6. Treated litter mates without limb deformity had an average cell size approaching normal.

The second series, with hind limb deformities, had improved histological appearances because of glutaraldehyde perfusion and fixation, and were submitted to more detailed population analysis of cell size. The result of cell size distribution in these animals, estimated with the particle size analyser, and based on the average of three sections from each ganglion, is shown in Fig. 6. Each graph is a mean for the second sacral ganglion, comparing that innervating a non-deformed hind-limb (N) with that innervating a limb with absence of the fibula (AF). The latter shows a peak of population in smaller cells, and the mean cell diameter in this ganglion was 25μ. The normal ganglion has a greater number of large cells, with a mean cell diameter of 30μ.

Fig. 7 demonstrates the comparative histology of a control animal and an animal with an absent fibula, the sections being taken at the S_2 ganglion. Primitive blood vessels accompany the primitive neurons.

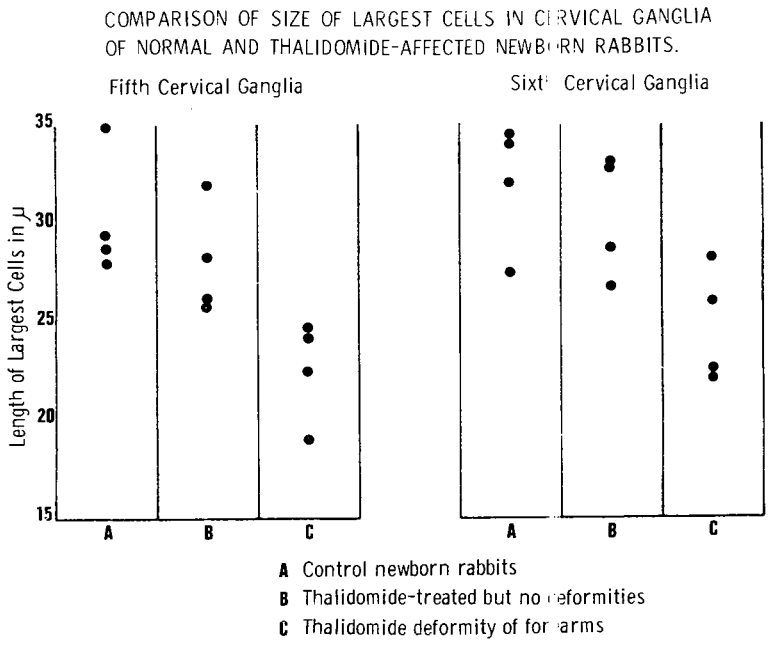

FIG. 4. Index of maturity. Comparison of first series.

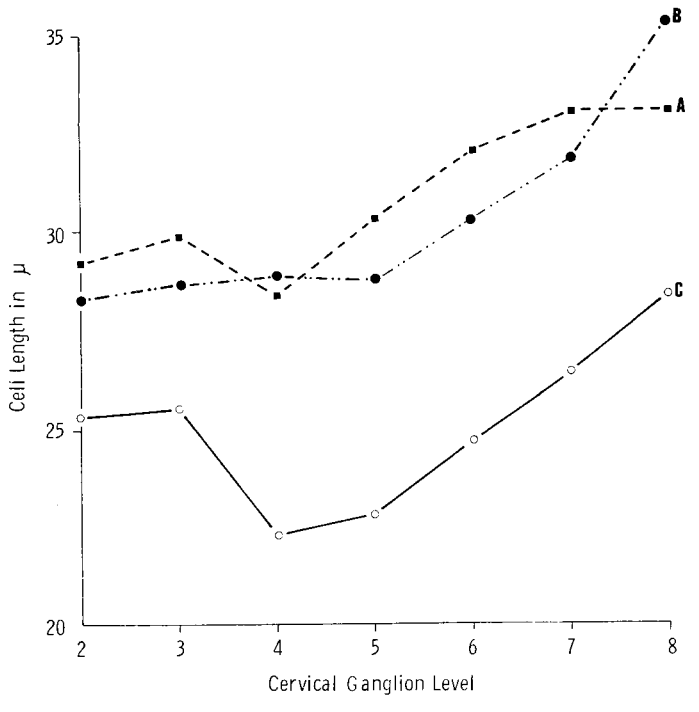

FIG. 5. Comparison of maximum cell size in cervical chains of three groups of rabbits.
A. Controls
B. Thalidomide-treated but not deformed
C. Thalidomide-treated, with absent radii and thumbs.

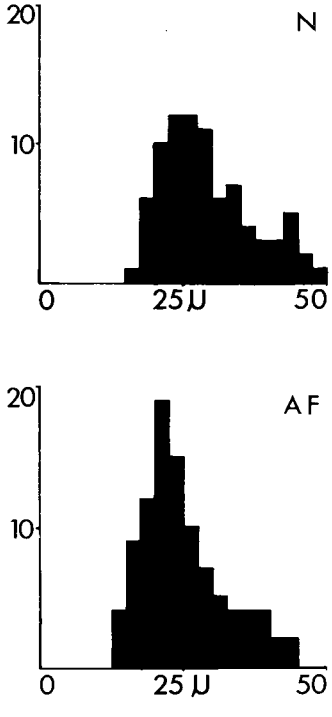

FIG. 6. Total population distribution in terms of cell diameters in the second sacral ganglia of hindleg without deformity (N) and hindleg with absent fibula (AF).

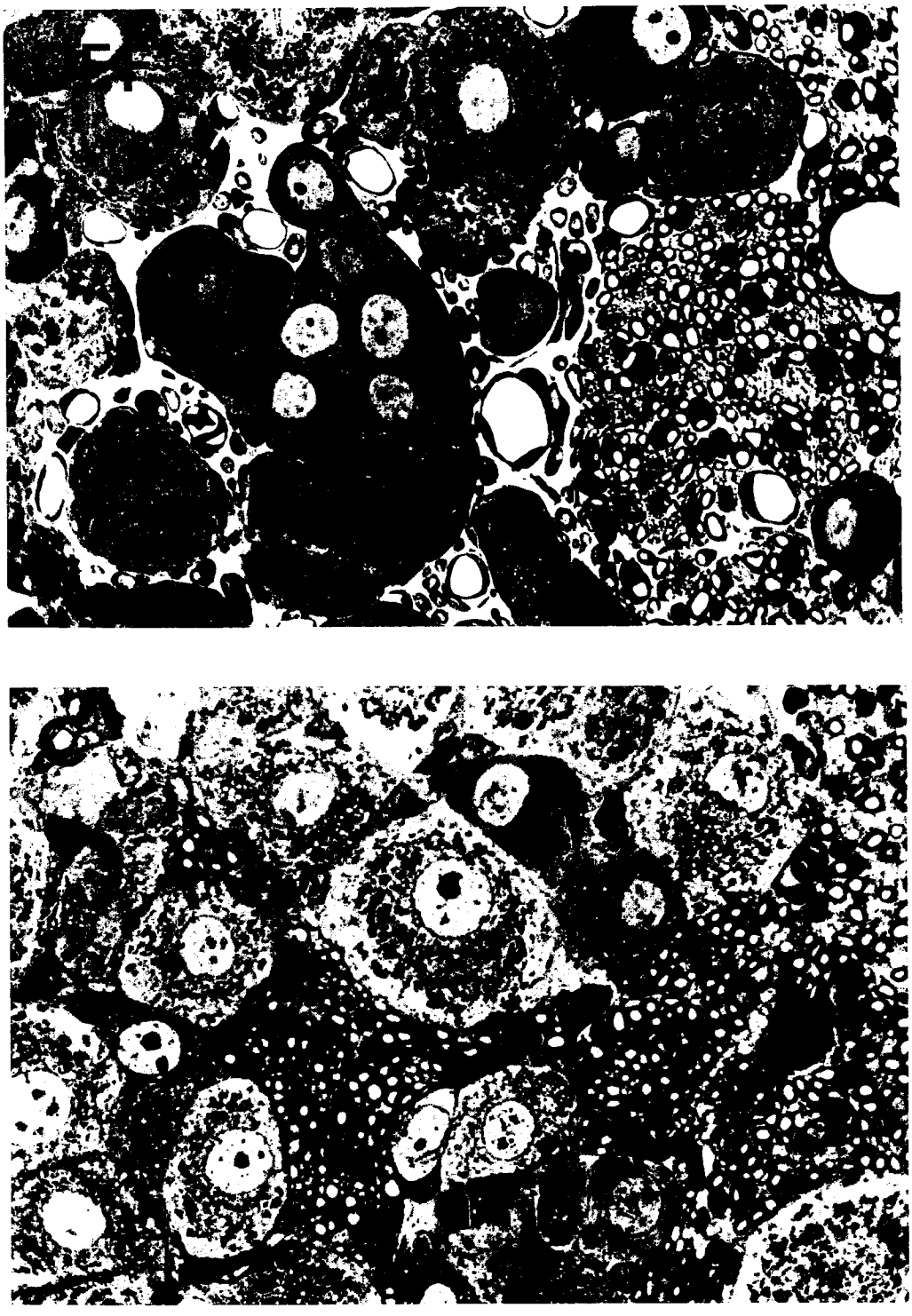

FIG. 7. Histology at second sacral ganglion of control (C – upper part of Fig.) and deformed (DEF – lower part of Fig.) rabbits. The deformity was absence of the fibula.

DISCUSSION

From these studies it has been concluded that thalidomide i nterferes with the normal process of neuronal maturation in dorsal root ganglia of the embryo. T ıe normal trophic function of the embryonic neural crest (Horstadius, 1950; Weston, 1970), and t e trophic function of the sensory nerve in particular (Singer, 1943, 1952, 1974), suggest a conne ion between this neuropathology in the embryo and disordered limb growth. Interference with tr phic neural activity is postulated as the mode of action of thalidomide in producing congenital li ıb deformities.

SUMMARY

The mode of teratogenic action of thalidomide is unknown. \ new radiological interpretation of thalidomide-induced limb malformations suggested that path logical changes should be sought in the sensory ganglia. Newborn rabbits with thalidomide-indı ced limb defects were examined histologically, and failure of maturation of dorsal root ganglion cel s was demonstrated. This neuronal immaturity supports the radiological hypothesis of embryonic : europathy, which is proposed as the underlying pathology of the limb deformities due to thalido ıide.

ACKNOWLEDGEMENT

This research was carried out in the Neurological Laboratory (Professor J.G. McLeod, Department of Medicine, University of Sydney, with the support of a grar from the Ramaciotti Foundation.

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OCULAR COMPLICATIONS OF VARICELLA

P.G. PROCOPIS*

Varicella may affect the eye in numerous ways (Rogers, 1964), ranging from local lesions of the lid or cornea to involvement of the optic nerve or ocular motor nerves with or without other evidence of encephalitis.

This paper reports the uncommon occurrence of internal ophthalmoplegia together with optic neuritis as a complication of varicella.

CASE REPORT

In December, 1974, a 6 year old boy developed a typical varicella rash. Two days later his mother noticed that his left pupil was dilated. He had no complaint of eye pain or visual disturbance.

On examination three weeks later the left pupil was dilated (8 mm), barely reacted to light, both direct and consensual, and did not react to accommodation (Fig. 1). The size and reactions, direct and consensual, of the right pupil were normal.

FIG. 1. Large left pupil.

* Department of Medicine, Royal Alexandra Hospital for Children, Sydney.

The visual acuity for near vision was J 1+ in the right eye and greater th n J 16 in the left. For distant vision the acuity was 6/6 in the right eye and 6/18 in the left. No refractive error was present for distant vision but near vision was corrected to J 1 with a + 2.5 dioptre lens. The right optic fundus was no mal but the left disc was hyperaemic with blurred margins. The left visual field was constricted to both red and white obj cts but no scotoma could be demonstrated. Eye movements were full and no ptosis was present. The remainder of the r eurological examination, and in particular the deep tendon reflexes, were normal. General physical examination was also ormal.

Full blood count, urea, electrolytes, calcium, phosphorus, fasting blood sugar a d serological tests for syphilis were normal. The complement fixation test for varicella was positive in a dilution of 1/128. Examination of the cerebrospinal fluid was normal. X-ray of the skull and optic foramina showed no abnormality.

In the ensuing four months the left pupil has remained dilated and barely eactive. However, visual acuity in the left eye has improved to 6/12 at distance, whereas near vision has remained worse than J 16. Instillation of 2.5% metacholine ("Mecholyl") into the left eye at two and three months after the onset produced o change in the size of the pupil. However, three and a half months after onset metacholine instillation produced pupill y constriction without any change in the accommodation defect.

DISCUSSION

Mydriasis has been rarely reported as a complication of varic lla (Bonamour, 1952; Ross, 1961; Rogers, 1964; Goldsmith, 1968). Full recovery occurred in only one of these patients.

In both the present patient and the subject described by Go dsmith (1968), the reaction of the pupil after instillation of dilute metacholine solution suggested nvolvement of the ciliary ganglion or the short ciliary nerves. This is the same site of involvement as in the classic Adie's tonic pupil, which reacts similarly to dilute metacholine solution. Such a re ction only occurs in a chronically denervated pupil, the mechanism being hypersensitivity of that p pil to its own synaptic transmitter. It is of interest that in the patient here reported it took three and a half months before hypersensitivity occurred. No reaction to metacholine occurred in the patient reported by Ross (1961). However, this author did not state how long after the onset of the mydriasis he metacholine test was performed. It is thus possible that a sufficient length of time had not passe l for chronic denervation to occur.

The occurrence of optic neuritis was suggested in the present p tient by the finding of a decreased visual acuity at 6 metres and a hyperaemic disc. Although n scotoma was demonstrated there was marked contraction of the visual field in the affected eye. This combination of optic neuritis and internal ophthalmoplegia has been termed "optico-ciliary ne ritis" (Mancall, 1955). In Mancall's patient, who presumably suffered from multiple sclerosis, invol ement of the ciliary ganglion was strongly suggested by the presence of a positive metacholine tes . Optico-ciliary neuritis as a result of varicella has not been previously reported.

SUMMARY

A case has been presented of internal ophthalmoplegia, prob bly due to ciliary ganglionitis and optic neuritis occurring during the course of a varicella infection.

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CONGENITAL DEFICIENCY OF HORIZONTAL GAZE

P. G. PROCOPIS*

An instance of congenital deficiency of conjugate horizontal ocular movement is reported.

CASE REPORT

A six year old boy was referred because of hyperactivity, short attention span and difficulty in learning to read. The pregnancy had been complicated by toxaemia requiring bed rest for two months. He was born by breech delivery four weeks before the expected date and weighed 6 lbs. at birth. He was not seen by his mother until 48 hours after birth and sucked poorly in the neonatal period. Motor milestones were normal, but speech developed slowly so that he did not speak intelligible sentences until the age of five years.

During his infancy the grandmother remarked that he seemed to stare in a peculiar way. Later his mother noted that he seemed to turn his head rather than his eyes when looking to the side.

On examination vertical eye movements were full but horizontal movements were markedly diminished. On attempting to look to the left very slight movement of the abducting left eye occurred and no movement of the adducting right eye. With attempted right lateral gaze very slight conjugate movement occurred. Gaze was defective both to command and with attempted pursuit. No head thrust was present. Random eye movements were absent. Convergence was present but weaker than normal. A small amount of opticokinetic nystagmus was elicited with the tape moving from left to right. No deviation of the eyes could be induced by moving the head from side to side or by rotating the whole body. No nystagmus was elicited by irrigation of the external auditory canals with water at 30°C and 44°C. These findings were confirmed by electronystagmography.

Neurological and general physical examination were normal.

DISCUSSION

A congenital defect of horizontal gaze is commonly due to ocular motor apraxia (Cogan, 1952), which is characterized by the impairment of horizontal gaze, involuntary deviation of the eyes to one side on rotation of the head, absence of the fast phase of the opticokinetic response and conspicuous head thrusts on attempted gaze to either side but full retention of normal random movements (Cogan, 1966). Reading difficulties may also occur.

The patient described above had some of the features of ocular motor apraxia, but the absence of deviation of the eyes on head rotation and the absence of normal random eye movements, two cardinal features of ocular motor apraxia, negate this diagnosis.

Zweifach, Walton and Brown, (1969) described five patients with congenital absence of horizontal gaze and absent vestibulo-ocular reflexes to both rotatory and caloric stimulation. Four of these patients had normal convergence. A midline pontine defect was postulated. Witzel (1958) reported a similar patient with a horizontal gaze defect and associated Klippel-Feil abnormality of the cervical spine.

* Department of Medicine, Royal Alexandra Hospital for Children, Sydney

SUMMARY

A patient with defective conjugate horizontal gaze distinct fr n congenital ocular motor apraxia is described.

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THE AUTONOMIC NERVOUS SYSTEM IN ALCOHOLIC AND DIABETIC NEUROPATHY

P.A. LOW, J.C. WALSH, C.Y. HUANG, and J.G. McLEOD*

Peripheral neuropathy is a complication common to diabetes mellitus (Mulder, Lambert, Bastron and Sprague, 1961) and alcohol abuse (Walsh and McLeod, 1970). By contrast, whilst symptoms which indicate an autonomic neuropathy such as postural hypotension, diarrhoea, abnormal sweating and impotence are common in diabetes mellitus (Rundles 1945; Sharpey-Shafer and Taylor, 1960), these are uncommon in alcoholic neuropathy. Autonomic dysfunction does occur in Wernicke's encephalopathy but here the lesion is central, affecting the descending sympathetic efferent outflow (Birchfield, 1964).

Tests of autonomic function have been performed in diabetic and alcoholic neuropathy with the aim of localizing the site of the lesion since published reports correlating physiological abnormalities with quantitative histological data on the autonomic nervous system are scarce.

Tests of autonomic function were performed on control subjects and on patients with diabetic and alcoholic neuropathy, and the physiological data were correlated with quantitative histological data obtained from examining the greater splanchnic nerve removed at autopsy from controls and patients with diabetic and alcoholic neuropathy. The investigations have been reported in full (Low, Walsh, Huang and McLeod, 1975a,b). The following comprise a report of the autonomic studies.

SUBJECTS

Control Subjects

Thirty-three healthy volunteers performed the Valsalva manoeuvre, and the Valsalva ratio was derived (Levin, 1966). The ages of these subjects ranged from 18 to 63 years (mean: 33 years).

The alterations in mean arterial pressure (MAP) and heart period (HP, the reciprocal of the heart rate expressed in m.secs.) following administration of phenylephrine (PE) and trinitroglycerin (TNG) were measured in 10 control subjects whose ages ranged from 22 to 60 years (mean: 40 years).

Diabetic Patients

There were 16 patients whose ages ranged from 27 to 58 years (mean: 41 years). The duration of diabetes ranged from 1 to 26 years. Twelve of the 16 patients were treated with insulin whilst

* Department of Medicine, University of Sydney

the other 4 were taking oral hypoglycaemic agents. Symptoms of autonomic dysfunction were present in 6 of the 16 patients. Nerve conduction studies were performed on all patients and were abnormal in 15 of the 16 patients.

Alcoholic Patients

There were 12 patients with a long history of alcohol abuse. Their ages ranged from 46 to 60 years (mean: 51 years). No patient had symptoms which indicated disordered autonomic function. Nerve conduction studies were performed on all patients and in each instance confirmed the presence of a neuropathy.

The clinical severity of the alcoholic and diabetic neuropathies was similar.

METHODS

1) Sweat test.
   Sweating was induced by raising ambient temperature and detected with a modified Gutmann's powder which had been previously dusted over the subjects. Areas of sweating became a deep purple colour and were charted.

2) Postural testing.
   MAP and HP were recorded with the patient in the supine position and at minute intervals for 5 minutes after he assumed the erect posture.

3) Valsalva manoeuvre.
   The subject was asked to maintain a column of mercury at 40-50 mm for 10-15 secs. and his heart rate was recorded by means of a continuously running electrocardiograph. The Valsalva ratio, which is the ratio of the longest R-R interval to the shortest R-R interval was derived (Levin, 1966) and the best of 3 responses was accepted.

4) Baroreceptor parameters.
   Stimulus-response curves were constructed using a method similar to that of Korner, Shaw, West and Oliver (1972). The MAP was raised using phenylephrine and reduced using trinitroglycerin. The induced alterations of HP were recorded. When the HP is plotted against MAP, the response of HP to alterations in MAP assumes the shape of a sigmoid curve in control subjects (Fig. 1). This response was quantitated by deriving 2 parameters:—
   a) The heart period range HPR (m.sec.) which is the difference between maximum and minimum HP in response to induced BP alterations.
   b) Mean gain, $\bar{G}$ (m.sec./mm), which is the slope of the curve between one standard deviation above and one below the estimated BP at the middle of the HPR (the median HP).

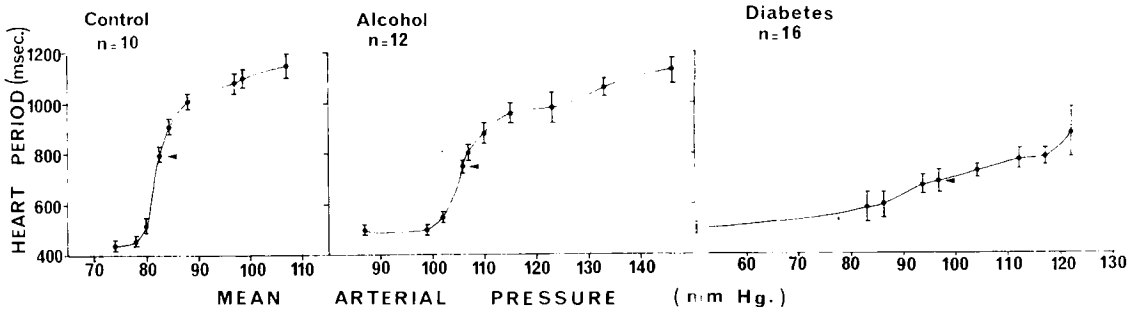

FIG. 1. The heart period response to alteration in mean arterial pressure in control, alcoholic and diabetic subjects. Arrow indicates resting values, and vertical bar 1 S.E.M.

RESULTS

1) Sweat test.

Abnormal sweat patterns were obtained in all of the 10 diabetics and all of the 10 alcoholics examined. Absent or reduced sweating occurred in a glove and stocking pattern; occasional small patches of anhidrosis also occurred over the trunk. The pattern was similar in the 2 groups.

2) Postural responses (Fig. 2).

There was a spontaneous postural hypotension of more than 20 mm Hg MAP in 7 of the 16 diabetic patients (44%), all of whom developed symptoms of syncope. By contrast spontaneous postural hypotension did not occur in any of the control or alcoholic subjects.

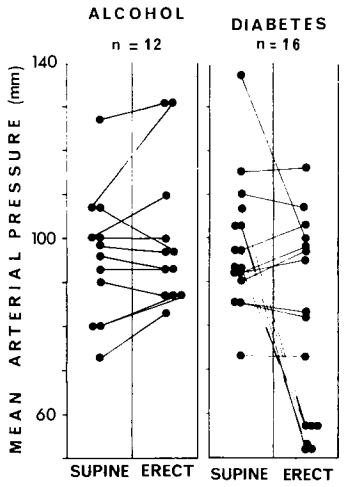

FIG. 2. Mean arterial pressure recorded in alcoholic and diabetic subjects in the supine and erect postures.

3) Valsalva ratio (Fig. 3).

The Valsalva ratio in 33 control subjects ranged from 1.45 to 2.0. The Valsalva ratio was within the control range in 7 of the 9 alcoholic subjects tested and mildly reduced in 2. By contrast, in 7 of the 11 subjects with diabetic neuropathy on whom the test was performed, the value fell below the control range.

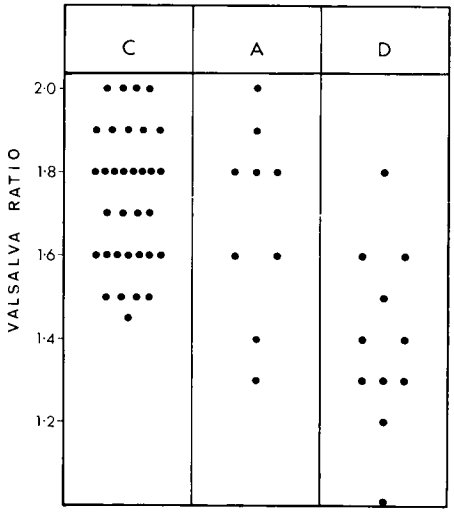

FIG. 3. The Valsalva ratio in 33 controls (C), 9 alcoholic (A) and 11 diabetic (D) subjects.

4) Response to phenylephrine (Fig. 4).

The pressor response to graded doses of phenylephrine was recorded in 10 control and 7 alcoholic subjects. The pressor responses of the alcoholic subjects fell within the control range. By contrast, 2 of the 8 diabetics (25%) on whom this response was recorded had denervation hypersensitivity with rises of 15 mm Hg and 32 mm Hg respectively, in response to 25 μg of phenylephrine. The abnormal response was sustained with subsequent boluses of the drug.

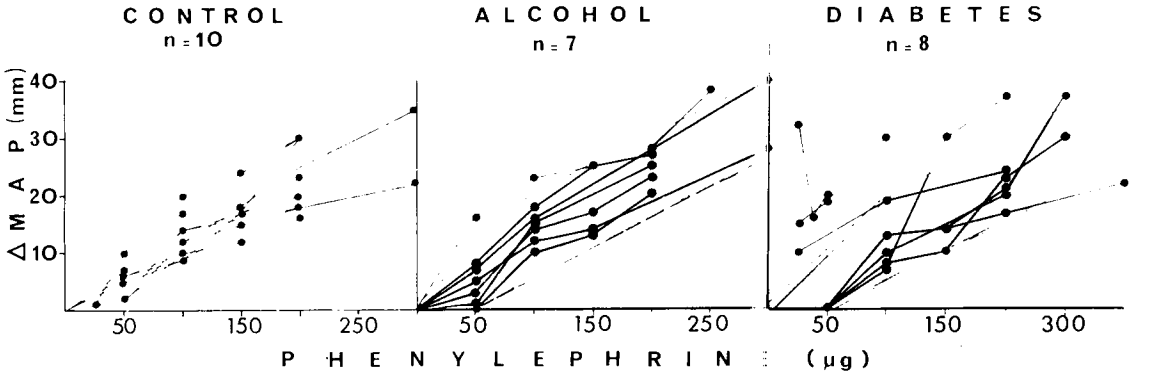

FIG. 4. Change in mean arterial pressure. ▲ MAP (mm Hg), with graded doses of intravenous phenylephrine (PE) in control, alcoholic and diabetic subjects. Shaded area indicates the control range.

5) Baroreceptor response curves (Figs. 1, 5; Table I).

The resting HP was 804 m.sec. (SE, 17) in controls and 743 m.sec. (SE, 33.6) in alcoholics. The difference is not significant. By contrast, the resting HP was 684.3 (SE, 44.4) m.sec. in diabetics which is significantly reduced ($P<.05$, Student "t" test). The HPR ranged from 520 to 860 m.sec. (mean, 692 m.sec.; SE, 30.4) in control subjects. The HPR of alcoholic patients fell within the control range in each instance. By contrast, the HPR of 7 of the 8 diabetics fell below the control range. The mean gain ($\overline{G}$) ranged from 21.2 to 45 m.sec./mm Hg (mean 33 m.sec./mm Hg; SE, 2.0) in control subjects. The $\overline{G}$ values of 2 alcoholics were at the lower limit of the control range and one was well below it. By contrast, the $\overline{G}$ in every diabetic on whom this was calculated fell below the control range.

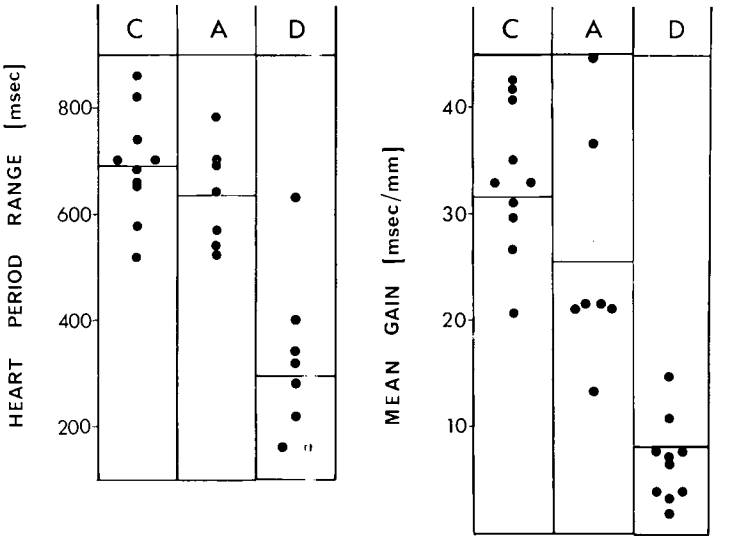

FIG. 5. The heart period range and mean gain in control, alcoholic and diabetic subjects. Horizontal bars represent the mean values of each group.

TABLE I

Resting Values and Parameters of Stimulus-Response Curves in Controls, Alcoholics and Diabetics.

	Controls	Alcoholics	Diabetics
Number of Patients	10	12	16
Resting blood pressure (mm Hg)	82.3 (SD. 8.0)	106 (SD. 14.5)	97 (SD. 52.4)
Resting heart period (m.sec.)	804 (SD. 53.8)	743.3 (SD. 116.4)	684.3 (SD. 177.2)
Heart period range (m.sec.)	692 (SD. 96)	634 (SD. 95)	294 (SD. 152)
Mean gain (m.sec./mm Hg)	33 (SD. 6.4)	26 (SD. 11.5)	8.3 (SD. 3.3)

DISCUSSION

The present studies confirm the high incidence of postural hypotension in diabetics.

The measurement of the response to the Valsalva manoeuvre has become a standard test of autonomic function. The Valsalva ratio provides a simple quantitative assessment of baroreceptor function and obviates the need for intraarterial catheterisation. Seven of 11 of our patients with diabetic neuropathy had a reduced Valsalva ratio. This figure is in agreement with that of two recent studies (Bishnu and Berenyi, 1971; Ewing, Burt, Campbell and Clarke, 1973).

However, although the Valsalva ratio is a useful screening test, baroreceptor function may be assessed more precisely by measuring the HP response to alterations in MAP, whether spontaneous or induced (Martin, Travis and van den Noort, 1968; Bannister and Oppenheimer, 1972). Phenylephrine, which is a directly acting adrenergic agent, was used as it produces little or no cardiac effects in doses used to produce vasoconstriction (Varma, Johnsen, Sherman and Youmans, 1960; Loggie and Van Maanen, 1972) and has been used to assess baroreceptor function in man (Robinson, Epstein, Beiser and Braunwald, 1966; Smyth, Sleight and Pickering, 1969).

Recently, baroreceptor function in the experimental animal and in man has been subjected to statistical analysis (Korner *et al.*, 1972; Korner, West, Shaw and Uther, 1974). The authors derived from their studies various parameters including HPR, median HP, and $\overline{G}$. These measurements help to define the *range* of heart rate response as well as the maximum *rate* of response to alterations in MAP. That is, one is able to quantitate not only the limits of a subject's heart rate response to major alterations in BP but also the rate of change of his heart rate to minor alterations in BP. Application of these methods to an analysis of baroreceptor function in the present study has demonstrated that baroreceptor function in patients with diabetic neuropathy is markedly abnormal. The resting heart period and heart period range are significantly reduced and the gain is insignificant throughout the range of BP alterations. In several patients the baroreceptor response curves were markedly abnormal even though the Valsalva ratios were near normal and in one case the Valsalva response recorded with an intraarterial needle was also normal. These findings confirm previous observations that measurements of heart rate response to changes in BP are a more sensitive index of disordered baroreceptor function than the Valsalva manoeuvre (Martin *et al.*, 1968; Bannister and Oppenheimer, 1972). The HPRs of alcoholics were normal but the $\overline{G}$ was at the lower limit of the control range in 2 alcoholics and reduced in 1. The alcoholics were older and their resting BP was higher. As $\overline{G}$ is reduced with increasing age and hypertension, the minor abnormalities seen in these patients with alcoholic neuropathy may be ascribed to these factors (Korner *et al.*, 1974).

SUMMARY

Tests of autonomic function were performed on 10 controls, 16 subjects with diabetic neuropathy and 12 subjects with alcoholic neuropathy. Abnormal sweating occurred in 10/10 alcoholics (100%) and 10/10 diabetics (100%) who were examined. An abnormal Valsalva ratio was present in 7/11 (64%) of diabetics and only 2/9 (22%) of alcoholics. Denervation hypersensitivity to phenylephrine

occurred in 2/8 (25%) of diabetics and was absent in alcoholics. A quantitative assessment of baroreceptor function was made. In diabetics there was a reduced resting heart period, heart period range and mean gain, whilst these parameters were essentially normal in alcoholics.

ACKNOWLEDGEMENTS

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A CASE OF SPONTANEOUSLY RESOLVING "PAPILLOEDEMA"

G. SELBY and G.C. HIPWELL*

An instance of spontaneously resolving papilloedema is described below.

CASE HISTORY

A 38 year old woman had seven bouts of "cluster" headaches between 1963 and 1974. Each consisted of severe right retro-orbital pain accompanied by lachrymation of the right eye and congestion of the right nostril. Blurring of vision developed in both eyes in May 1974, associated with bilateral tinnitus and a mild suboccipital pain.

On examination her visual acuity on the right was 6/18, and on the left 6/60. The peripheral visual fields were normal. There was an enlarged blind spot in both eyes. Ophthalmoscopic examination revealed severe bilateral papilloedema and oedema of maculae and retinae with small heamorrhages surrounding both optic discs (Fig. 1). Neurological examination

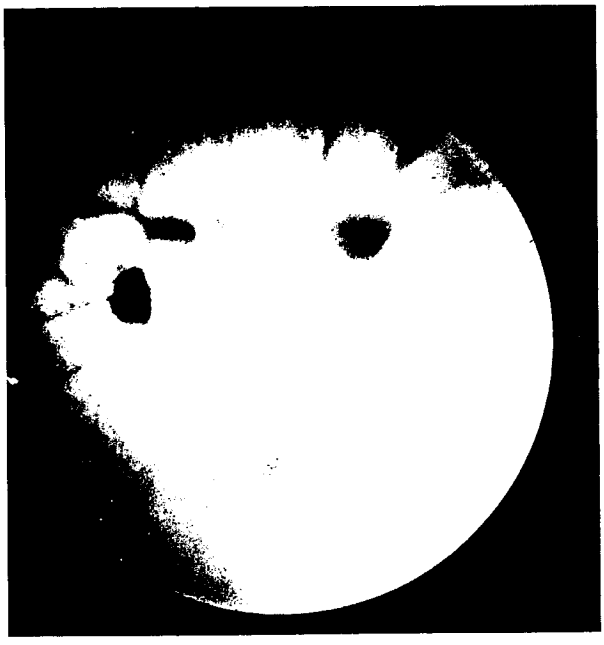

FIG. 1. Optic fundus showing papilloedema with haemorrhages surrounding the optic disc.

*The Royal North Shore Hospital, Sydney.

was otherwise unrewarding. The patient was grossly overweight (16½ stone) due to over-eating. Her blood pressure was 145/90. Full blood count, E.S.R., E.C.G., radiographs of chest and skull were all normal. The biochemical profile was normal except for a fasting cholesterol level of 260 mg% and a triglyceride level of 125 mg%. The E.E.G. showed minor left temporal slow activity interpreted as significant. An attempt at a ventriculogram failed. A lumbar air encephalogram showed a ventricular system of normal size and in a a normal position. The CSF had a normal cell count and chemical composition. Full coagulation studies, protein and lipoprotein E.P.G., fibrinogen titres and euglobulin lysis were all normal.

After the ventriculogram there was a transient mild right hemiparesis with the appearace of extensive vitreous and subhyaloid haemorrhages surrounding both optic discs. These haemorrhages resolved gradually. The C.S.F. pressure was 90 to 100 mm. The patient was treated with a short course of intravenous dexamethasone and with an 800 calorie diet. She lost almost two stone weight during her 25 days in hospital.

By August 1974, three months after visual symptoms began, her visual acuity in the right eye was 6/6-9 and in the left 6/18 correcting to 6/9. There was no papilloedema and no retinal or subhyaloid haemorrhages. In November 1974 there was distortion of vision in the left eye due to macular oedema. A retinal fluorogram was normal and the visual distortion improved. When she was last assessed in February 1975 she complained of some brief episodes of rotational vertigo, but there were no abnormal clinical signs. No recurrence of papilloedema or of retinal haemorrhages had occurred.

DISCUSSION

The patient's papilloedema, retinal haemorrhages and later vitreous and subhyaloid haemorrhages were not due to raised intracranial pressure, as the C.S.F. pressure readings were normal. Benign intracranial hypertension was regarded as excluded by the normal air encephalogram. Cluster headaches are not usually associated with retinal lesions similar to those in the patient here reported. Laboratory tests did not support the diagnosis of Eales' disease, vasculitis or the hyperviscosity syndrome. The cause of the severe bilateral temporary oedema of the papilla, macula and retina, and of the retinal and vitreous haemorrhages, remains obscure.

SUMMARY

A case of spontaenously resolving bilateral papilloedema in an obese 38 year old woman subject to cluster headache is reported. The aetiology of the condition remained obscure after neurological and biochemical investigation.

NEUROMYELITIS OPTICA FOLLOWING INFECTIOUS MONONUCLEOSIS

P.M. WILLIAMSON*

The neurological complications of infectious mononucleosis are varied and may involve almost any part of the nervous system. The incidence of neurological manifestations is difficult to determine since series are based on inpatient records and only the more severe cases are admitted to hospital. Such series report incidences of 0.7% to 5.0% (Bernstein and Wolff, 1950; Bergin, 1960; Hoaglund, 1960; Schnell, Dyck, Bowie, 1966).

There are few reports of optic neuritis (Bonynge and Von Hagen, 1952; Tanner, 1954), including one report of retrobulbar neuritis (Shecter, Lipsius and Rasansky, 1955) in association with mononucleosis. Additionally there are reports of papilloedema without significant loss of visual acuity (Ashworth and Motto, 1947; Blaustein and Caccavo, 1950; Piel, Thelander and Shaw, 1950). Transverse myelitis is also a rare complication (Schnell *et al.*, 1966; Cotton and Webb-Peploe, 1966; Silverstein, Steinberg and Nathanson, 1972).

The following case history is submitted as the first reported instance of neuromyelitis optica following infectious mononucleosis.

CASE REPORT

A 29 year old male clerk presented in mid April, 1973 with a sore throat, tonsilitis, fever and malaise. His WCC was "consistent with infectious mononucleosis" and his Paul Bunnell test was positive. In early May, he had pain in the left orbit and his left visual acuity progressively diminished over a week. He was admitted to hospital in mid-May.

Examination: V.A. (without correction) R 6/5, L 6/60. There was a left centrocaecal scotoma and inferior nasal visual field defect. His left direct pupillary response to light was poor. The optic discs were normal. The WCC was normal but the Paul Bunnell test was strongly positive. His condition was stable and he was discharged after six days on no specific treatment.

In late May he developed leg pains and weakness with numbness in the feet and perineum. By early June he had low back pain, difficulty in opening his sphincters, increasing leg weakness and perineal numbness with itching of his inner thighs. He was readmitted to hospital. He was then unable to walk unaided and had moderate to marked global weakness both lower limbs. The right knee jerk was mildly increased as were the left knee and both ankle jerks. Plantar and cremasteric reflexes were unobtainable. Abdominal reflexes were normal. Hypalgesia and hypthermaesthesia were present below T12 on right and below the knee on the left. Vibration sensation was midly depressed at the ankles. Proprioception was normal. The upper limbs were normal.

A myelogram was normal. CSF: 60 mononuclear cells, 6 polymorphs, 550 RBC; protein 45mg%, EPG normal; cultures (including viral) negative; VDRL negative. His Paul Bunnell test was less markedly positive. He was treated with prednisone 60mg/day, analgesics, catheterisation and physiotherapy.

There was rapid improvement. After ten days of therapy motor power and sphincters were almost normal. Lower limb reflexes were bilaterally brisk and plantar reflexes were flexor. There was mild hypalgesia below the knees. V.A. (without correction) was R 6/5, L 6/9, with a slight increase in the size of the left blind spot.

Prednisone dose was tapered to cease at end of July. By late August complete recovery of vision and other neurological functions had occurred.

* The Royal North Shore Hospital, Sydney

DISCUSSION

In this patient, retrobulbar neuritis did not begin until a little over two weeks after the onset of the glandular fever. A period of almost three weeks separated the onset of the ocular and spinal manifestations. Such a temporal relationship is not uncommon in neuromyelitis optica.

In the reported cases of infectious mononucleosis with either optic neuritis or transverse myelitis, complete recovery has generally occurred although in one case of spinal cord involvement, the patient had mild residual defects (Silverstein *et el.*, 1972). Recovery has been associated with the use of corticosteroids (Cotton and Webb-Peploe, 1966) and B.A.L. (Bonynge and Von Hagen, 1952), but in other cases who recovered fully no specific treatment was used. Rapid recovery beginning at the time of commencement of corticosteroids was a feature of the present case. Possibly this was coincidental, but other authors have noted dramatic improvement in neurological manifestations when corticosteroids or ACTH were used (Frenkel *et al.*, 1956; Huber *et al.*, 1951; Schnell *et al.*, 1966).

Pathological reports of nervous system lesions in infectious mononucleosis are rare. Foci of inflammatory cells in the meninges or around cortical blood vessels were found in five of six fatal cases (Custer and Smith, 1948). Degenerative parenchymal lesions have also been reported (Bergin, 1960; Dolgopol and Husson, 1949). All of these patients died shortly after the onset of an acute illness. Pathological changes, principally affecting grey matter, included vascular congestion, perivascular haemorrhages, cellular necrosis and degeneration and perivellular oedema. Amber *et al.* (1971) reported on the brain biopsy from a patient who had developed progressive focal symptoms suggesting a mass cortical lesion one month after the diagnosis of infectious mononucleosis. An inflammatory demyelinating lesion in the white matter was demonstrated. The authors concluded that it was a postinfectious demyelinating disease. The nature, timing and course of the neurological manifestations in the current case also suggest that postinfectious demyelination had occurred.

SUMMARY

A case of moderately severe neuromyelitis optica following infectious mononucleosis is described as the first reported instance of this complication. Total recovery occurred. Rapid improvement followed the commencement of corticosteroids. It is postulated that the pathological process was one of postinfectious demyelination.

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PERIODIC ALTERNATING NYSTAGMUS

L. de SILVA, B.P. COOPER, and J.G. McLEOD*

Periodic alternating nystagmus is a form of horizontal or horizontal-rotary jerk nystagmus which undergoes cyclic changes in direction and amplitude. The condition was considered exceedingly rare, since it was first described by Borries (1920). Up to 1970, 40 cases had been reported in the world literature. Only three of these were in English (Towle and Romanul, 1970). However, in 1971, Davis and Lawton Smith described eight further cases and considered that the condition was not as rare as had previously been thought. About 50 cases have now been reported. The purpose of the present report is to describe a typical case and to discuss the subject.

CASE HISTORY

The patient, A.M., a 44 year old man, emigrated to Australia from Malta 10 years ago. He had enjoyed apparent good health until March, 1973, when, during a visit to Malta, he experienced sudden, transient attacks of loss of balance, each lasting only a few seconds. A few months later, grand-mal epileptic seizures commenced and he was treated with phenytoin, 100 mg t.d.s. On his return to Australia in March, 1974 another attack occurred and carbamazepine 100 mg b.d. was added to the regimen. An electroencephalogram (E.E.G.) and brain scan were normal. Over a period of two weeks, the patient became progressively drowsy, apathetic, depressed and unsteady on his feet so that he was unable to walk without assistance. In July, 1974, he was admitted to the Parramatta Psychiatric Centre.

There was nothing relevant in the patient's past history or family history.

Examination revealed that the patient was apathetic, withdrawn and depressed. His speech was staccato in nature. There was horizontal jerk nystagmus which was subsequently noted to be of the periodic alternating type. Each phase of nystagmus lasted about 100 seconds, with a quiet interval of 10 seconds. Horizontal nystagmus was present on upward gaze. There was inco-ordination of upper and lower limbs, and his gait was grossly ataxic. Reflexes were brisk and plantar responses were flexor. There were no sensory abnormalities.

Because anti-convulsant toxicity (serum phenytoin 38.6 μg/ml; normal range 10-20 μg/ml) was suspected phenytoin was withdrawn and phenobarbitone substituted. Later, the carbamazepine was also withdrawn. However, his condition showed little improvement and he was transferred for further investigation to Sydney Hospital in August, 1974.

Full biochemical, haematological and serological screening was normal. Plain chest and skull radiographs were also normal.

Lumbar puncture was performed on three ocassions. Cell counts were 13, 16, and 14 lymphocytes/ mm.^{3} and C.S.F. protein was 74, 93 and 96 mg% respectively. No organisms were cultured.

E.E.G.s indicated a right temporal lesion. Brain scans were negative. Bilateral carotid arteriography (B.C.A.) showed no significant abnormality. A pneumoencephalogram (P.E.G.) showed no definite abnormality though there was some possible dilatation of the aqueduct and the 4th ventricle.

Electronystagmography (E.N.G.) confirmed the characteristic features of periodic alternating nystagmus (Fig. 1). Eye closure tended to intensify the nystagmus (Fig. 2), and it disappeared with sleep. Caloric testing was able to overcome or reverse the nystagmus in the appropriate direction. Optokinetic stimulation had little effect on the nystagmus.

On the basis of the above investigations it was felt that the aetiology of the condition in this patient could be an encephalitis or a cerebellar degeneration. Because of the possibility of a demyelinating encephalitis he was given a course of steroid therapy under cover of anti-tuberculous drugs. On this therapy slight clinical improvement was noted, the patient seeming less apathetic and depressed. However, there was little change clinically in other respects. A repeat lumbar puncture one month later revealed a considerable improvement in the C.S.F. It now contained only 1 lymphocyte per mm.^{3} and the

* Sydney Hospital and Parramatta Psychiatric Hospital, Sydney

C.S.F. protein was 65 mg%. On follow-up after discharge from Sydney Hospital there has been little further change in his clinical condition apart from a diminution in the deep reflexes of his lower limbs.

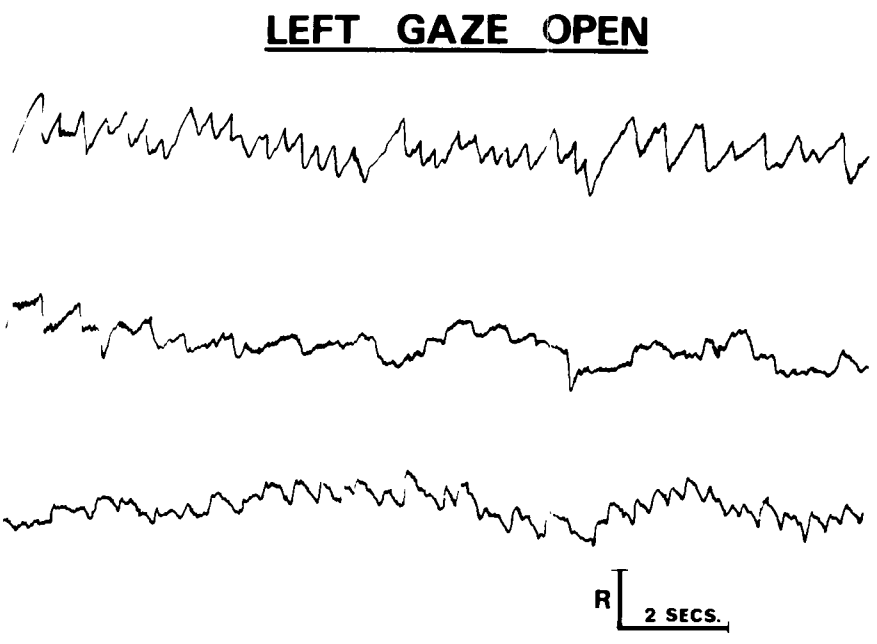

FIG. 1. E.N.G. in left gaze with eyes open showing the alternation in direction of the nystagmus.

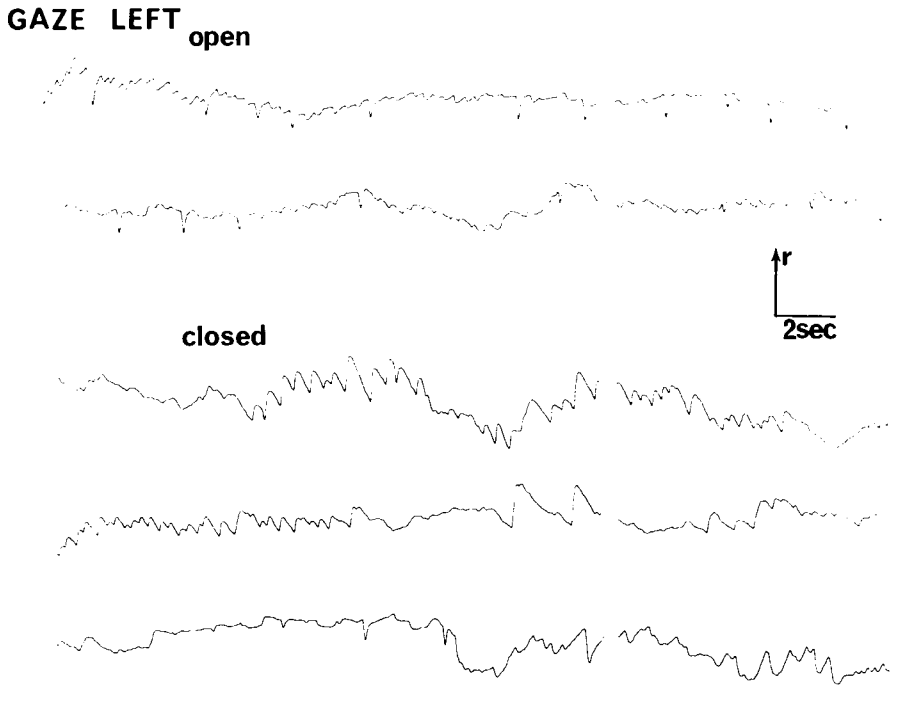

FIG. 2. E.N.G. showing effect of eye closure.

DISCUSSION

The typical clinical features of periodic alternating nystagmus were confirmed by E.N.G. studies and by caloric and optokinetic tests. The duration of each phase of the cycle remains quite constant in any given individual. In the reported cases the duration of the phases of the nystagmus has varied from 1 to 6 minutes and of the quiet interlude from 4 to 20 seconds. Hence, the condition can easily be overlooked if nystagmus is not observed for a sufficient length of time. Each phase of the nystagmus in our patient's cycle lasted about 100 seconds and the quiet interlude about 10 seconds. The persistence of horizontal nystagmus during vertical gaze occurs in only one other condition, viz. congenital nystagmus. The effect of sleep on this condition has, to our knowledge, not been hitherto reported. The supression of the nystagmus by sleep which we observed makes this condition no different from other forms of nystagmus. A few cases have been idiopathic and the aetiological factors in the other reported cases have been varied.

The aetiology of the condition in our patient has not been definitely established. However, investigations have excluded most of the known aetiological factors and indicate that the likely aetiology is either an encephalitis or a cerebellar degeneration. The presence of a lymphocytic pleocytosis favours the former condition. Although the serum phenytoin level was initially high there was no significant improvement in the patient's condition when anticonvulsant therapy was withdrawn. Only three cases have been studied pathologically (Towle and Romanul, 1970). The lesions, respectively, were an arachnoid cyst, an Arnold-Chiari variant malformation, and multiple sclerosis. In all cases the site of involvement was the upper part of the medulla. The mechanism has not been firmly established. On the available evidence it seems most probable that the condition represents a state of central vestibular hyperexcitability (Jung and Kornhuber, 1964). In apparently normal individuals, nystagmus following rotational vestibular stimulation sometimes alternates in direction, and this may represent vestibular hyperresponsiveness. Jung and Kornhuber (1964) mention a patient with demyelinating disease who demonstrated this phenomenon for some years and then developed spontaneous periodic alternating nystagmus. It may be postulated that there is some mechanism in normal individuals which inhibits to a varying degree the vestibular neurones, and that those in whom this inhibition is weak tend to develop periodic alternating nystagmus following vestibular stimulation or even spontaneously. On the basis of such a hypothesis one may expect periodic alternating nystagmus to result either from a central lesion destroying the inhibitory mechanism or from a peripheral lesion causing an imbalance in the input from the labyrinths on the two sides in an individual in whom the inhibitory mechanism is intrinsically weak. Such a hypothesis may explain how periodic alternating nystagmus has occurred not only in central lesions but also, occasionally, in peripheral lesions such as chronic otitis media (Kestenbaum, 1961). On the basis of the pathological studies the localisation of this inhibitory mechanism appears to be lower than had previously been thought, and it is noteworthy in this connection that the superior vestibular nucleus has been shown to have a predominantly inhibitory function (Highstein and Ito, 1971).

SUMMARY

A typical case of periodic alternating nystagmus is described. Periodic alternating nystagmus is a form of horizontal or horizontal-rotary jerk nystagmus of which the most characteristic feature is an alternation in direction at regular intervals. The condition appears to be not as rare as has been believed previously and may indicate a lesion in the upper part of the medulla.

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OPSOCLONUS WITH MYOCLONUS

J.T. HOLLAND*

According to Cogan (1954), Halliday (1967) and McLean (1970) the term "opsoclonus" was coined by the Polish neurologist Orzechowski in 1913. His words to describe the eye abnormality were "connant l'impression d'une grande agitation des globes oculaires, chaotique, variable et presque impossible à analyzer" (Cogan, 1954). These words are appropriate to describe what is the outstanding abnormality although Orzechowski also recognised the associated, more generalised myoclonic movements which involve the body as a whole. In the past 20 years there have been a number of reports of this rare condition which perhaps should be looked upon as a syndrome due to a number of possible causes rather than a disease entity *sui generis*.

The descriptive terminology applied to this syndrome has been varied although most of its names have attempted to indicate both the chaotic nature of the eye movements and the generalised myoclonic muscle movements (see Table I). Reference has also been made to some cerebellar features

TABLE I

Synonyms for Opsoclonus

Ataxic conjugate movements of the eye	(Walsh, 1947)
Myoclonic encephalopathy of infancy	(Kinsbourne, 1962)
Ocular oscillations & truncal myoclonus	(Barringer, Sweeney & Winkler, 1968)
Dancing eyes, dancing feet: infantile polymyoclonia	(Dyken & Kolar, 1969)
Infantile polymyoclonia – opsoclonia	(Moe & Nellhaus, 1970)
Oculo-cerebello-myoclonic syndrome	(Lemerle *et al.* 1969)*
Polymyoclonia with opsoclonus	(McLean, 1970)
Rapid irregular movements of eyes and limbs (R.I.M.E.L.)	(Pampiglione & Maia, 1972)

* Cited by Brandt *et al.* (1974).

by most authors (Smith and Walsh, 1960; Soloman and Chutorian, 1968; Barringer, Sweeney and Winkler, 1968; Martin and Griffiths, 1971; Brandt, Carlsen, Genting and Helwig-Larsen, 1974) including Orzechowski himself (Smith and Walsh, 1960) although he made no emphasis of this feature ... "we can always find a few features of cerebellar disease ... but what dominates the clinical picture is ... the myoclonus". Two comments may be made. Firstly, the main cerebellar abnormality referred to seems to be a truncal ataxia, sitting and walking, which affects all age groups; secondly, these cerebellar abnormalities seem to feature much more prominently in the children and especially those suffering from neuroblastoma. In the patient here described the truncal and gait ataxia as well as the abnormality of finger-nose and heel-knee testing seemed wholly to be the result of disorganisation of posture and movement by the superimposed myoclonus rather

* Royal Newcastle Hospital, Newcastle.

than due to primary cerebellar involvement. This point is also made by Dyken and Kolar (1968) and McLean (1970).

CASE REPORT

A female aged 34 years was admitted to Royal Newcastle Hospital on 1[illegible].9.73 with a history of an upper respiratory tract infection beginning 14 days previously and lasting 2 to 3 days. As this infection resolved she became "giddy" with movement of her head and on occasions vomited. Her own doctor prescribed prochlorperazine (Stemetil), with little relief except for the vomiting. Within a day or two following commencement of the "giddiness' she began to experience jerky movements of her body, again made worse by movement. Examination on admission showed irregular chaotic conjugate movements of her eyes at rest, with the eyes open or shut. These movements were mainly in the horizontal direction; on occasions they were vertical but never rotatory. They were made worse by eye movement and seemed to be associated with irregular blinking of the eyelids. Similarly, most of the musculature of her arms and legs, abdomen and diaphragm, but not the palate or pharynx, showed irregular brief myoclonic movements even at rest. This myoclonus was considerably enhanced by movement or even by maintaining a posture. On attempting to stand the movements became so marked as to make unassisted stance almost impossible. Examination of her nervous system otherwise showed no abnormality and in particular, with allowance made for the exaggerated myoclonic movements, no cerebellar inco-ordination could be demonstrated. Likewise general examination was unrevealing.

Withdrawal of the Stemetil which had been continued until 25.9.73 and the intravenous infection of 2mgm of benztropine (Cogentin) had no effect on the movements. C.S.F. examination on 25.9.73 revealed an opening pressure of 65mm H_2O, a protein of 35mgm%, a sugar of 65mgm%, and 45 cells (40% RBC, 60% lymphocytes). Repeat C.S.F. examination on 1.10.73 showed an opening pressure of 165mm. H_2O, protein 65mgm%, albumin 43mgm% (normal 8-24), IgG 12mgm% (normal 1.5-4.0). A cell count was not performed. Virus studies from pharyngeal washings and faeces together with paired blood specimens after 10 days failed to show abnormality, except for measles complement fixation titres which suggested recent contact. Her E.E.G. was normal. Full blood count and E.S.R. were normal.

Nitrazepam (Mogadon) in dosage up to 10mgm t.d.s. gave considerable relief from the movements. At the time of her dischrage, almost 3 months after admission, she was able to walk unaided with minimal action myoclonus and very diminished opsoclonus of her eyes. She felt that her unsteadiness persisted for a further 3-4 months after discharge. She is now extremely well except for the presence of a marked startle response to unexpected noise or fright.

DISCUSSION

For an accurate description of opsoclonus, Orzechowski's own words, as translated by Smith and Walsh (1960), cannot be improved upon

> "... the eyes are in a continual state of agitation; the eyes are shaking and are displaced by very rapid and unequal movements which occur generally in the horizontal plane. Very often these movements are not made by series but each series will end with a sudden elevation followed by a fall of the eyes, which is followed by a short pause ... when the phenomenon is less marked, the difficulties appear at the moment when the eyes change their position, whether this change is intentional or reflex. The difficulty is particularly intense at the beginning of movement and the intensity decreases at the moment when the eyes achieve their point of fixation. Between the horizontal shakings which always predominate can be seen sudden jerks which occur in other directions".

Most authors indicate that the movements continue during sleep, although they are then less marked. The movements are almost invariably conjugate. Irregular myoclonic movements of the eyelids such as occurred in the case reported in this paper are rarely referred to, although they have been described by Martin and Griffiths (1971). It is difficult to know if these movements should be considered to be part of the opsoclonus or part of the more generalised myoclonus. However the eyelid movements are very closely related to the eye movements.

The differentiation of opsoclonus from ocular dysmetria and ocular flutter has been made by Cogan (1954). Ocular dysmetria is characterised by short duration conjugate oscillations of the eyes of diminishing amplitude on attempted fixation or refixation in the primary position of gaze. Movement from the primary to the secondary position of the eyes is not interfered with. It appears to be a reliable indicator of cerebellar disease. Ocular flutter is very similar in being best seen on fixation or refixation of the eyes, after movement from one position to another has ceased. These terminal oscillations are few in number and of small amplitude and may even occur spontaneously. However, once again the movement of the eyes from one fixation point to another is not interrupted. Like ocular dysmetria this abnormality is also very suggestive of cerebellar disease (Cogan, 1954). The more generalised myoclonic movements may be just observable at rest and

even during sleep. They are moreover grossly exaggerated both in their frequency and in extent by movement, and in particular by the maintenance of posture of limbs and by sitting or standing, which may be made utterly impossible. It has already been suggested that this is the explanation of the truncal and gait ataxia and perhaps, in many cases, the cerebellar signs referred to in the literature on the condition.

There is one other observation that Orzechowski also made, namely "... another characteristic is ... a state of anxiety and inquietude; and intensity of these motor phenomena is increased under the influence of emotions or of external excitation" (Smith and Walsh, 1960). This was certainly true of the patient here reported. Indeed, although the patient is now well without any abnormal signs, she is aware that the slightest unexpected noise or fright elicits an exaggerated and abnormal startle response.

With the exception of Cogan's (1954) two patients, both of whom died, and some of the children with neuroblastoma, examination of the nervous system is otherwise normal and the patient's mental state is clear and unaffected. Laboratory investigations, with the sole possible exception of the C.S.F., are likewise helpful in those cases where underlying disease cannot be discovered e.g. neuroblastoma (where urine tests for V.M.A. may be positive, and the tumour itself found), occult carcinoma, Lafora body disease or lipoidosis. The C.S.F. in the present patient initially showed an abnormal number of mononuclear cells and repeat examination six days later showed an elevation of the protein level and IgG. Similar findings of increased mononuclear cells, raised protein and raised IgG levels were reported by Dyken and Kolar (1968). Others have also reported elevated numbers of mononuclear cells and protein (Baringer *et al.*, 1968; McLean, 1970). These authors have also documented abnormal colloidal gold curves with a rise in the middle part of the curve. E.E.G. examination has either been normal or has shown only minor abnormalities (Pampiglione and Maia, 1972).

Concerning aetiology (see Table II), an association with neuroblastoma in childhood has now been well documented and removal of the tumour has, without exception, been followed by a lasting cure of the movement disorders. Therefore when this condition is found in childhood,

TABLE II

Suggested Aetiologies for Opsoclonus

1. Viral (Valeri, 1939*; Cogan, 1954)
   – polio (Marmion and Sandiland, 1947; Brewis, 1960*; Swanson, Luttrell and Magladery, 1962*)
2. Post-infective (Barringer *et al.*, 1968)
3. Immunopathy (Dyken and Kolar, 1968)
4. Neuroblastoma – in infancy (Kinsbourne, 1962; Soloman and Chutorian, 1968; Moe and Nellhaus, 1970; Martin *et al.*, 1971; Brandt *et al.*, 1974)
5. Occult carcinoma (Ross and Zeman, 1967)
6. Lafora body disease (Harriman and Millar, 1955*)
7. Lipoidosis (Bird, 1948*)
8. System degeneration (Yakovlev, 1942*)

* Referred to by Halliday (1967)

neuroblastoma should be looked for diligently. However, in the majority of children, and in adults, as a rule no underlying disease is found. Although no virus has ever been isolated in a sporadic case, encephalitis is often invoked as the likely cause. Halliday (1967) does refer to case reports by Marmion and Sandilands (1947), Brewis (1960) and Swanson, Luttrell and Magladery (1962) concerning patients suffering from polioencephalitis. However this has not been the common experience. Nonetheless, there is circumstantial evidence to suggest an infective or post-infective viral aetiology in some cases; there is often a preceding upper respiratory or gastrointestinal infective illness associated with a fever, and C.S.F. examinations have, on occasions, shown elevated mononuclear cell counts and protein and IgG values as in the case here reported. In addition two autopsy reports from the literature have suggested a possible encephalitis on the basis of the presence of

perivascular lymphocytic infiltrations (Cogan, 1954; Ross and Zeman, 1967). Concerning the remaining aetiological possibilities, the evidence for a primary immunopathy (Dyken and Kolar, 1968) is not convincing as the changes in the C.S.F. are non-specific. Only one case associated with carcinoma has been reported (Ross and Zeman, 1967), three with verified Lafora body disease (Halliday, 1967), one with lipoidosis (Halliday, 1967) and one with "system degeneration of Yakovlev" (Halliday, 1967).

An understanding of the underlying pathophysiology is even more difficult, especially in view of the fact that only two cases have come to autopsy. Cogan's (1954) case I "... revealed an encephalitis characterised by perivascular lymphocytic infiltration chiefly in the hypothalamus, midbrain and pons. The cerebral cortex and basal ganglia were normal". This is the sum total of the report. The situation is further complicated by the doubt that the case was indeed suffering from the same syndrome since the patient had other neurological symptoms and signs prior to death. The case of Ross and Zeman (1967) once again has doubt associated with it as to whether it is truly representative of the syndrome; the patient also had a carcinoma of the lung, and the changes described in the cerebellum and olives may have been related to the malignancy without being responsible for the opsoclonus. However, once again perivascular lymphocytes were noted "throughout the parenchyma" of the brain as well as being seen focally in the subarachnoid space of the spinal cord, and in the periventricular regions and the diencephalon. One is forced to agree with McLean (1970) that "until a *bona fide* case of polymyoclonia with opsclonus comes to autopsy, there can only be speculation about the pathology", as well as the pathophysiology.

One is able to be a little more sure about prognosis and treatment. In regard to the former, except for those cases associated with underlying disease e.g. neuroblastoma, the outlook is uniformly excellent, complete recovery taking place within weeks to months. Except for the case reported by McLean (1970) and the cases of Pampiglione and Maia (1972) of the R.I.M.E.L. syndrome, which seemed in no way different to the syndrome outlined as above, the presently reported case experienced symptoms for one of the longest durations as yet recorded. McLean's 50 year old man was considered to have had abnormal eye movements persisting for some two years. Case I of Pampiglione and Maia (1972) would seem to have had signs for at least one year; their case II had signs for nearly two years before full recovery occurred.

In relation to treatment it must be pointed out again that full recovery in any case is the rule. However, there is suggestive evidence, in children at least, that a course of "the neurologist's steroid", i.e. ACTH, may hasten recovery (Kinsbourne, 1962; Dyken and Kolar, 1968; Pampiglione and Maia, 1972). With the present patient there was no doubt that the nitrazepam did help to control the movements but there is no evidence that the course of the disease was in any way shortened thereby.

SUMMARY

A further case of opsoclonus with myoclonus is described. When this syndrome occurs in childhood an associated neuroblastoma should be excluded. In the majority of cases at all ages no underlying disease will be found, although a preceding history of minor upper respiratory or gastrointestinal infection may be elicited, suggesting that a possible encephalitis is affecting brain stem mechanisms may be the cause. The prognosis is, as a rule, excellent although full recovery may not occur for many months. Corticosteroids and nitrazepam may have a place in the treatment of severely affected patients with distressing symptoms.

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THE OCULAR MYASTHENIA SYNDROME

W.J.G. BURKE*

Myasthenia gravis frequently presents with diplopia and ptosis. In a small proportion of cases the weakness remains confined to the ocular muscles for long periods and at times may be confined to them indefinitely. It has been observed that when only the extra-ocular muscles are affected for 18 months or more, there is little chance of involvement of other muscle groups subsequently.

The difficulties in differential diagnosis presented by ocular palsies, particularly variable ocular palsies, are well known. The variability of the ocular palsy, either spontaneous or in relationship to factors such as exercise, pyrexia, pregnancy or intercurrent illness, along with a partial positive response to neostigmine or edrophonium, may strongly suggest the possibility of myasthenia gravis when the true diagnosis is progressive external ophthalmoplegia, multiple sclerosis involving the brain stem, intercranial tumours, brain stem vascular disease or thyroid ophthalmopathy.

CASE REPORT I

A 15 year old boy presented in mid 1973 with ptosis and diplopia due to variable weakness of elevation of both eyes and of abduction of the right eye. To several observers his response to intravenous edrophonium appeared diagnostic of myasthenia gravis, and there was an apparent partial but sustained response to oral neostigmine maintained over the next few months. About 12 months after the onset of his diplopia he showed increasing ataxia, variations in mood and behaviour and long tract signs appeared in the lower limbs. Subsequent investigation revealed a tumour, probably a glioma involving the posterior part of third ventricle and upper brain stem. He has made good progress after ventriculo-venous shunt and radiotherapy.

There is still no complete agreement on the site of the disturbance of neuro-muscular transmission in myasthenia gravis. Ballantyne and Hansen (1974), from recent E.M.G. studies, suggest the presence of a presynaptic dysfunction in myasthenia gravis. The dysfunction takes the form of a terminal neuropathy in the fine intramuscular nerve fibres; this is responsible for both the increase in distal motor latencies and the reduction in duration of motor unit potentials found in the condition.

The following case reports indicate that ocular myasthenia may appear in the course of multiple target organ disease, presumably related to disordered antibody production.

CASE REPORT II

A 19 year old girl presented in 1959 with sudden onset of cerebellar ataxia of limbs and gait. She had signs of mitral incompetence and a raised E.S.R. Her neurological signs disappeared over the next six weeks and she had no cardiac decompensation associated with the mitral valve lesion. About 12 months later she developed diplopia, bilateral ptosis and variable ocular palsies which were completely abolished by intravenous edrophonium. She was maintained symptom free for most of the time while taking oral neostigmine. Over the next three to four years her ocular myasthenia gradually disappeared and she has required no further neostigmine since then. In 1964 she developed a florid thyrotoxicosis which

* St. Vincent's Hospital, Sydney

required thyroidectomy. This was followed by myxoedema which was controlled with oral thyroxine. About two years after the thyrotoxicosis she developed a severe ulcerative colitis which was controlled by steroid therapy and azothioprin; the colitis gradually disappeared over the next two years. At about the same time she had recurrent relapses of diffuse rheumatoid arthritis and for many years has been taking oral steroids, the dose gradually diminishing to her present intake of prednisone 5 mg daily. Now, 17 years after the onset of symptoms she is quite well, still taking prednisone 5 mg daily. Further reduction in her steroid dose will provoke joint pains, although this may indicate merely her dependence on continued steroid therapy.

CASE REPORT III

In 1955 a 55 year old oil company executive presented with a one month history of double vision, ptosis, difficulty in maintaining head posture, tiredness of the jaws when chewing, and recurrent weakness of the limbs on exercise. He had restriction of upward and inward movement of the right eye and obvious right ptosis. There was ready fatigueability in the muscles concerned with head posture and also in the proximal muscles of all limbs. He had a rough diffuse systolic murmur related to a long standing aortic stenosis. His ocular and limb muscle weakness was dramatically reversed by intravenous edrophonium and he maintained a good response to oral neostigmine. His myasthenia gradually went into complete remission over the next seven to eight years. In 1965 he developed increasing anaemia. This was a true pernicious anaemia due to vitamin B_{12} deficiency and responded completely to intramuscular vitamin B_{12} therapy. In 1967 he had a bout of bronchitis accompanied by severe coughing. During this illness he developed severe headaches with a return of his right ptosis. At this time he showed evidence of a partial right third nerve palsy. This made a complete recovery after removal of a right subdural haematoma which was apparently induced by his coughing. When he died from his aortic stenosis in 1972 he had no evidence of residual myasthenia in limbs or external ocular muscles.

CASE REPORT IV

A male, 67 years of age, had presented to an ophthalmic surgeon for correction of a bilateral severe ptosis which had gradually developed over the previous three to four years. He had weakness of elevation of the eyes, but also variable weakness of the muscles of mastication and also weakness of retrocolic muscles. His weakness gave a diagnostic response to intravenous edrophonium and also showed a satisfactory response to oral neostigmine medication. Twelve months later he presented with gradually increasing paraplegia with spastic weakness of the lower limbs and loss of vibration and joint sense in the lower limbs. He was found to have a megaloblastic anaemia and had subacute combined degeneration which responded completely to intramuscular vitamin B12 therapy.

In occasional patients there is a long history suggesting myasthenic weakness of ocular muscles and sometimes of limb muscles as well. This does not compel the patient to seek medical attention. The disorder may gradually but completely subside without treatment.

CASE REPORT V

A 13 year old girl was seen two years ago, mainly because of increasingly severe migraine type headaches. Her mother said that from the age of four she had had bouts of double vision, initially occurring when she had a high temperature. Later, during school days, she had bouts of double vision, weakness in the limbs and slurring of speech which were precipitated by extra activities such as skipping, swimming in races or running. She had to give up all competitive sport because the effort provoked the appearance of diplopia, slurred speech and a weak, jelly-like feeling in the limbs. On initial examination she had full ocular movements and normal power in all limbs. On exercise she showed a moderate weakness in abduction of the shoulders and flexiion of the hips, recovering in about one minute. This post-exercise weakness was completely abolished by intravenous edrophonium. At present she is quite well and on no neostigmine therapy and, at the time of writing, has no weakness after exercise. Anti-nuclear factors were detected in her blood and immuno-fluorescent studies showed a positive response for parietal cell antibodies and a strongly positive response for skeletal muscle antibodies.

CASE REPORT VI

A 40 year old married woman was first seen in the Intensive Care Ward at St. Vincent's Hospital. She had developed prolonged apnoea and diffuse muscle weakness following an operation for plastic correction of longstanding bilateral ptosis. Her ocular and limb weakness showed a diagnostic response to intravenous edrophonium. She has remained well in the two years since then, while taking oral neostigmine. She has a history dating back to childhood and consisting of diplopia, slurred speech and muscle weakness, developing after exercise and preventing her from partaking in all competitive sport during her adolescence. She had "learned to live with this" during her subsequent adolescence and young adult life and had raised three children.

The following five cases are examples of a purely ocular myasthenia with no evidence of involvement beyond the extra-ocular muscles. Their clinical course has been uniformly satisfactory.

CASE REPORT VII

A 48 year old Greek born male presented in January, 1970 with a two week history of diplopia, which developed suddenly one morning after a late night. He inclined his head to one side to avoid the diplopia and on examination showed limitation of abduction and upward and outward movement of the right eye. Intravenous edrophonium completely abolished the diplopia and the ocular paresis and the patient maintained a satisfactory response to oral neostigmine. Over the next six weeks he developed a prominent left ptosis but this gradually receded. All systemic investigations showed no abnormalities. When last seen in September, 1972 he was symptom free, was taking pyridostigmine bromide 60 mg b.d. and 180 mgms at night. He was advised to gradually cease his medication over the next six months.

CASE REPORT VIII

A 23 year old man presented in November, 1974 with a three week history of horizontal diplopia which was abolished by covering either eye. The diplopia was accompanied by heaviness of the eyelids at the end of the day, forcing him to tilt his head backwards. He had a heavy lidded appearance and the right upper eyelid drooped about 50 per cent more after exercising by carrying out upward and downward movements of the eyes. There was no weakness elsewhere and intravenous Tensilon immediately abolished his right ptosis. When seen one month later he had no further ptosis or diplopia, but complained of "slowness in focus" when turning his gaze. At this stage he had a full range of ocular movements and no ptosis and was on no treatment. General systemic investigation showed no abnormalities.

CASE REPORT IX

A 48 year old Portugese woman presented in June, 1974 with a two month history of fluctuating left ptosis. For the previous two years she had had some difficulty in clearing saliva from her throat. She had a prominent left ptosis which varied in degree during examination and was increased by exercising eye movements. There was no muscle weakness elsewhere and the ptosis was completely abolished by intravenous edrophonium. Since then she has had a mild and variable left ptosis partially responsive to oral neostigmine. However, she has not been able to tolerate oral neostigmine, but her only disability is a mild left ptosis.

CASE REPORT X

An Australian born farmer, 72 years of age, presented on 18.7.73 with diplopia of five weeks duration. He had no limb weakness. There was a slight left ptosis and marked impairment of lateral eye movements on both sides. There was slight inequality of the pupils and the eye signs initially suggested the possibility of an internuclear ophthalmoplegia. However, his ptosis and diplopia immediately disappeared with intravenous edrophonium. General medical investigations, including chest radiographs and thyroid function tests, showed no abnormalities. When last seen in December, 1974 he was quite well, had no diplopia or muscle weakness and was taking oral pyridostigmine bromide 60 mgms t.d.s. and 90 mg at night, together with spironolactone 25 mg q.i.d. This medication was to be suspended gradually over the next six months.

CASE REPORT XI

A 34 year old housewife presented in 1958 with a three month history of weakness of finger movements, mainly in the right hand, causing drooping of the fingers. This first appeared temporarily during her pregnancy 18 months previously. Two months after this pregnancy she had developed a fairly severe polyarthritis. At that time she had weakness, mainly in the extensors of the elbows, paresis of the long extensors of the fingers causing finger droop, and her weakness showed a prompt response to intravenous edrophonium. Since then she had constant residual weakness in the extensors of the elbows in spite of oral neostigmine therapy. In October 1973, she presented with a prominent right ptosis of some weeks duration together with intermittent diplopia. At that time she was taking pyridostigmine bromide 60 mg six times daily. The ptosis was abolished by intravenous edrophonium and has since disappeared, although with emotional stress, embarrassment, tiredness after exercise or with exercising the eye muscles she develops a fairly prominent right ptosis. She had noted that the ptosis occasionally alternated with periods of retraction of the right upper lid.

It seems that an isolated intermittent ptosis abolished by edrophonium and provoked by emotional disturbance, fatigue or exercising the eye muscles is a separate entity. It is distinct from other forms of the myasthenic syndrome and is rarely associated with muscle weakness elsewhere.

Some cases which present as an apparent true ocular myasthenia, may subsequently show signs such as nystagmus which may indicate a central brain stem cause for their disorder, possibly a demyelinating disease involving the brain stem oculo-motor nuclei and their connections.

CASE REPORT XII

A 30 year old housewife and mother of a young family presented in November 1958 with a recent history of marked tiredness together with ptosis and diplopia. At that time she had bilateral ptosis with ocular divergence on looking up and nystagmus in the abducting eye on gaze to either side, accompanied by some weakness of abduction. There were no neurological abnormalities elsewhere and general systemic investigations showed no abnormalities. Her ptosis and diplopia disappeared with intravenous edrophonium and she has taken oral pyridostigmine bromide since then, initially 60 mg eight to nine times daily. She now takes only 120 mg each morning and has no diplopia, except for the mornings when she fails to take her dose of pyridostigmine. Her ocular palsies have always been very variable, sometimes appearing only during medical examination and then being more severe if she appears under emotional stress. At present she has a fine but sustained nystagmus to the right. She has no ptosis or strabismus and only mild diplopia on looking to the extreme right.

Perhaps the initial response to intravenous edrophonium was a false positive one, although impressive. Her course over later years has been more in keeping with a mild internuclear ophthalmoplegia, although no evidence of neurological disorder has ever appeared elsewhere.

Ocular myasthenia usually presents as part of a true myasthenia gravis, but some cases of variable ocular palsy remain entirely confined to the external ocular muscles, particularly the lid elevators. Some cases may be related to a neuropathy involving the oculo-motor nuclei themselves in the brain stem. One can only re-emphasise that there is a need to carefully exclude all other varieties of intracranial disorder, particularly space occupying lesions which may present as "an almost classical" ocular myasthenia.

SUMMARY

Twelve cases of ocular myasthenia are reported. The problems of diagnosis are discussed and the sometimes benign nature of the condition is pointed out.

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FAMILIAL CEREBELLAR ATAXIA WITH SEX-LINKED RECESSIVE INHERITANCE

P.J. SPIRA and J.W. LANCE*

Since the first description of an inherited ataxia by Friedreich in 1863, many families with spino-cerebellar disorders have been reported. The majority of authors describe conditions with features similar to those of Friedreich's families, but it is apparent that many different forms exist and that some forms seem to be limited to single families.

The present report describes a spino-cerebellar ataxia with features differentiating it from those previously reported. This kindred is of special interest as it displays sex-linked recessive inheritance, a very rare occurrence in the heriditary ataxias.

The pedigree (Fig. 1) shows 63 members of the family, of whom 12 were examined by the authors. These 12 included 5 affected males, 2 carrier females and 5 clinically unaffected individuals. Details of some other members were obtained, either from hospital records or from the 12 examined cases. There was no evidence of any affected individuals prior to the first generation indicated in the pedigree.

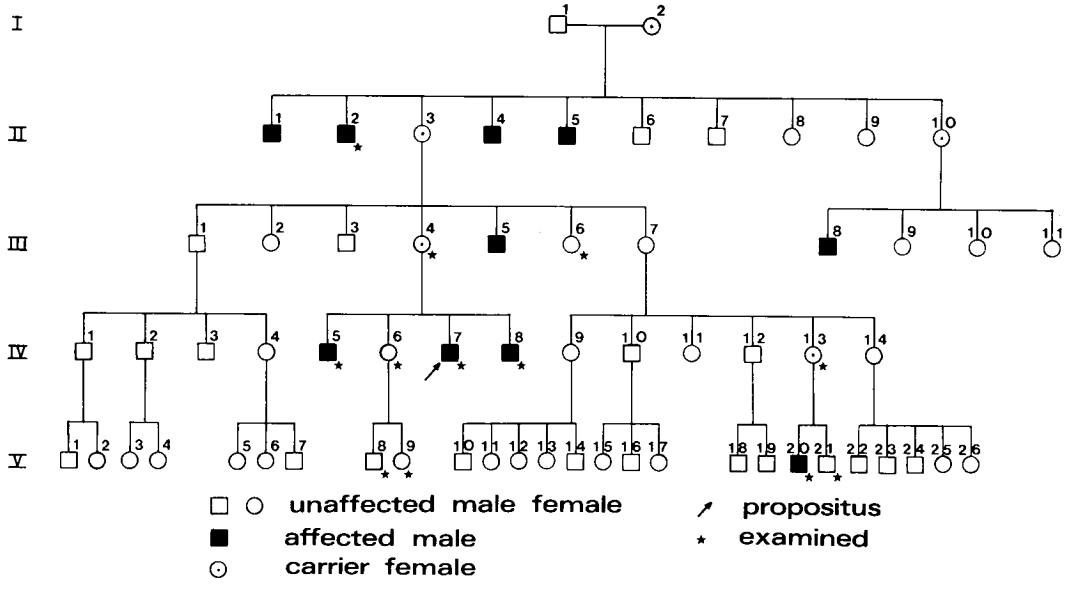

FIG. 1. The pedigree.

* The Division of Neurology, Prince Henry Hospital, Sydney.

CASE REPORTS

CASES I-1 & 2

Both were born in South Australia and moved to New South Wales where most of their descendants now reside.

CASE II-1

This subject died in 1971, at the age of 71, following a myocardial infarction. According to hospital notes and his brother's verbal report he had had a progressive ataxia since the age of 16 years. This had resulted in his becoming wheelchair bound and he was permanently institutionalised for the last 20 years of his life.

Physical examination 3 months before his death showed a pleasant, co-operative, slow thinking man, who was orientated in time and place. He was continent of urine and faeces. Pes cavus was noted. Power and tone were reduced in the upper and lower limbs, more markedly in the latter. Reflexes were hyperactive bilaterally and plantar responses were flexor.

The findings of the post-mortem examination are presented later in this report.

CASE II-2

This man is now aged 76 and is the only surviving affected member of the second generation. At the age of 13 he noted the onset of difficulty in running and weakness of his lower limbs. By the age of 17 years he required crutches in order to walk. At 20 he was found to be suffering from pulmonary tuberculosis and he was hospitalised for a prolonged period. Following discharge he was unable to walk even with crutches and he has been wheelchair-bound since. He has been institutionalised over the past 25 years.

Examination revealed a patient who was unable to walk but could propel himself in a wheelchair. He was orientated in time and place and gave a good, though slow, history. He was continent but suffered from urgency of micturition.

Corrected visual acuities were R. 6/9 and L. 6/6. Ophthalmoscopy revealed a small pigmented patch at the right macula but there was no evidence of optic atrophy. Speech was slurred and he demonstrated intention tremor, dysmetria and dysdiadochokinesis but no nystagmus. The patient had pes cavus and scoliosis. There was obvious muscle wasting in the lower limbs and some distal wasting of the upper limb musculature. Tone was minimally reduced in the arms and markedly diminished in the lower limbs. There was a mild pyramidal weakness in the upper limbs, while there were no voluntary movements of the lower limbs. All reflexes were hyperactive with the exception of the ankle jerks which were absent. Plantar responses were extensor. Pain and temperature sensibility was normal, while there was minimal reduction in proprioception at the toes and vibration sense was absent below the tibial tuberosities. Two point discrimination was reduced on the soles of the feet.

CASE III-4

The history was unremarkable and there was no pes cavus, kyphoscoliosis or any other neurological abnormality noted on examination.

CASE III-6

No abnormality was noted in the history or examination.

CASE IV-5

A male, aged 33. The patient commenced walking at the age of 18 months and was apparently normal until his 6th year when clumsiness of upper and lower limbs was noted. This has been gradually progressive and at present the patient is able to walk only with the help of a walking stick. His upper limb ataxia has resulted in marked difficulty with writing since the age of 8. He was continent and sexual function was unimpaired.

On examination he was found to be an alert, jovial patient. Visual acuity was normal and he was not colour blind. There were no fundal or retinal abnormalities. Pes cavus, scoliosis and increased lumbar lordosis were noted. The patient's gait was disturbed by a marked cerebellar ataxia with a superimposed spastic diplegia. While walking the patient displayed a slight truncal ataxia and titubation. Other cerebellar features included mild slurring dysarthria, nystagmus, intention tremor, dysmetria, dysdiadochokinesis and an abnormal heel-shin test. A discrepancy between the bulk of upper and lower limb musculature was noted (Fig. 2). Despite wasting of some of the lower limb muscles no fasciculations were seen. Tone was normal in the upper limbs while spasticity with the clasp knife phenomenon was found in the lower extremities. There was weakness of shoulder abduction and a pyramidal weakness was present throughout the lower limbs. Deep tendon reflexes were hyperactive, being more markedly increased in the lower limbs. Abdominal reflexes were present and plantar responses were extensor. Spinothalamic and dorsal column sensibility was intact and there was no Rombergism.

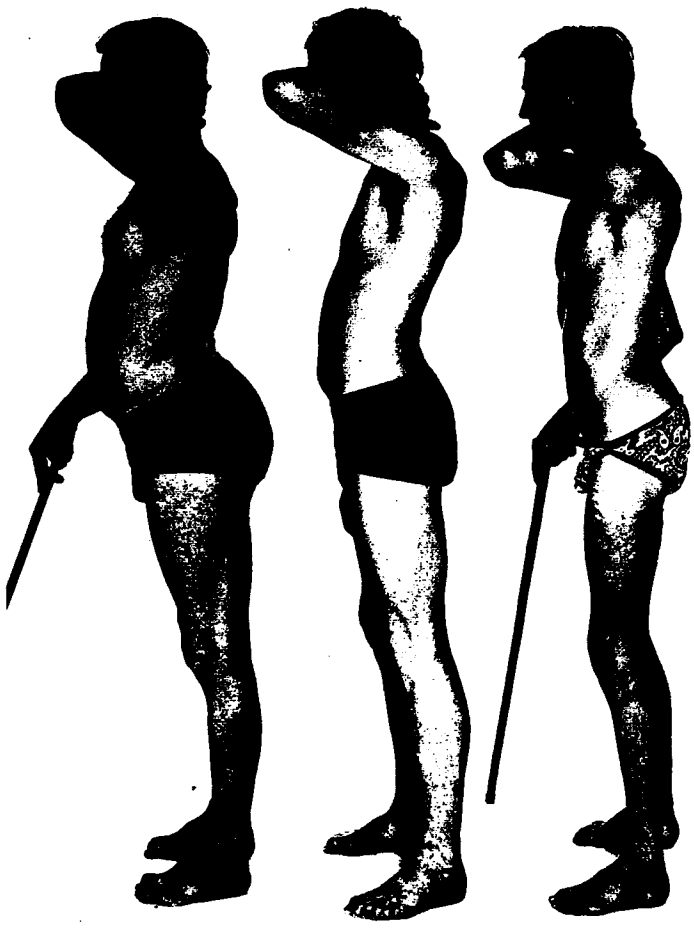

FIG. 2. Cases IV-5, 7 and 8 (left to right).

CASE IV-6

No abnormality was noted in the history or physical examination.

CASE IV-7

A male aged 28. The propositus was first seen in 1965. He had commenced walking when aged 2 years and was normal until 15 years of age, when he first had difficulty in running due to lower limb clumsiness. When 18 he had the onset of deterioration in vision in his left eye. Initially this was progressive but it has been static over the past 8 years. His gait disturbance has gradually increased and some upper limb ataxia has become apparent over the past 10 years. There has been no incontinence or disturbance of sexual potency.

Except for the ocular findings, neurological examination was not significantly different from that in Case IV-5. The patient had horizontal and vertical nystagmus. There was no strabismus or diplopia; visual acuities were R. 6/5 and L. 6/36. The right disc was paler than the left but there was no optic atrophy or degenerative retinal changes. The visual disturbance was due to uniocular astigmatism.

CASE IV-8

This male, aged 23, commenced walking when 18 months old. At the age of 6 he had the onset of progressive clumsiness

of gait and upper limb ataxia. He has remained continent and has had no disturbance of sexual potency. Apart from a more marked spasticity and pyramidal weakness in the upper limbs, features on physical examination were identical to those seen in Case IV-5.

CASE IV-13

No abnormality was noted in the history or physical examination.

CASES V-8 & 9

No abnormalities were noted.

CASE V-20

This patient was aged 3 years when first seen. He had been late to walk (2 months) and remained clumsy on his feet. He fell frequently. The parents only became worried when a tremor was noted in the upper limbs whenever the patient reached for objects.

On examination he had an unsteady gait and obvious ataxia of the upper limbs. Nystagmus was also present. There was no pes cavus or scoliosis. Tone was increased in the lower limbs and knee and ankle jerks were exaggerated. Plantar responses were flexor.

CASE V-21

This child was aged 11 months. No abnormality was found in the physical examination.

SUMMARY OF CLINICAL FEATURES

The first expression of this condition is the late onset of walking (18 months to 2 years). Within the first or second decade an ataxia of the upper and lower limbs becomes evident and this is gradually progressive. By the early 20's the patient requires walking sticks in order to reduce unsteadiness of gait. The two oldest members (Case II-1 and 2) were wheelchair-bound by the age of 30 and required permanent hospitalisation by the age of 50 as they could no longer look after themselves.

Incontinence, dementia and impairment of vision are not features of the condition. Life expectancy does not seem to be affected.

On examination, pes cavus, scoliosis and increased lumbar lordosis are seen. The patients display an obvious cerebellar ataxia associated with a slurring dysarthria, intention tremor and dysmetria. There is a very slowly progressive wasting of lower limb musculature and minimal wasting distally in the upper limbs. In the younger cases spasticity is noted, but hypotonia is seen later in the disease. A pyramidal weakness with hyperactive deep tendon reflexes and extensor plantar responses is also observed. Clinical sensory abnormalities were noted only in Case II-2, and these abnormalities were minimal.

The patients were questioned specifically to determine the possible presence of other sex-linked abnormalities. They were not colour blind (Ishihara plates) nor was there a history suggestive of haemophilia or glucose-6-phosphate dehydrogenase deficiency.

INVESTIGATIONS

Electrocardiography

Electrocardiograms were obtained from all the affected members who were examined. There were no abnormalities noted in the 4 younger cases while in Case II-2 ischaemic changes only were found.

Electroneurography

Nerve conduction studies performed on 5 patients showed very similar changes despite wide variation in clinical disability. The results for Case IV-5 are outlined in Table I. Sensory action potentials were reduced in amplitude but were found in all nerves sampled in each of the 5 cases. Lateral popliteal mixed nerve action potentials were also present in all cases, although reduced in amplitude. The most marked changes were the slowing of motor nerve conduction velocities indicating a predominantly motor neuropathy.

TABLE I

Nerve Conduction Studies: Case IV-5

R. Median Nerve	: S.A.P. 6 μV, 42.8 m./sec. Mixed n.a.p. 6 μV, 47.3 m./sec. Motor C.V. 34.4 m./sec. Terminal latency (S.C.N.) 4.7 m.sec.
E.M.G.	: No spontaneous activity A.P's mildly enlarged and polyphasic I.P. mildly reduced
R. Lateral Popliteal Nerve	: Mixed n.a.p. 0.8 μV (needle electrodes) 39.3 m./sec. Motor C.V. 36.1 m./sec.
R. Sural Nerve	: S.A.P. 4 μV, 38.7 m./sec.

The ability of sensory fibres of the median nerve to recover following a supramaximal stimulus train of 500 cps for 2 minutes was also assessed in Cases IV-5 and IV-8. Fibres with a conduction velocity of 20 to 30 m./sec. did not exhibit post-tetanic depression of function as has been found in demyelinating neuropathy (Cragg and Thomas, 1964).

This suggests that the neuropathy concerned is due to drop-out of the larger fast fibres and not to pathological slowing of fibre conduction.

Post-mortem Findings — (Case II-1)

Post-mortem examination on Case II-1 was performed in 1971.

Nervous system findings: the brain weighed 1090gm and the cerebral cortex showed slight diffuse atrophy with widening of the sulci. The cerebral arteries were moderately atheromatous.

Macroscopically the cerebellum and its folia were small.

Microscopic examination of the cerebellum showed almost complete loss of the Purkinje cells and an increased number of glial cells. Many corpora amylacea were seen in the Purkinje cell and molecular layers. There was thinning of the granular layer with a reduction in the number of cells. The dentate nucleus was composed of a thin layer of plentiful but shrunken neurones. Many astrocytes surrounded the nucleus. The neurones contained much lipochrome pigment.

The inferior olive contained fewer neurones than normal and again many astrocytes were present. Many corpora amylacea were seen in the region of the vestibular nuclei. There was a fall out of neurones in the vestibular nuclei and in the inferior cerebellar peduncle.

No abnormalities were seen in the pons, putamen or caudate nuclei.

The spinal cord showed partial loss of myelin from the posterior columns, the lateral columns and from the area occupied by spino-cerebellar tracts. The posterior column changes were more marked in the fasciculus gracilis. Many corpora amylacea were present in the spinal cord.

Popliteal nerve sections showed bilateral perineural fibrosis and a fall out of the larger myelinated nerve fibres.

DISCUSSION

The ataxia seen in this kindred has some features in common with Friedreich's ataxia, but several observations distinguish it from that condition. The long survival of the affected members, the

absence of dementia, the retained exaggerated tendon reflexes and the relatively minimal sensory changes are all points against the diagnosis of Friedreich's ataxia. Hughes, Brownell and Hewer (1968) in their electrophysiological studies of peripheral nerves of patients with Friedreich's ataxia found motor conduction velocities within the normal range but sensory action potentials could scarcely be recorded. The predominant motor changes in our kindred and the presence of sensory action potentials in all nerves sampled is in direct contrast with their findings and further differentiates this ataxia from the Friedreich's form.

The pedigree (Fig. 1) shows 10 affected members, all males, the condition being handed on by clinically unaffected females as is typical of sex-linked recessive inheritance. Since none of the affected members has ever fathered children, the possibility that this is a sex-limited condition cannot be excluded. However, as ataxias with autosomal inheritance and similar features to that seen in this family do not show variation in expression in the two sexes (Hariga and Moutschen, 1969) it is difficult to suggest a reason for sex-limitation in the hereditary ataxias.

The spino-cerebellar ataxias are usually inherited as autosmal recessive traits while a smaller number demonstrate autosomal dominant transmission (Bell and Carmichael, 1939; Sjögren, 1943; Hariga and Moutschen, 1969). Most of the ataxias with hyperactive reflexes belong to the autosomal dominant group (Sjögren, 1943). There are very few reports of sex-linked inheritance in the spino-cerebellar ataxias, and clinical features vary between the families described. Turner and Roberts (1938) reported a family with Friedreich's ataxia in which only males were affected with transmission through the females. In Van Bogaert and Moreau's (1939) kindred features of Friedreich's ataxia were associated with those of peroneal muscular atrophy. Three brothers were described by Papp-worth and O'Mahoney (1954) with mental deficiency, cerebellar signs, absent tendon reflexes, pes cavus, claw hands, peroneal muscular atrophy, facial and truncal obesity and premature arcus senilis. In this family the form of inheritance was not clearly established.

Malamud and Cohen (1958) reported a rapidly progressive disorder in which cerebellar ataxia was associated with extrapyramidal signs. This was transmitted by clear sex-linked inheritance.

The condition we describe has features distinguishing it from these other sex-linked recessive ataxias.

Despite extensive clinical and autopsy examination the hereditary spino-cerebellar ataxias have defied adequate classification. The problem in nosology is due to the diversity of clinical features exhibited by these conditions.

The observation of three forms of inheritance of the ataxias suggests that at least three different genes are involved. This raises the possibility that the variations between the ataxias may in part be due to them being imperfect phenocopies. The ataxias have been divided into two major groups, one with diminished or absent reflexes (Friedreich's ataxia) and the other with normal or exaggerated reflexes (spastic or Marie's ataxia). That this is an unsatisfactory classification is apparent from the lack of homogeneity in either group. Moreover, the classification of these conditions has been confused by the use of eponyms such as Friedreich, Sanger-Brown, Pierre-Marie and others where the features of the conditions described varied in some way from the original report.

Therefore, until more is known about the biochemical disorders involved in the ataxias and an aetiological classification can be devised, it would be desirable to make more liberal use of terms such as "Atypical spino-cerebellar ataxia" in any condition that does not fit classical descriptions and to concentrate on characterising the features of the ataxia involved.

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SUMMARY

A kindred with spino-cerebellar ataxia is reported. Transmission was by sex-linked recessive inheritance which is very infrequent in the hereditary ataxias. The features observed in this family differentiate their type of ataxia from the varieties previously described.

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MICROEMBOLISM AND THE VISUAL SYSTEM. PART II: THE CONSEQUENCE OF EMBOLI IN THE MICROCIRCULATION OF NERVOUS TISSUE, ESPECIALLY THAT COMPRIZING THE VISUAL SYSTEM

I.M. WILLIAMS,* N.C.R. MERRILLEES** and P.M. ROBINSON***

Migrating thrombi have serious effects on the structure of nervous tissue (Williams, Hohmann, Merrillees, Opperman and Robinson, 1975). It is probable that visual symptoms arising in the occipital cortex in patients who have undergone cardiopulmonary bypass surgery are due to migrating thrombi. The clinical and pathological evidence associating emboli, in particular migrating thrombi, in the microcirculation with neuro-ophthalmic disturbances is reviewed. The identification of such emboli has been described by Williams (1975c). The present paper presents evidence that migrating thrombi cause the neuro-ophthalmic and other neurologic disturbances in some patients after cardiopulmonary bypass surgery.

INTRODUCTION

Cerebral damage in patients who have undergone cardiopulmonary bypass procedures has been ascribed to inadequate cerebral blood flow and embolism (Brierley, 1967; Aguilar, Gerbode and Hill, 1971). The introduction of filters that remove platelet aggregates from perfused blood during cardiopulmonary bypass has greatly reduced the mortality and morbidity: patients regain consciousness quickly and are less frequently confused (Swank and Osborn, 1971). Brennan, Patterson and Kessler (1971) demonstrated experimentally that the depression in cerebral blood flow and metabolism after cardiopulmonary bypass correlated with the titres of microparticles in the bypass circuit and could largely be avoided by filtering the blood.

OCULAR MICROEMBOLI

The retina offers a unique opportunity to observe microcirculatory events. Observations of the retinal microcirculation of 35 patients during cardiopulmonary bypass operations revealed migrating white thrombi in 10 of 14 patients who either developed neurological complications after operation, or died, whilst no migrating thrombi were seen in 20 of 21 patients who recovered uneventfully (Williams, 1971; 1973; 1975b). Of the 14 patients, 8 regained consciousness after operation; and of these 8 patients, 5 had neuro-ophthalmic disturbances other than retinal emboli. The series was not random, and included 7 patients undergoing cardiopulmonary bypass surgery for the second

* Monash University Department of Medicine, Melbourne
** Melbourne University Department of Anatomy
*** Melbourne University Department of Anatomy

time, only 1 of whom recovered uneventfully. Filters were included in the bypass circuit of each patient.

Capillary occlusions of fat and of simethicone (dimethylpolysiloxane with silica, the defoaming agent used during the oxygenation of blood in cardiopulmonary bypass procedures) were detected in tryspsin digest preparations of retinal vessels of patients at necropsy (Williams, 1975a). The simethicone emboli were easily seen with phase contrast microscopy, and the silicon therein was confirmed by electron probe x-ray microanalysis (Williams, Stephens, Brunckhorst and Brodie, 1975). Kuwabara (1975) subsequently found identical retinal emboli in patients after cardiopulmonary bypass surgery.

Experimentally, we failed to find retinal thrombi in animals undergoing cardiopulmonary bypass perfusion identical to that used in patients, whereas we found many retinal thrombi when filters were omitted (Williams, Farmer and Dixon, 1974). The incidence of capillary occlusions of fat and of simethicone was unaffected by filtration (Williams and Davis, 1973).

Because migrating retinal thrombi formed *in situ* and, despite filtration, appeared in those patients who developed neurological complications and in those who failed to survive cardiopulmonary bypass surgery, we suggest that migrating thrombi are evidence of a pathological process common to these patients.

In 10 patients, 15 white retinal thrombi were seen; the majority moved very slowly, paused 10 minutes or more at bifurcations and obstructed small vessels that were easily seen with a direct ophthalmoscope. Microinfarction was seen only twice, and pin-point haemorrhages adjacent to an occluded artery only once. (Hypoxia during 20 minutes of ineffective circulation prior to bypass may have contributed to the formation of retinal haemorrhages in this patient.) A collagenous mass found in a retinal vessel of one patient after cardiopulmonary bypass surgery, and interpreted as a white embolus in the initial report of this study (Williams, 1973), is not included in this group of 15 white retinal thrombi mentioned in the present review. The origin of the collagenous mass is discussed elsewhere (Williams, 1975a).

Refractile specks and plaques (which may have been simethicone or cholesterol) also seen in the retinal and choroidal circulations of patients during cardiopulmonary bypass surgery were unrelated to the incidence of neurologic deficit or death.

CEREBRAL MICROEMBOLI

Brierley (1967) described three types of brain damage after cardiopulmonary bypass surgery—

1. focal areas of nerve cell damage, often perivascular, commonest in the parieto-occipital cortex, which he considered to be due to inadequate cerebral blood flow and air embolism.
2. generalized ischaemic damage due to circulatory arrest.
3. emboli of fat, antifoam, valvular vegetations and fragments of teflon patches.

He also found brain damage due to sustained hypotension in which the hippocampus was spared and cerebellar damage consistently severe.

Aguilar *et al.* (1971) described focal haemorrhages, acute neuronal necrosis and embolic material (which included fibrin platelet aggregates, crystalline material and fat) in the small cerebral vessels of the brains of patients after cardiopulmonary bypass surgery.

Our preliminary studies revealed cellular changes, principally in the occipital cortex, which probably represented the focal areas of nerve cell damage which Brierley (1967) found commonest in the parieto-occipital cortex. The cellular disturbance, examined by light microscopy was subtle: there were patches of cortex in which the cells showed changes consistent with early infarction. Relatively small amounts of simethicone (detected with phase contrast microscopy) accumulated in the brain. As expected, we found more simethicone in the brains of those patients who underwent long bypass perfusions. Simethicone also was found most readily in the occipital cortex (Fig. 1a) and in the same blocks we found small amounts of intravascular fat (Fig. 1b). Although simethicone and the changes of early infarction were found in the same sections, the distribution of simethicone was such that it did not account for the infarcted tissue. Similarly, the small amount of intravascular fat did not account for the early infarction.

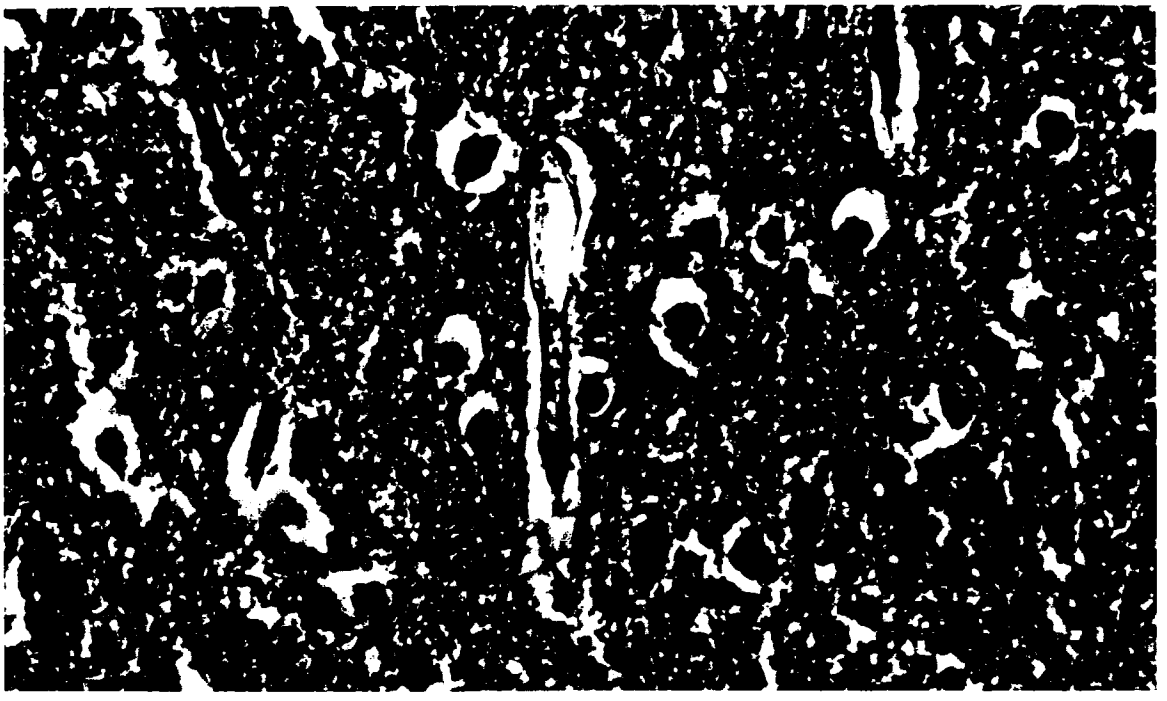
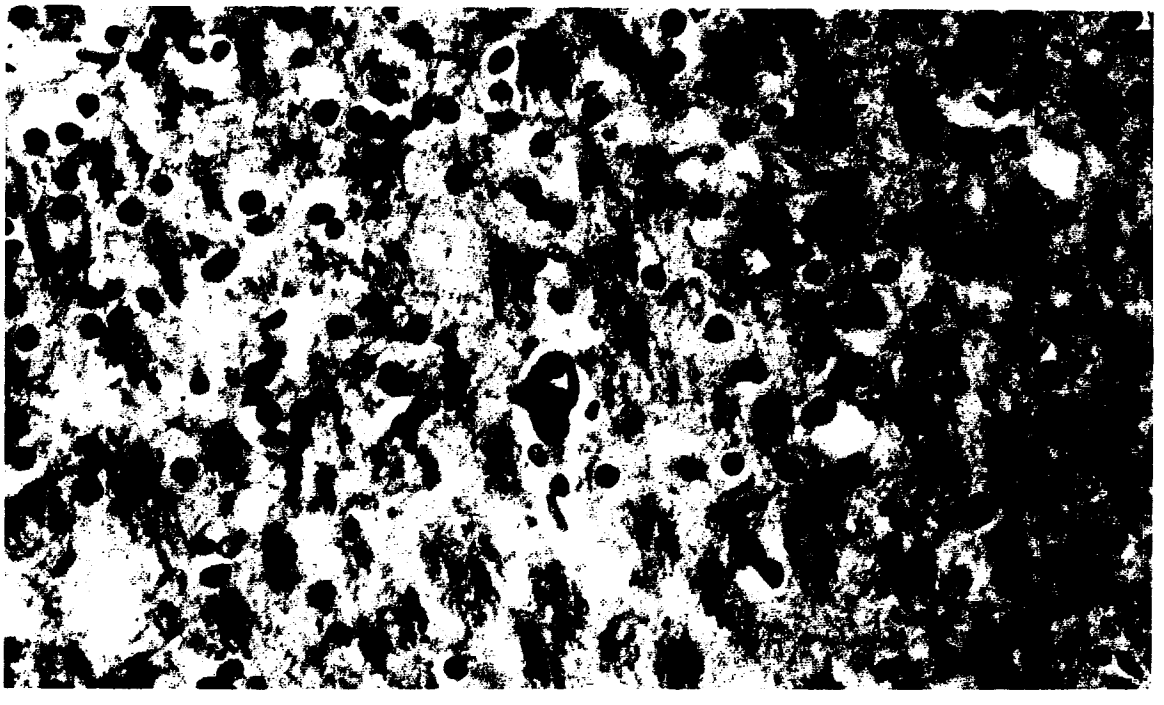


FIG. 1. Sections of occipital cortex from a patient after cardiopulmonary bypass surgery.
a. Phase contrast microscopy demonstrates an embolus of simethicone (dimethylpolysiloxane with silica) in a small vessel. Periodic acid-Schiff reagent counterstained with haematoxylin. X 800.



b. Fat embolus in a small vessel. Oil red 0. X 500.

CELLULAR RESPONSE TO MICROEMBOLI

Because migrating retinal thrombi were seen during cardiopulmonary bypass operations, principally in those patients who developed neurological complications and in those who failed to survive, whereas retinal emboli of fat and of simethicone apparently occurred in all patients, we postulated that migrating thrombi are more damaging to nervous and other tissues than are emboli of simethicone and of fat (Williams *et al.*, 1975).

To investigate the effects of microthrombotic emboli on nervous tissue at a cellular level, we inserted cotton threads to produce a thrombus which partially occluded the lumen of the major artery (the common carotid artery) supplying the nutrient vessels of the superior cervical ganglion of the rat, and then examined the change in fine structure of the ganglion. (We chose autonomic ganglia because they have a relatively simple neural organization which has been described in detail in the literature.)

In all experiments, the fine structure of the superior cervical ganglion on the same side as the surgical procedure (left) was compared with the fine structure of the superior cervical ganglion on the opposite (right) side which served as a control.

We regularly found substantial changes in fine structure in the superior cervical ganglion when threads had been placed in the common carotid artery on the same side for varying periods of time from 30 to 180 minutes, whereas no changes, or very few, were found in the fine structure of the control ganglion. Although two threads always produced a thrombus in the common carotid artery, more than two threads were needed to produce changes in fine structure in the superior cervical ganglion in large rats. We suspected that two threads failed to reduce the flow of blood in the experimental ganglia of large rats sufficiently to allow migrating thrombi enough time to pause and liberate "toxic" constituents.

In one large rat in which six threads were placed in the left common carotid artery for 180 minutes (the longest experiment with threads), we found changes in fine structure in both the left and right superior cervical ganglia. Microaggregates may pass through the capillary circulation and be distributed at random. We frequently found microaggregates in the retinal capillaries of dogs which had undergone total cardiopulmonary bypass perfusion without filtration (Williams *et al.*, 1974). We suggested that widely distributed microaggregates induced the changes in fine structure in both the left and right superior cervical ganglia of the rat in which threads were placed for 180 minutes (Williams *et al.*, 1975).

In contrast, total obstruction of the blood supply of the left superior cervical ganglion failed to regularly produce changes in either the left or right ganglion. (That the blood supply to the left superior cervical ganglion was totally obstructed by our clamping technique, had been demonstrated by carbon black injections in a previous set of experiments.) Similarly, intermittent obstruction of the left common carotid artery failed to regularly produce changes in fine structure in the left superior cervical ganglion. Since we found few platelet aggregates in the sections of nervous tissue, we concluded that the changes in fine structure were due primarily to products of thrombosis, and not to impaired nutrition consequent upon blockage of small vessels by microaggregates.

DISCUSSION

Nachman (1974) has pointed out that damaged platelets may initiate inflammatory responses within circulating blood by liberating their intracellular granules, which alter the permeability of blood vessel walls. We suggest that the intracellular substances which are released from platelets, leak out of blood vessels and induce changes in surrounding tissue. Platelets also release an enzyme which leads to the production of chemotactic activity which initiates leucocyte accumulation in perivascular tissue (Nachman, 1974). In other words, platelet plugs, even whilst migrating, produce vascular and probably perivascular damage secondary to the release of intracellular constituents.

Because thrombi that partially occluded the major arteries supplying the nutrient vessels of the superior cervical ganglia in rats regularly produced changes in fine structure in those ganglia and because platelet aggregates were rarely found in the sections of the ganglia, it is probable that

platelet aggregates – in the presence of a sluggish blood flow – liberated constituents which altered the permeability of the vessel walls and induced "toxic" changes in the adjacent nervous tissue (Williams *et al.*, 1975).

We suggest that in patients undergoing cardipulmonary bypass surgery, migrating thrombi (some of which form *in situ*) induce a cellular disturbance by liberating "toxic" constituents in that part of the cerebral microvasculature where blood flow is most sluggish, particularly in the posterior part of the occipital cortex. Furthermore, the sluggish blood flow favours the formation of more migrating thrombi. In this area, supplied by the terminal branches of the psterior and middle cerebral arteries, simethicone also accumulated but it failed to elecit a cellular change visible with the light microscope. In patients who had undergone two open-heart operations, we found retinal capillaries (the cells of some of which had lost their nuclei), blocked by simethicone, and in some areas, simethicone excited a mild histiocytic response (Williams, 1975a). It is probable that simethicone injures capillary walls when it remains *in situ* for weeks or months.

The clinical impression that visual symptoms are common in patients after cardiopulmonary bypass surgery, may be explained by vascular pathology in the occipital cortex. In the series of 35 patients, the 5 patients who developed a neuro-ophthalmic disturbance (other than retinal embolism) after operation, had symptoms consistent with lesions in the occipital cortex (Williams, 1975b). This observation needs to be investigated in a larger series. We found no symptoms due to retinal lesions even in those patients in whom small retinal vessels were observed being occluded during cardiopulmonary bypass surgery.

Platelet aggregates occur in other clinical conditions. They are found in the small meningeal and intracerebral arteries of patients in whom arteries supplying the brain are occluded by gross arterial thrombi or grossly visible emboli from the heart or other intrathoracic source (Jorgensen and Torvik, 1969). Patterson (1975) has shown that that blockage of the microvasculature of the brain which occurs after cardiopulmonary bypass in dogs, also occurs in dogs that have undergone thoracic surgery without bypass. This suggests that any major surgery may be complicated by platelet aggregates in the cerebral microvasculature.

Experimentally, we found that a continuous infusion of dipyridamole in dogs (which had received heparin) during prolonged cardiopulmonary bypass perfusion without filtration, greatly reduced the number of platelet aggregates in retinal vessels and eliminated fat emboli in the retina (Williams *et al.*, 1974).

Mielke, de Leval, Hill, Macur and Gerbode (1973) pointed out that dipyridamole in pharmacological doses *in vivo* does not influence platelet aggregation, but does have an influence on adhesion. Agents which have a known activity against platelet adhesion are the most effective in preserving platelets during extracorporeal oxygenation, and of the drugs tried by Mielke *et al.*, (1973), dipyridamole was the most effective. Aspirin was ineffective in preserving platelets.

The clinical use of dipyridamole and other drugs which primarily impair platelet adhesion, and those which primarily influence platelet aggregation when given in pharmacological doses, needs further investigation experimentally and in clinical trials. The mode of administration may be as important as the choice of drug. Dipyridamole, given in a small dose as a continuous infusion in the presence of an anticoagulant, may reduce the morbidity in some cerebrovascular accidents, especially where the major vessels supplying the brain are partially occluded.

ACKNOWLEDGEMENTS

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THE VALUE OF THE BRAIN SCAN AND CEREBRAL ARTERIOGRAM IN THE STURGE-WEBER SYNDROME

B. McCAUGHAN, R.A. OUVRIER, K. DE SILVA and A. McLAUGHLIN*

In 1957 Poser and Taveras reported a detailed analysis of the angiographic features of the Sturge-Weber syndrome. Kuhl, Bevilacqua, Mishkin and Sanders (1972) described the appearance of the brain scan in this condition. Despite these reports, it seems that the changes described are not well known.

The present paper describes eight patients (three in detail) with the Sturge-Weber syndrome. All had cerebral scans. Four also had cerebral arteriography. The patients varied in age from 2 months to 23 years. All had "port wine" stains involving at least the first division of the trigeminal nerve on one side and all had evidence of intracranial pathology as evidenced by at least one of the following: focal seizures, visual field defects, hemiparesis, EEG disturbances or intracranial calcification on skull x-ray.

CASE REPORTS

CASE I

This patient was seen at the age of 2 months because of right-sided focal fits.

On physical examination there was a bilateral facial naevus more marked on the left, and a right homonymous hemianopia and right hemiparesis were present. The skull radiograph revealed no abnormality whilst there was a left-sided slow wave abnormality in the EEG. In the early arterial phase of the dynamic brain scan there was a decreased isotope uptake on the left side and in the later venocapillary phase an increased uptake on the left. The static study demonstrated diffusely increased uptake in the anterior and left lateral projections without any focal accumulation (Fig. 1). Cerebral angiography confirmed the brain scan findings. There was a prolonged circulation time in the left hemisphere compared with the right (22 sec. compared with 10 sec.). The early phase of the angiogram demonstrated an obstruction in the angular gyrus branch of the middle cerebral artery with retrograde filling (Figs. 2 and 3). In the later phase there was a diffuse capillary-venous blush throughout the left hemisphere. In the venous phase there were anomalies of the deep cerebral veins.

CASE II

This patient, a girl of 7, was first seen at the age of 8 months with left-sided focal seizures. In these episodes she would stare, become limp and turn her head to one side. These episodes lasted several hours and recurred every few months. In at least one attack clonic jerking of one side of the body was noted. She was treated with anticonvulsants until the age of four years. At the age of 3 years, she was examined by a neurologist who noted no abnormalities apart from the facial naevus and slight left-sided hyperreflexia. Specifically, the visual fields were thought to be normal. At the age of five and a half years, the child presented with severe bifrontal headache, vomiting and drowsiness. She was afebrile, irritable and miserable. There was mild neck stiffness and a complete left homonymous hemianopia. Otherwise the neurological

* Department of Neurology, Royal Alexandra Hospital for Children, and Department of Nuclear Medicine, Royal Prince Alfred Hospital.

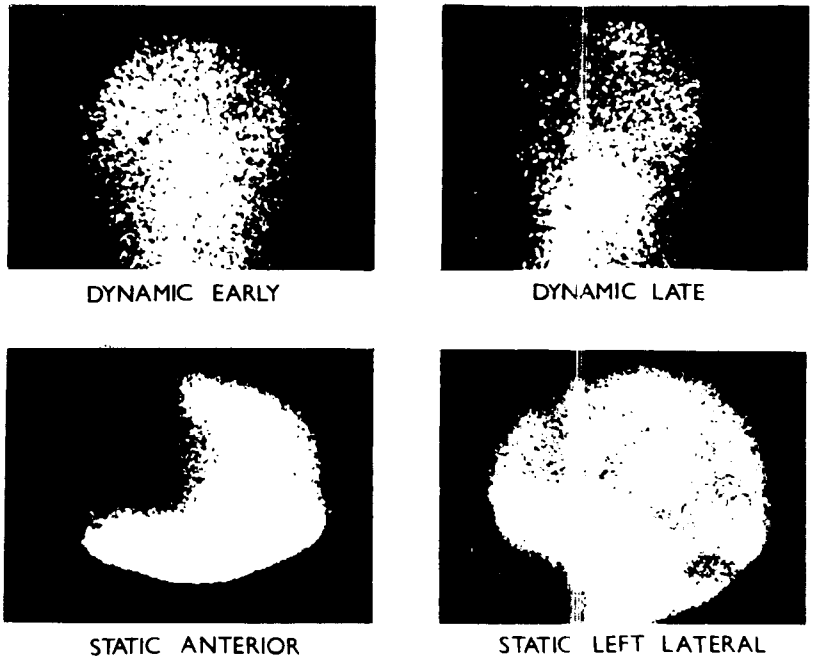

FIG. 1. Dynamic and static brain scans of Case I.

FIG. 2. Arterial phase of left carotid angiogram of Case I. showing failure to display angular gyrus branch of middle cerebral artery.

FIG. 3. Late capillary – early venous phase of left carotid angiogram of Case I. showing retrograde filling of angular gyrus branch of middle cerebral artery.

examination was normal. CSF was normal. The EEG showed a right occipital slow wave focus not previously present. Carotid angiograms showed markedly increased perfusion over the right hemisphere and no arterial occlusions. She improved rapidly without specific therapy but the field loss persisted when re-examined one month after discharge. Six months later, however, it had disappeared. There was never any suggestion of fitting during this episode. This child's hemianopia, which persisted for at least a month, must surely have been associated with infarction or ischaemic damage.

Physical examination at the age of 7 years revealed a right-sided facial angioma that extended to the vertex of the cranium (Fig. 4). There were no neurological deficits. Rail track calcification in the posterior temporal region was seen in the skull radiographs and a right temporo-occipital slow wave focus was present on the EEG. The dynamic brain scan showed a markedly increased perfusion of the right hemisphere both in the initial and late phases. The static study demonstrated an increased uptake principally in the right parieto-occipital area (Fig. 5). Cerebral angiography showed an area of diffuse pooling of contrast in the venocapillary phase in the right temporoparietal area extending into the occipital region, just anterior and superior to the region of calcification in the plain skull radiograph. There were abnormal deep cerebral veins but no arterial occlusions.

FIG. 4. Facial appearance of Case II.

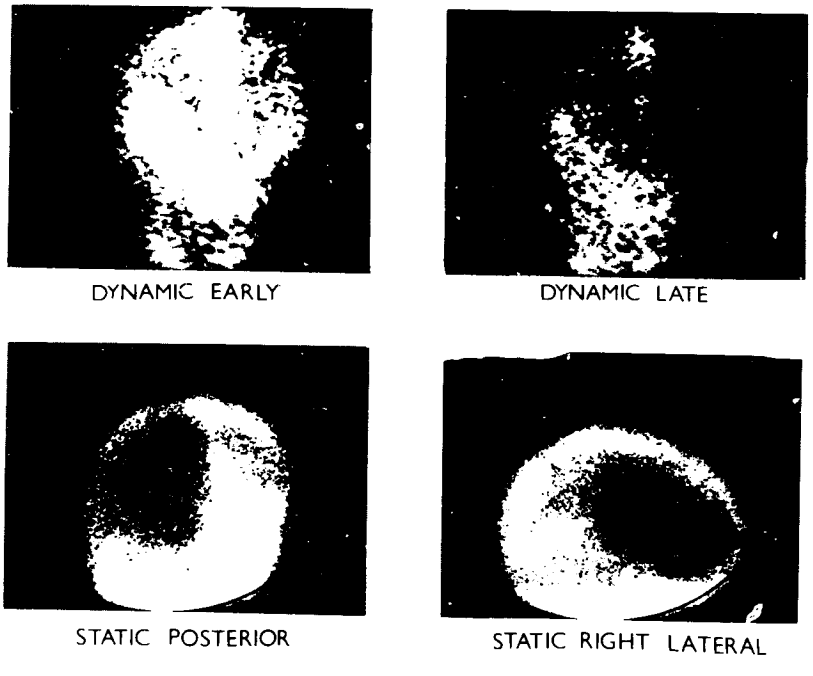

FIG. 5. Dynamic and static brain scan of Case II.

CASE III

A child now 4 years of age was born with a typical "port wine" stain over the right side of the face and was treated for right-sided congenital glaucoma within a few months of birth. At four months of age he had several episodes of left-sided twitching without loss of consciousness. These episodes lasted up to 20 minutes at a time. Anticonvulsants caused considerable improvement in the episodes though occasional attacks persisted until he was about 18 months old when they stopped completely. From the age of 12 months he was subject to attacks in which he would suddenly lose strength in the left side of the body. These would come on very rapidly, almost instantaneously, and would last from half an hour to a week. In only one attack was twitching ever noted and the mother could not be sure whether the twitching preceded the weakness or followed it. At the age of 3 years he was readmitted for investigation of these episodes which were then occurring up to four times in a month and were associated with generalised headache.

On examination, he had a left hemianopia and a minimal left hemiparesis. The skull radiograph showed calcification in the occipitoparietal region and the EEG showed some depression of amplitude over the right hemisphere. Brain scan showed the typical decreased early perfusion and excessive late isotope concentration in the right hemisphere. Angiography showed slow circulation over the right hemisphere (Fig. 6) and the typical venocapillary abnormality previously discussed (Fig. 7). No arterial occlusions were seen.

It was considered that the child was suffering from transient ischaemic attacks. No change was made in his anticonvulsant regime but he was given aspirin (150 mg nocte). At follow-up five months later, the parents reported no further attacks.

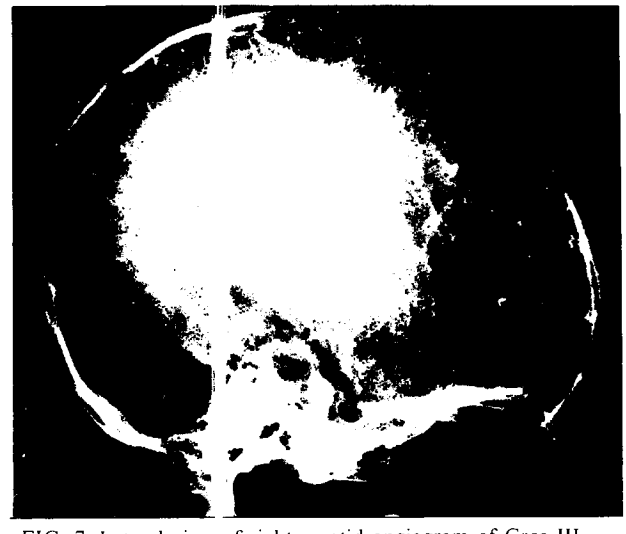

FIG. 7. Lateral view of right carotid angiogram of Case III, showing a veno-capillary abnormality in the parietal region.

FIG. 6. Axial view of arterial phase of right carotid angiogram of Case III. The left sided arteries are better filled than the right.

DISCUSSION

The static brain scan was abnormal in all eight patients, demonstrating an increased uptake of isotope in the affected hemisphere. The uptake was usually diffusely increased throughout the hemisphere, although in three of the patients a localised or focal accumulation could also be seen in the relevant lateral projection.

A dynamic scan was performed in six of the patients. In four of these the pattern was the same as in the first patient described above – there was a decreased isotope uptake representing a decreased flow in the arterial phase on the affected side with a later increased uptake in the venocapillary phase. In one patient the dynamic study was within normal limits while the other patient (Case II) had a considerably increased perfusion of the affected hemisphere.

The brain scan is superior to the skull radiograph and EEG in identifying and localising the cerebral lesion. In only four of the patients was calcification noted on the skull radiographs and

even then it was often very faint. One patient without intracranial calcification showed marked cranial asymmetry and unilateral calvarial thickening. The brain scan is positive from birth whilst the classic rail track calcifications of the cerebral gyri takes several years to develop, or may never appear at all (Peterman, Hayles, Dockerty and Love, 1958). Furthermore, the changes are much more extensive than suggested by the area of calcification. The EEG was eventually abnormal in seven of the eight patients but was less often abnormal in early life.

The angiographic findings confirm the brain scan findings and are in agreement with those of Poser and Taveras (1957). The abnormality on the brain scan and angiogram correlates with the great increase in number and size of superficial veins and capillaries with a presumed alteration of the blood brain barrier in the cortex adjacent to the affected hemisphere.

Apart from the delayed circulation, the cerebral arteriogram also demonstrates the occasional presence of arterial thromboses,often in major vessels. One of the cases of Poser and Taveras had an occlusion of the middle cerebral artery and occlusions of the posterior cerebral artery have also been reported (Stehbens, 1972). Deep venous abnormalities, often with absence of the internal cerebral vein, are frequent.

The authors believe that the combination of marked prolongation of circulation time in the affected hemisphere as shown by scan and angiogram, coupled with the not infrequent finding of arterial occlusions in major vessels, is the basis of the stepwise deterioration that is seen in many patients with this disease – these deteriorations being on the basis of major infarctions of cerebral tissue. We also suggest that many of the episodes of altered central nervous system function reported by these patients and interpreted as seizures are in reality transient ischaemic attacks. We do not, of course, deny that true epileptic seizures very frequently accompany the disease. Inhibitory epilepsy however, seems less likely. This point is illustrated by Cases II and III.

A survey of pathological reports and textbook treatises on the Sturge-Weber syndrome (Stehbens, 1972; Greenfield, 1963; Roizin, Gold, Berman and Bonafede, 1959; Wohlwill and Yakovlev, 1957, Alexander and Norman, 1960) has not revealed any descriptions of major cerebral infarctions. Nor, on the other hand, has any mention been made of the abnormal deep venous anatomy so well demonstrated in several angiographic series. Perhaps such details have been overshadowed by the very obvious superficial pathology.

The suggestion that stepwise deterioration is on an ischaemic rather than an epileptic basis is obviously of more than academic interest. The episodes may, perhaps, respond better to measures aimed at reducing platelet aggregation than to anticonvulsants. Alexander seems to imply that all patients with the Sturge-Weber syndrome should have resection of the involved areas of cortex as early in life as possible, yet the Mayo Clinic series (Peterman *et al.*, 1958) indicated that almost 50% of the patients are not retarded and are, therefore, presumably better with their abnormal hemisphere in situ.

It is possible that serial brain scans with dynamic studies coupled with clinical evaluation of progress will eventually allow separation of those patients with minimal cerebral involvement from those in whom marked hypoperfusion will lead to progressive infarction of the affected hemisphere, and in whom hemispherectomy should be performed early.

SUMMARY

In a series of eight patients with the Sturge-Weber syndrome, the brain scan was shown to be the most accurate, non-invasive, diagnostic test, being abnormal in all eight patients. In four cases examined by cerebral arteriography, this study was also conspicuously abnormal.

Some of the neurological disturbances occurring in these patients are more likely to be due to transient ischaemic attacks and cerebral infarctions than to epilepsy.

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THE CHIASMAL ENIGMA*

BRODIE HUGHES†

The optic chiasma has always had a strange fascination for me. It seems incredible that this tiny structure, hardly larger than a nail on one's finger, should convey to our brains and thence to our minds, all that we shall ever know visually of the world outside us. Its general structure has been known for centuries and yet its exact organisation still eludes us.

Over many years I have studied closely the disturbance of function resulting from lesions of the chiasma. The present paper is a distillation of that experience together with some theories to add strength to the liquor. The pattern of visual field disturbance resulting from compression of the optic nerves and chiasma by pituitary tumours is well-known and was fully documented before the First World War, in particular by Harvey Cushing and Clifford Walker (1914). The orderly sequence of events whereby depression appears in the upper temporal fields, spreads to the lower temporal and then the lower nasal, and, lastly, to the upper nasal fields, commended itself to the minds of writers of that time. This sequence of events has been described in innumerable text books and papers since, usually with the added titbit that the field loss goes clockwise on the right and anti-clockwise on the left.

The experience of many clinicians since that time has, by and large, confirmed these events. Yet if we consider the presumed anatomy of the proximal optic nerves and chiasma, no more unlikely sequence of events could occur. It is interesting to note that although the description of this series of field changes is usually ascribed to Cushing and Walker, who gave the first detailed description of such changes with chiasmal compression, in many of their cases the initial field disturbance in the nasal field was in the upper rather than in the lowest part. Most would agree, however, that with advanced chiasmal compression involving the nasal field, loss of central and peripheral field is nearly always encountered first in the lower rather than in the upper field.

Compression from below of the central area of the chiasma or the under-surface of the optic nerves by a midline mass, should certainly involve the peripheral crossing fibres from the upper temporal fields initially.

As the size of the tumour increases and it rises from the sella in front of the chiasma, it is reasonable that the superior crossing fibres from the lower temporal field would be next compressed, distorted or their blood supply embarrassed. At this stage, however, a strange phenomenon can often be seen and was described by the early writers on his subject. A portion of the temporal field, usually far out on the periphery, and rather more below than above the horizontal meridian, remains unaffected and may persist long after the nasal field has become involved. In some cases

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† Birmingham, United Kingdom

a pseudo-temporal island is created by the progress of the hemianopic temporal scotoma. These scotomas often occur in posterior chiasmal compression and lie in the central and intermediate field. As field loss progresses the scotoma breaks through to the periphery above and below, leaving an isolated area of the temporal field.

As the tumour continues to grow, the fibres 'next on the list' so to speak, from the classical description, are those from the lower nasal field which lie superiorly and laterally in the terminal optic nerves and chiasma. But these fibres are farthest away from the tumour and most protected from its effects and, in addition, the fibres subserving the temporal island are just in the same position. It seems wholly unlikely, therefore, that the lower nasal field should be affected before the upper, or if it is, that the temporal island should persist in spite of the loss of the whole of the lower nasal field, yet this is just what does occur in case after case. The lower lateral fibres from the upper nasal field, which one would expect to be affected early, are not only not so affected but it is common for the upper nasal field to be preserved to a very late stage in compression. The temporal island has perplexed many people and undoubtedly the residual field left by a breaking-through scotoma has accounted for much of the perplexity. In such cases the island is rather a large one, is situated in the intermediate field and has a high visual acuity.

The true temporal island, however, is usually situated far out on the periphery of the field, often more below than above the horizontal meridian and has a low visual acuity. Operative findings suggest that this type of island is usually associated with dehiscence of the lateral areas of the chiasma. Other writers, notably Gros, Vlahovitch, Roligen, Mohasseb and Costeau (1961) and Schneider, Kriss and Ellis (1970) have described a similar condition. If the histological architecture of the chiasma is examined it may be seen that there is a triangular area on either side bounded laterally by the direct fibres and medially by the crossing fibres. This area is relatively free of fibres and, therefore, constitutes a point of weakness. In addition, it contains most of the small vessels entering the chiasma from the superior surface. It is not uncommon at operation to see dehiscence of this area or even small portions of tumour protruding through the chiasmal fibres. This area, however, which I have termed the arterial portal, does not really lie between crossed and uncrossed fibres. The most lateral of the inferior crossing fibres from the upper temporal field pass soon after crossing into the most lateral area of the chiasma to join the uncrossed fibres and, therefore, pass lateral to this portal. In addition, the superior crossing fibres from the lower temporal field pass medial to the portal, right to the posterior area of the chiasma. The effect, therefore, of such a dehiscence may be to separate these sets of fibres from each other. In most cases, therefore, the posterior area will be the last to be affected and the residual temporal island may remain long after the temporal field elsewhere has been lost and the nasal field is affected. The involvement of fibres from the upper temporal retina subserving the lower nasal field is a most unlikely development in progressive compression. These fibres lie laterally and superiorly in the terminal optic nerves and chiasma, in the position, in fact, where they are most remote from tumour pressure. In addition, as the pituitary tumour enlarges the optic nerves become rolled outwards, thus taking these fibres even further away from the sources of compression.

One explanation that has been proposed is that the upper and outer portions of the optic nerve are compressed between the embrace of the anterior cerebral arteries and the tumour. The original description of this is ascribed to Turck (1852). Many further cases have been reported and it is noteworthy that in most of them there was either no loss in the nasal field or very little, and also that, owing to rotation of the optic nerves, the grooves were usually on the medial side of the optic nerve and histology showed degeneration in this area. My own experience of many operations for pituitary tumour is that arterial grooving is seen rather infrequently. I have one picture in which a photograph was taken of a compression groove which seemed to be of some depth and to have haemorrhage around it. However, pre-operative fields taken within twenty-four hours of operation did not show any nasal field loss nor did post-operative studies taken the next day.

It would seem unlikely, therefore, that grooving from the anterior cerebral arteries is a usual or even a common cause of lower nasal field loss. Other suggestions have been made, such as

elevation of the nerves by the tumour and compression against the edge of the optic canal by the sharp dural band that occurs here. I have never observed this phenomenon at operation nor do I know of any recorded example where damage in this area has been demonstrated histologically. Hedges (1969) posed a simple mechanical explanation and demonstrated that as the optic nerves were elevated by a tumour, the inferior fibres were less stretched than the superior ones and therefore the major damage would occur in this superior area.

Those with considerable operative experience will know that the situation found at operation displays very considerable variation. Pituitary tumours are seldom the simple, rounded masses, beloved of the surgical artist, but are irregular in shape, have knobs and bumps in unlikely places and often grow more on one side than another. A curious fact, however, is that the progress of visual field loss is much more constant and orderly from case to case than is the growth and shape of the tumour. This would suggest to my mind, as it has to others, that direct local compression by the tumour mass is not the major factor in the disturbance of function in this portion of the visual pathway. It has been proposed, therefore, that this march of events, so similar from case to case, is predetermined by both the fibre anatomy and by the vascular pattern of supply to the optic nerves and chiasma.

The anatomy of the vascular supply of the chiasma has been studied by many workers particularly Steel and Blunt (1956) and Dawson (1958). As well there have been beautiful studies of the angioarchitecture by Francois, Neetens and Collete (1956). It has been established that the lateral and inferior area of the chiasma and proximal optic nerves receives a separate blood supply from a vessel running in from the lateral side, a direct branch of the carotid or of one of the hypohyseal vessels. This has been termed the lateral chiasmal artery (Hughes, 1958). This vessel is, in essence, as far removed from the tumour as it could be and, therefore, presumably only affected at a very late stage in the process of compression. This may be the major factor in the preservation of the upper nasal field. The early involvement of the lower nasal field, a generally accepted fact, can be explained on several grounds. The vessels supplying this area enter the arterial portal of the chiasma and might be expected to be involved at an early stage as the weak triangle of the chiasma is compressed by tumour and some dehiscence takes place. In some cases the strangling embrace of the anterior cerebral arteries may aggravate this situation and also the stretching of the superior fibres postulated by Hedges (1969) may also play a part. Nevertheless, the constancy of this sequence of field loss from patient to patient suggests most strongly that there is a single common factor and that of vascular involvement seems to be the most likely.

Turning to another unsolved problem in relation to the chiasma, we can consider the distribution of fibres in the proximal optic tract. The final position of fibres in the distal optic tract is such that a peripheral temporal fibre of the same side, uncrossed, lies adjacent to a peripheral nasal fibre from the corresponding portion of the retina of the other side. This means that either the uncrossed fibres have to adapt to the crossed or vice versa. Some controversy has centred around the question as to whether it is the crossed or uncrossed fibres that make the adaptation. The primitive chiasma consists wholly of crossed fibres so that one might expect that it would be the direct, and phylogenetically newer fibres that would make the adaptation. A typical concept of the fibre arrangement in this area may be taken from Traquair (1957). He supposed that the situation in the proximal optic tract looks much the same as in the optic nerve except for the fact that one half of the fibres come from the other side. Most text books of this century do, in fact, illustrate such a state of affairs. Yet this idea is wholly unacceptable for it would indicate that the fibres in the chiasma had to undergo a double revolution so that at the posterior chiasmal angle the most medial fibres of the optic nerve would become the most medial fibres of the optic tract and so on. It is known that the fibres in the distal optic tract are arranged so that those from corresponding parts of either retina lie together. Thus these fibres would have to undergo yet another revolution. There is no anatomical evidence of such a double turn-about and so complex a state of affairs would seem intrinsically unlikely, though some strange contortions are encountered in human anatomy. Anyone who troubles to read through the massive literature on this subject must come to the conclusion that the attractive diagrams produced by most authors, e.g. Hughes (1954),

must be based largely on speculation. One must accept that in terms of human anatomy the exact fibre distribution in the chiasma remains largely unknown. Most of the exact work has been done on sub-human primates and the most acceptable, and recent, comes from Hoyt and Luis (1962; 1963). Their work was done on the Java macaque by making small retinal lesions and following the fibre degeneration. They have given an exact picture of the chiasmal anatomy in that animal and its extrapolation to the human, though not wholly justified, provides us with many ideas which are compatible with clinical experience.

Of particular interest is the course of the direct, uncrossed fibres. In the proximal optic nerve these occuped an adjacent upper and lower sector on the lateral aspect but, even at this level, there were a few scattered fibres in the medial portions of the nerve. In the anterior chiasma, the lower fibres remained inferior and the superior ones formed a crescent above and laterally. In the central chiasma the lower fibres occupied the whole of the lateral portion of the chiasma, an area in which one would think they would be especially vulnerable to pressure from below. These fibres, one may remember, subserve the invulnerable upper nasal field. In this area, the upper fibres lie above and extend rather more into the centre of the chiasma.

The findings of Hoyt and Luis (1962; 1963) in relation to the posterior part of the chiasma are significant. They found that the inferior fibres swung laterally into the optic tract and the superior ones medially, so that they had undergone a rotation of 90°. More importantly, the larger fibres from the peripheral retina swung down to occupy an inferior position and the smaller fibres from the intermediate retina swung from medially upwards to occupy a superior position. This seems clearly to imply that in these fibres there has been a revolution and that this has occurred so that they may be laid adjacent to homonymous fibres from the opposite retina, whose relative positions do not change. This would seem to be a more sensible arrangement and more in keeping with the development of the chiasma than the schemata propounded by so many authors.

These authors' findings in relation to the crossed fibres also hold some interest. These fibres form a much more diffuse bundle in the optic nerve and occupy most of its cross section. In the chiasma the inferior fibres begin to cross at once and some loop into the opposite optic nerve. The most peripheral fibres sweep into the lateral area of the chiasma where they intermingle with the lower direct fibres and enter the lateral and inferior portion of the optic tract with their relative positions unchanged. This intermingling with direct fibres takes place in the chiasma and is probably complete before they enter the optic tract. The superior fibres cross superiorly in the chiasma to reach its superior and posterior border. There is no indication of looping into the optic tract and histological examination of a number of human chiasmas, I have only very seldom found evidence of such looping. These fibres then swing down and cross the midline to occupy an inferior position adjacent to the inferior crossed and uncrossed fibres. These are a discrete bundle and remain so in the proximal portion of the optic tract. Intermingling with the direct fibres does not take place until a more posterior area of the tract.

Much interest has been shown in the incongruous fields resulting from proximal lesions of the optic tract. If this fibre anatomy can be extrapolated to the human then one would expect this incongruity to take the form of incongruous loss, or preservation, of the contralateral lower temporal field, and such is usually the case.

The course of the macular fibres differed strikingly from that usually accepted, for most authors conceive these as a rather small discrete bundle occupying the central area of the optic nerve and crossing in the posterior and inferior area of the chiasma. This supposed fact has often been used as an explanation of the scotomatous fields resulting from posterior and inferior chiasmal compression. In the Java macaque, the macular fibres were much smaller than the peripheral ones and so easily identified. They occupied the temporal sector of the optic nerve but were quite diffuse in their distribution and intermingled with the peripheral fibres. In the chiasma they crossed at once in the anterior and superior position and as more posterior sections were examined crossing macular fibres could be found in all areas. A relatively small area in the anterior and inferior position was the only one found to be free of macular fibres. In the optic tract also their distribution was diffuse and they were found over at least two-thirds of its cross section. Hoyt and Luis (1962;

1963) commented that the histologist would get the impression that the chiasma was a macular structure surrounded by a few peripheral fibres. There seemed, from their work, to be little indication of the intermingling of upper and lower fibres and these two groups appeared to remain separate and as rather discrete bundles. This may explain, in part, the quadrantic nature of some field defects although in this respect one might postulate that a quadrantic blood supply is more likely to give such a defect than simple mechanical pressure on two discrete bundles.

It was interesting to note that in the Java macaque, the fibres from monocular temporal crescents, although adjacent to each other in the retina, apparently became widely separated in the chiasma. The upper fibres, from the lower temporal crescent, cross in the posterior dorsal part of the chiasma whilst the lower ones, from the upper crescent, cross in the inferior and extreme lateral area, about as far apart as they could be.

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OBITUARY

Dr. Oliver Latham

The distinguished neuropathologist, Dr. Oliver Latham, died in Sydney in the latter part of 1974. Sir Kenneth Noad has prepared the following obituary for the Australian Association of Neurologists.

"There would be few Australian neurologists who have not heard of Oliver Latham. He was the doyen of neuropathologists in this country.

Born in Ireland, educated there, and at Harrow, graduated in Medicine in Sydney, he was a cosmopolite who never lost the charm of his native land.

Most of his working life in neuropathology was passed in a dimly lit laboratory in the basement of the old Medical School of Sydney University. It was the typical professor's room of the cartoonists. Shelves crammed with specimens, slides and papers only needed a few spiders' webs to complete the picture. Yet from this inauspicious centre issued a stream of papers on all sorts of subjects – mostly neuropathological of course, and written in collaboration with pathologists and clinicians because his rooms were a Mecca for those interested in Neurology who had a problem.

His interests were wide but multiple sclerosis and the various types of encephalitis were the topics appearing most often in his prodigious bibliography.

He was a dear man, always willing and anxious to help and much beloved by all who knew him and worked with him.

The untimely death of his only son, a Sydney neurosurgeon, clouded the last days of his long life and he died on 26 October 1974, aged 97 years."