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EDITORIAL

Clinical and Experimental Neurology is now in its 28th year. It began life in 1963 under the title *Proceedings of the Australian Association of Neurologists*, edited by the late E. Graeme Robertson. Over the years, as well as acquiring a new name (in 1977) it has undergone its share of vicissitudes, and several changes of publisher. This year, the Australian Association of Neurologists has resumed its earlier role of publisher, and the annual volume has been produced by means of so-called 'desk-top' publishing, with the assistance of various agencies within The University of Queensland. This change has entailed a considerable increase in editorial and typing work, and I wish to thank my co-editors and particularly my secretary, Mrs. Margaret Carew, for their willingness to shoulder this additional burden. With increased experience, it is hoped that some of the delays and imperfections in the present volume will not occur in future issues. However, the change to desk-top publishing has made necessary some alterations in the instructions to authors, particularly in relation to the submission of text and the size of illustrations that is acceptable. It is hoped that prospective authors will try to comply with these instructions to expedite the publication of future issues.

It has not been the policy of Clinical and Experimental Neurology to publish book reviews. However, this year Sir Sydney Sunderland's new monograph *Nerve injuries and their repair: a critical appraisal*, published by Churchill Livingstone, of Edinburgh, was offered for evaluation. Sir Sydney has been a member of the Australian Association of Neurologists since its inception, and is one of the few survivors of that small group present at the original meeting in the Anatomy Department of Melbourne University on 25 October 1950 at which the Association was founded. He has had a long and distinguished career in Australian neuroscience, first as Professor of Anatomy and later as Professor of Experimental Neurology in the University of Melbourne, and subsequently as Emeritus Professor. For a time he was Dean of the Faculty of Medicine at Melbourne, and held the very influential office of Chairman of the Australian Universities Commission. His authoritative and massive monograph *Nerves and nerve injuries* has appeared in two editions and established his reputation as a foremost authority on the pure and applied anatomy of the peripheral nervous system. Now, in his eightieth year, he has produced a new, and smaller, though still very considerable work evaluating the relevant anatomy, physiology and principles of surgery of peripheral nerve injuries. It is very clearly written, and well illustrated, mainly with line drawings, and contains much of interest to the

neurologist. The new book is a further very great achievement and I believe all members of the Australian Association of Neurologist would want to offer their congratulations to Sir Sydney, and to wish him well in the next phase of his singularly productive retirement.

M.J. Eadie
Editor

The E. Graeme Robertson Lecture

VERTEBROBASILAR EMBOLISM

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The name of Graeme Robertson evokes very fond memories of my training period in neurology. Of course we all owned, read, and studied Robertson's monograph on pneumoencephalography. I vividly recall somersaulting patients to fill the temporal horns using the method described by Robertson. Dr. Derek Denny-Brown, my program chairman at the time, was fond of telling stories about Robertson, his friend and fellow registrar at Queen Square. There were vivid descriptions of Robertson taking meticulous photographs of the iron railings and adornments in some of the then seedy neighborhoods around the Boston City Hospital. Robertson was immersed in the picture-taking and impervious to the dangers of traffic and the local thugs who haunted the environs. Dr. Denny-Brown spoke very highly of Robertson, mentioning him on a level with F.M.R. Walsh, Gordon Holmes, and Charles Symonds, very heady company indeed. The sheer tenacity of Graeme Robertson's scholarly activities, in neurological matters such as pneumoencephalography, and in his massive tomes on photography, should provide a fine example for neurologists. It is truly a great honor for me to be asked to deliver the Graeme Robertson lecture this year.

HISTORICAL BACKGROUND

By the turn of the 20th century, neurological clinicians had already come to the notion that occlusive lesions in the posterior circulation were usually thrombotic, that is due to in situ thrombosis of arteries previously damaged by degenerative atherosclerotic changes. Gowers wrote in 1903 'A woman aged 60 was brought unconscious to the hospital with symptoms that pointed to obstruction in the basilar artery. Of the two lesions that seemed possible, atheromatous thrombosis and embolism, the rarity of the latter made the former more likely. She died and thrombosis of the basilar artery was found as anticipated[1].' The idea that embolism is not common in the posterior circulation has persisted for nearly a century. Herein, I plan to review data from my own

experience and that of others that suggest that embolism is and always was a common, albeit neglected, cause of posterior circulation infarcts.

The history of the concept that posterior circulation ischemia is generally due to atherosclerotic disease causing hemodynamic insufficiency is rather short. The story begins with the classic paper of Kubik and Adams on occlusion of the basilar artery written in 1946[2]. At that time, Kubik and Adams were both neuropathologists and their study was a necropsy analysis of patients dying with brainstem infarction due to basilar artery occlusion. They emphasized that the disorder was invariably fatal, that thrombosis was usually but not always engrafted upon atherosclerotic narrowing, and that the neurological signs during life should allow for ante-mortem diagnosis. There then was little interest in stroke treatment and very little available technology to define brain or vascular lesions during life. During the early 1950s, Miller Fisher, later a collaborator and colleague of Raymond Adams and my mentor in the field of stroke, working in a Veterans' hospital in Canada after the 2nd world war, brought the concept of transient ischemic attacks (TIAs) to the attention of the medical community[3]. Fisher pointed out that patients with strokes often had premonitory warning signs that might allow clinicians an opportunity for treatment before the stroke occurred. Fisher also emphasized that the pathology in the vascular bed often occurred in the neck in the internal carotid artery, where it might be accessible for treatment, rather than intracranially as the then current teaching dictated[3].

During the 1950s and early 1960s a number of clinicians began to collect and describe series of patients with TIAs that included symptoms that had been present in Kubik and Adams fatal cases of basilar artery occlusion. Denis Williams[4], Fang and Palmer[5], Denny-Brown[6], Siekert, Millikan and their Mayo Clinic colleagues[7,8] all reported examples of a condition they called 'vertebro-basilar insufficiency'. These authors reasoned that the condition that Kubik and Adams had shown to be generally fatal could be diagnosed, at least sometimes, during life and before severe neurological damage had occurred. Early recognition allowed an opportunity for treatment. The Mayo Clinic group gave patients with so-called vertebro-basilar insufficiency coumadin, the then in vogue investigational drug for brain ischemia[3]. They found that some patients did very well, and many did not have severe or fatal outcomes. Reasoning from the results of this early uncontrolled therapeutic trial that, without treatment, the patients would have died or been left severely afflicted (as Kubik and Adams' patients had been), it was concluded that coumadin must represent effective treatment for vertebro-basilar insufficiency. The neurological community at large considered the issue settled. In the decades since, the question clinicians have asked was whether or not to give coumadin, or heparin, acutely to a given patient

with vertebro-basilar territory ischemia. Customarily, no particular laboratory evaluation was performed until the advent of neuroimaging. Then CT or MRI scans were usually obtained. Seldom were cardiac or vascular imaging tests or angiography performed. Following the fashion of the 1950s, most patients with posterior circulation ischemia were thought to have either penetrating artery disease with lacunar infarction or occlusive disease of the large arteries (vertebral, basilar, or posterior cerebral arteries) with resultant hemodynamic insufficiency. Since little vascular investigation was considered indicated or useful, little data accrued to corroborate or disprove this hypothesis or to change the investigational and therapeutic modus operandi.

During these same decades, patients with anterior circulation ischemia were managed quite differently. Would anyone now be content with a diagnosis of 'carotid insufficiency'? Experience taught that there were heterogeneous vascular lesions within the anterior circulation that included lacunes, ulcerative plaques, stenosis, or occlusion at the internal carotid artery origin, stenosis of the internal carotid artery within the siphon, middle cerebral artery occlusive disease and embolism arising from the heart, aorta, or proximal internal carotid artery. Treatment depended on the nature of the vascular lesion so that brain imaging, angiography and later ultrasound, and cardiac investigations, became commonplace. Treatment was based on the location, severity and nature of the vascular lesion and the severity of the brain damage. Considerable data on the frequency and nature of ischemic anterior circulation lesions accrued from these investigations and from examination of carotid endarterectomy specimens[9].

For the past 2 decades, I have taken a different approach. Reasoning that the 2 circulations are more alike than dissimilar, and that logical treatment should depend on knowledge of the vascular mechanism of the ischemia irregardless of the anatomical circulation involved, I and my colleagues have investigated patients with both anterior and posterior circulation disease rather thoroughly, using technology available at the time. Our results show clearly that, contrary to general belief, embolism, both cardiogenic and intra-arterial, plays a very important role in the posterior circulation, just as it does within the anterior circulation. In fact, a review of the experience of the previously reported results of others confirms this view. In this lecture, I plan first to review previous data from necropsy and angiographically-studied series of others and ourselves, on the mechanisms of posterior circulation infarcts, and then to describe our recent experience with a series of 88 patients with brainstem or cerebellar infarcts who were investigated intensively.

ANALYSIS OF THE MECHANISMS OF LESIONS IN POTENTIAL RECIPIENT ARTERIES

An embolus should be thought of as arising from a source or donor site and travelling and residing at least temporarily at a destination or recipient arterial site. Ideally, to be certain that an ischemic process is embolic, the donor and recipient sites and even the nature of the embolus (clot, fibrin-platelet clumps, cholesterol crystals, calcium, etc.) should be identified. In practice, often only the donor or recipient site is recognized.

Let us begin the analysis by reviewing studies of patients with infarcts within potential recipient arteries. Small emboli, and fragments of large emboli, are usually thought of as passing into the most distal branches of the arterial system that they enter. The posterior cerebral arteries are the end branches of the vertebrobasilar system and therefore should, theoretically, be the commonest recipient sites for posterior circulation embolism. Castaigne and colleagues analyzed the arterial pathology in patients with posterior cerebral artery territory infarction among a large series of necropsy studies of patients with posterior circulation infarcts[10]. Among 30 posterior cerebral artery territory infarcts, only 3 were attributed to thrombosis of the posterior cerebral artery superimposed upon atherosclerotic stenosis. In 8 patients, clot within the basilar artery extended into the posterior cerebral artery, while in the others thrombi originated more proximally[10]. In 15 patients (50%) emboli arose from occlusive lesions in the proximal vertebrobasilar system and one patient had a recognized cardiac source of embolism. Recently, Dr Michael Pessin and I and our colleagues at the New England Medical Center in Boston studied a series of 35 patients, all of whom had a homonymous hemianopia and occipital infarction in the posterior cerebral artery territory on CT scans[11]. The most common mechanism of infarction in this series was embolism. Embolism of cardiac origin was documented in 10 patients (28.5%); in 6 patients (17%) intraarterial emboli arose from occlusive lesions in the proximal vertebral and basilar arteries. In another 11 patients, the clinical and angiographic findings, including a sudden onset and a sharp cut-off of the mainstem posterior cerebral artery or its branches, suggested embolism but no definite source was identified. In some of these latter patients, cardiac or vascular investigations were incomplete. In all, 27 of the 35 patients (77%) probably had embolic posterior cerebral artery territory infarcts. In the other 8 patients, the occlusive process was attributed to migraine in 5 or to systemic disease with hypercoagulability in 3[11].

'Top of the basilar' ischemia in the territory of both posterior cerebral arteries and the penetrating arteries to the thalamus and midbrain has traditionally been

considered embolic, but the vascular mechanisms have seldom been investigated in detail[12]. My colleagues and I have shown that atherostenosis of the distal third of the basilar artery does occur[13], especially in blacks[14], so that some rostral basilar artery territory infarcts are undoubtedly thrombotic. Mehler recently reported a series of 61 patients with rostral basilar and posterior cerebral artery territory infarcts[15]. Not all were intensively investigated for the mechanism of infarction; only 39 (64%) had angiography. Eight patients were thought to have intra-arterial embolism; in 5 of these 8, emboli arose from the extracranial vertebral artery, 1 arose from the intracranial vertebral artery, and 2 patients had both extracranial and intracranial vertebral artery potential sources[15]. Fourteen patients had embolism of cardiac origin, and an additional 6 patients had infarcts attributed to embolism but the source was not identified. In all, 28 patients (47.5%) had documented embolism, and this is a minimal estimate considering the limitations of the investigations performed[15].

The superior cerebellar artery, a basilar artery branch near the distal end of the basilar artery, just proximal to the posterior cerebral artery origins, has also been considered a vessel potentially susceptible to embolism because of its location. Amarenco and his colleagues recently studied the mechanism of superior cerebellar artery territory infarction in 33 patients studied at necropsy[16]. In 18 patients (54%), the cause of the cerebellar infarct was judged to be embolism of cardiac origin, and 7 other patients (21%) had intra-arterial embolism. The authors considered that the mechanism of superior cerebellar artery occlusion was thrombosis engrafted upon atherosclerotic disease in only 6 patients[16]. In another recent study of superior cerebellar artery territory infarction, 2 of 3 patients had intra-arterial emboli arising from the more proximal vertebrobasilar system[17]. In an older study, Thompson reported 5 patients with what he called 'cerebellar embolism'[13]. Among these patients, all studied at necropsy, 4 infarcts were limited to the superior cerebellar artery territory and one involved the superior cerebellar artery and posterior inferior cerebellar artery territory. Four of the 5 patients had cardiac sources of embolism; 2 had atrial fibrillation, 1 had thyrotoxic heart disease, and 1 had aortic valve disease[18]. The fifth patient had extensive ulcerative atheromatous arterial lesions proximally and Thompson considered that these were the likely sources of embolism to the cerebellum[18].

Even occlusion of the proximal and middle portions of the basilar artery is sometimes embolic. In their classical necropsy report of the pathological and clinical findings in 18 patients with basilar artery occlusion, Kubik and Adams included 7 patients (39%) in whom the mechanism of occlusion was considered embolic[2]. Recently clinicians in Aachen, Germany have reported the findings in 85 patients who were given intra-arterial thrombolytic therapy in an attempt to

lyse acute posterior circulation thrombi[19,20,21]. Nearly all patients had angiographically documented occlusion of the basilar artery during the early hours after the onset of symptoms of brainstem and cerebellar ischemia. Among the 85 patients, 28 (33%) had proximal, potentially embologenic, arterial lesions. The proximal sites of severe atherostenosis or occlusion involved the intracranial vertebral artery in 16, the extracranial vertebral artery in 15 and the proximal subclavian artery in one[21] The possibility of cardiac sources of embolism was not commented on[19,20,21].

Occlusion of the intracranial vertebral artery is most often associated with cerebellar infarction in the posterior inferior cerebellar artery territory or with lateral medullary ischemia[22]. Sypert and Alvord reported an autopsy series of 28 patients with cerebellar infarcts, most located within the posterior inferior cerebellar artery territory[23]. In 6 of their patients (21%) embolic occlusion of the intracranial vertebral artery supplying the posterior inferior cerebellar artery territory infarcts was the mechanism of the cerebellar infarction. The emboli were all cardiac in origin, 3 being related to recent myocardial infarction and 3 to atrial fibrillation[23]. The great majority of these patients did not have angiography during life and the proximal vertebral artery and subclavian arteries were not examined in detail at necropsy to assess their role as potential intra-arterial sources of embolism. Amarenco and colleagues recently reported a necropsy study of 28 cases of cerebellar infarction in posterior inferior cerebellar artery territory[24]. In 15 patients the cerebellar infarction was limited to the posterior inferior cerebellar artery territory, while in the others the anterior inferior cerebellar artery and superior cerebellar artery territories were also involved. Only 5 of these patients also had lateral medullary infarcts, indicating that these 2 lesions (i.e. lateral medullary and posterior inferior cerebellar artery territory cerebellar infarcts) are most often not present together. This is contrary to common belief[24]. Arterial occlusions were found at necropsy in 20 of the 28 cases, most often in the intracranial vertebral artery (15 cases) and less often in the posterior inferior cerebellar artery territory (6 cases). The mechanism of these occlusions was considered embolic in 7 of these 20 cases (35%). Among the 8 patients in whom no occlusion was found, 6 had potential cardiac sources of embolism. In total, 13 of the 28 posterior inferior cerebellar artery territory cerebellar infarcts (46%) probably arose from cardiogenic emboli[24]. Disease of the extracranial vertebral artery and subclavian arteries was not commented upon or sought in this series, so that other patients surely had intra-arterial embolism.

Lateral medullary infarcts are usually thought of as being due to thrombotic occlusion of the intracranial vertebral artery. However an embolic aetiology of the lateral medullary syndrome has been reported, and in many series the

causative vascular mechanism has not been studied. The first case report of an embolic lateral medullary syndrome was given by Hallopeau and involved a patient later studied at necropsy by Charcot[25]. In this patient there was extensive ulcerated atheromatous plaque in the arch of the aorta, which the authors believed was the source of emboli to the intracranial vertebral artery. Fisher, Karnes and Kubik studied 17 patients with the lateral medullary syndrome at necropsy to analyze the pattern and mechanism of the vascular occlusive process and the clinicopathological correlations[25]. Three of their patients had embolic vertebral artery occlusions; 2 arose from cardiac disease (congenital heart disease and bacterial endocarditis). Another patient had multiple scattered brain infarcts and no occlusion at necropsy, again suggesting embolism, but no definite source was identified. Fisher and his colleagues also reviewed 3 prior reports of embolism causing lateral medullary infarcts[25].

A number of findings in relation to recipient arteries supplying infarction zones are considered very suggestive of embolism. These pathological findings include: absence of occlusion or severe stenosis in supply arteries and blockage of superficial branch arteries, especially if multiple. Similarly suggestive of embolism at angiography are abrupt occlusion of arterial branches, especially when peripheral, or filling defects representing emboli within arteries. Arteries ranging from the intracranial vertebral artery to the posterior cerebral arteries are involved, but the commonest sites seem to be the posterior cerebral artery and posterior inferior cerebellar artery territories.

ANALYSIS OF POTENTIAL CARDIAC AND ATHEROSCLEROTIC VASCULAR SITES FOR POSTERIOR CIRCULATION EMBOLISM

Embolism donor sites should always be considered only potential, since the finding of a source known to be a frequent site of thrombus formation does not necessarily mean that embolism has actually occurred. Finding a hungry little boy near an open cookie jar does not necessarily mean that he stole the cookies. Newer techniques have recently been able to uncover a wide variety of cardiac lesions known to be associated with embolism. Few studies have, however, been directed toward identifying the destination of the emboli. I have been involved in 3 large stroke registries, each of which collected information about the recipient regions for cardiac embolism. In the Harvard Stroke Registry, 16% of emboli from the heart involved the verte-brobasilar system (11% posterior cerebral artery, 5% vertebral artery or basilar artery)[26]. In the Michael Reese Stroke Registry, 15% of emboli caused posterior circulation infarcts[27], and 13% of emboli involved the vertebrobasilar system in the Stroke Data Bank[28]. Among

1290 patients in the Stroke Data Bank with brain infarcts, 416 (32%) had potential cardio-embolic sources including 250 (20%) in a high risk group and 166 (12%) in a medium risk group[28]. The most frequent cardiac lesions in the high risk group were atrial fibrillation, valvular disease and surgery, mural thrombi, ventricular aneurysms, and cardiomyopathy. In the medium risk group were mitral annulus calcification, mitral valve prolapse, and congestive heart failure. These studies probably underestimated the proportion of emboli that went to the posterior circulation. At times, the clinical findings do not allow accurate localization, and CT, the neuroimaging technique used in all 3 registries cited, often misses small brainstem and cerebellar lesions. About 1/5th of the brain blood flow goes to the posterior circulation (2/5ths go to each carotid territory); the cumulative average registry figure of about 15% is close to the likely estimate of 1 in 5. Ulcerated lesions of the aorta can also serve as donor sites for intracranial embolism but the frequency of posterior circulation involvement has not been studied.

Proximal arterial lesions that are potential donor sites for distal intra-arterial embolism within the posterior circulation also have not been routinely studied in patients with vertebrobasilar territory infarcts or TIAs. Neither routine ultrasound nor angiography of the extracranial and intra-cranial arteries has been pursued in large series of reported cases of posterior circulation infarcts.

The commonest pathology leading to intra-arterial embolism is the development of atherosclerotic plaques with superimposed occlusive thrombosis or deposition of fibrin-platelet aggregates. The most frequent sites for plaque occurrence within the vertebrobasilar system are: the vertebral artery origin in the neck, the intracranial vertebral artery especially the region between the dural penetration and the origin of the posterior inferior cerebellar artery, and the basilar artery[22,29,30]. Hutchinson and Yates in the 1950s emphasized the frequency and importance of atherosclerosis at the origins of the vertebral arteries from their parent subclavian arteries[31,32]. The plaques spread to the vertebral artery orifices from the subclavian arteries or originated within the first few centimeters of the vertebral arteries. Atherosclerosis at this site paralleled disease at the internal carotid artery origins[32]. My colleagues and I later showed that atherosclerosis at the internal carotid artery and vertebral artery origins in the neck usually occurred in conjunction with coronary and peripheral vascular occlusive disease[26], and was more common in white men than in women, and was rare in blacks and individuals of Chinese or Japanese ancestry[14,33,34].

I had previously reported 2 examples of intracranial posterior circulation embolism arising from an extracranial vertebral artery occlusion[35,36]. George and

Laurian also described 2 patients with intra-arterial embolism to the basilar artery arising from occlusion of the proximal vertebral artery[37], and Fisher and Karnes also included similar examples among their patients with 'local embolism'[33]. Labauge *et al* discussed intra-arterial embolism as an occurrence in their series of 100 patients with angiographically documented vertebral artery occlusions[39]. I have recently seen 3 patients admitted within 2 weeks to the New England Medical Center in Boston, all of whom had intra-arterial embolism arising from proximal vertebral artery disease. Two had tight stenoses, and one patient had a recent complete occlusion of the vertebral artery. All had cerebellar infarction, and 2 also had lateral thalamic and posterior cerebral artery territory infarcts. Figs 1 to 4 show the neuroimaging and angiographic studies in one of these patients.

Pelouze, in a very important recent single case report, described an instance of embolism arising from an ulcerated plaque located at the vertebral artery origin[40]. The patient was a man with numerous attacks of vertigo and brainstem dysfunction not responsive to aspirin treatment. Angiography showed an irregular lesion at the vertebral artery origin and a B-mode ultrasound scan suggested an ulcerated plaque. An endarterectomy was performed and the proximal vertebral artery contained an ulcerated plaque. After surgery, the attacks ceased[40].

Using modern ultrasound technology, Hennerici and colleagues showed a significant frequency of proximal vertebral artery and subclavian and innominate artery lesions in patients with known coronary and peripheral atherosclerosis and risk factors for stroke[41]. In 183 of 426 patients (43%) there were abnormalities of flow in one or both extracranial vertebral arteries. Doppler velocity findings had a 90% agreement with angiography in detecting extracranial subclavian and vertebral artery lesions[41]. Clearly atherosclerotic lesions at the vertebral artery origin are common. As of today, we still have no reliable data on the frequency of irregular or ulcerative lesions similar to the abnormality described by Pelouze[40].

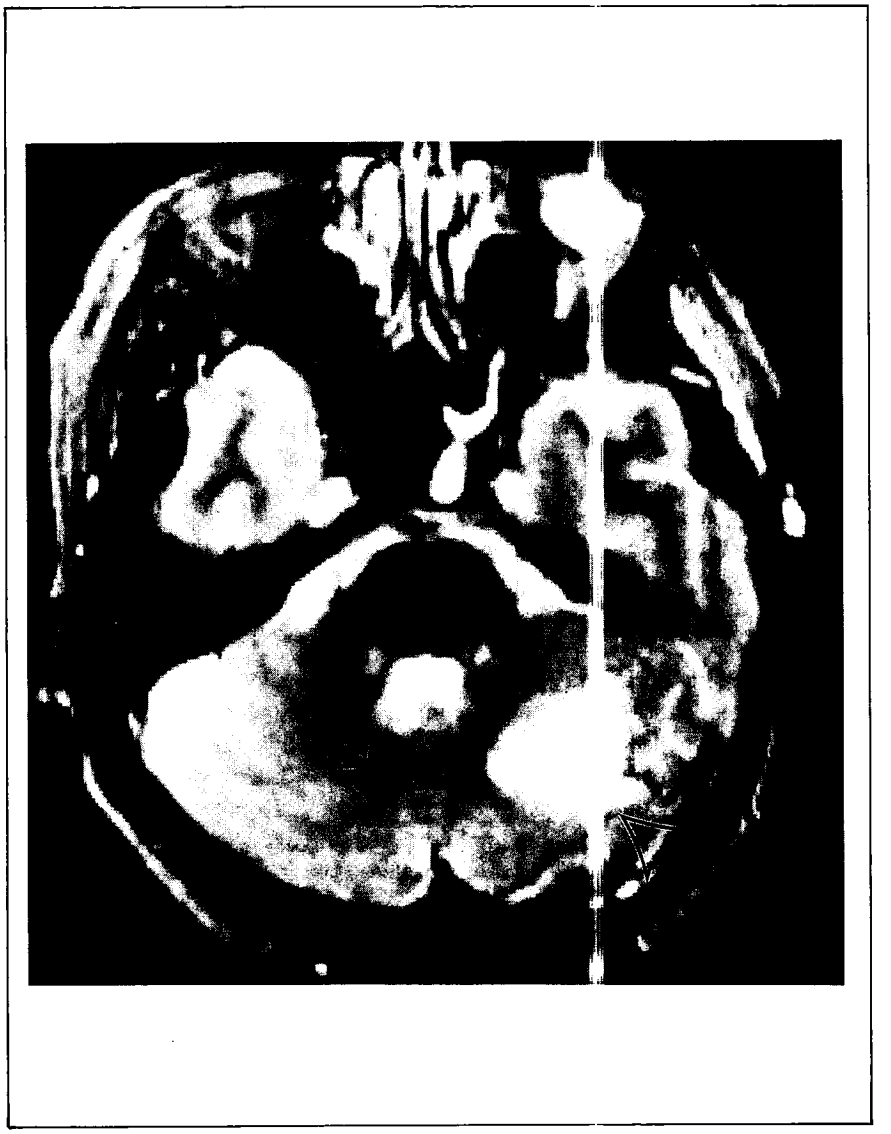

Fig 1 MRI T2 - weighted axial section showing large right lateral cerebellar infarct (large open arrowhead) and small paramedian cerebellar infarct (small black arrow).

Fig 2 MRI T2 - weighted sagittal section to the right of midline. The cerebellar infarct on this section is in the posterior inferior part of the cerebellum (posterior inferior cerebellar artery).

Knowledge of the frequency of carotid artery ulceration and also accompanying lesions such as fissures, fibrin-platelet clumps, and mural thrombi has come from careful microscopic examination of carotid endarterectomy specimens removed at surgery[9]. When vertebral artery reconstruction is performed, the usual surgical procedure is to bypass or anastomose the vertebral artery to the carotid artery, rather than to carry out a vertebral artery endarterectomy. Few vertebral endarterectomy specimens have been available for study. The major pathological studies of the extracranial vertebral arteries were performed in the 1950s and 1960s, antedating knowledge gained more recently from analysis of carotid endarte-rectomy specimens. There are no studies of surgical or necropsy sections of the proximal vertebral arteries using modern histopathological techniques.

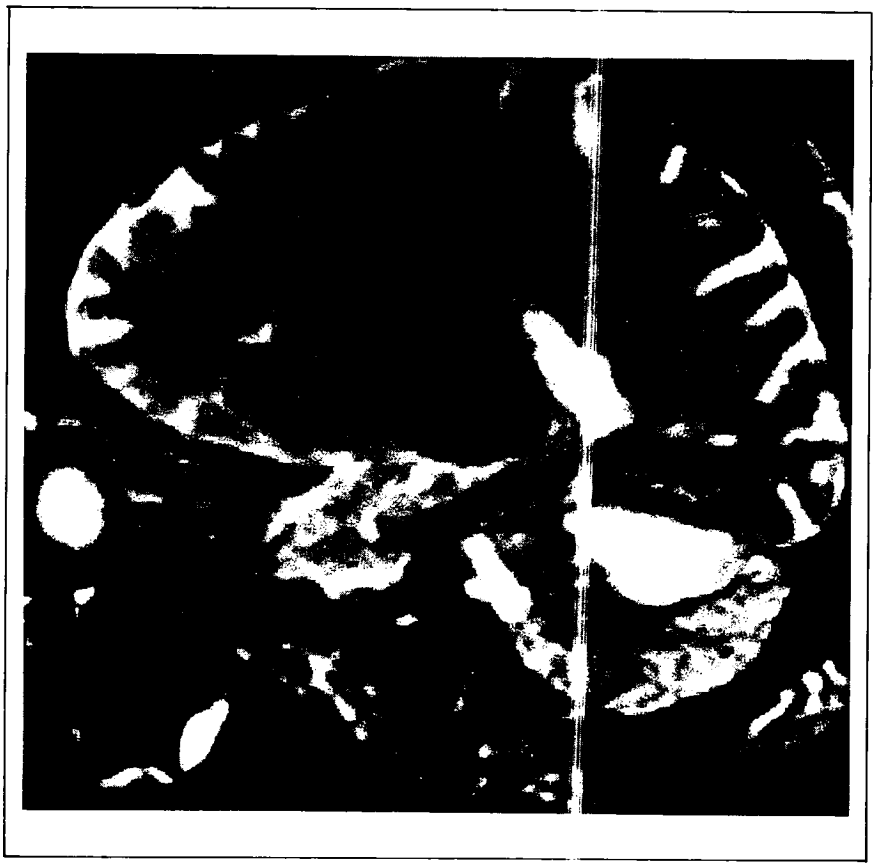

Fig 3 MRI T2 - weighted sagittal section to the left of midline. On this section cerebellar infarction is above the sulcus and in the superior cerebellar artery territory.

Within the anterior circulation, a similar situation is commonplace. Thus a patient will be admitted with the sudden onset of a middle cerebral artery territory branch infarct. Ultrasound and/or angiography will show a recent internal carotid artery occlusion in the neck and embolization from the fresh thrombus into the middle cerebral artery. Embolism arising from atherosclerotic lesions of the proximal vertebral artery is much more common than presently recognized or diagnosed. In the future, ultrasound and magnetic resonance angiography should allow noninvasive detection of proximal vertebral artery lesions in the neck.

Fig 4 Angiography showing very tight stenosis of the right vertebral artery at its origin from the subclavian artery (arrow).

Thrombosis of the intracranial vertebral artery can also serve as the nidus for distal intra-arterial embolization. Fisher, Karnes and Kubik, in their classic clinicopathological study of lateral medullary infarcts that I have already referred to, were probably the first to recognize that the intracranial vertebral artery might be a source for embolism[25]. The authors noted 'Attention might be drawn here to a special feature of the pathological findings, namely the occurrence of embolism from the vertebral artery occlusion'[25]. In 4 of their 17 patients, embolic material was found in the superior cerebellar artery or posterior cerebral artery or their branches, without atherosclerosis at these sites. Pessin and I and our colleagues reported 2 patients with occlusion of an intracranial vertebral artery and distal intraluminal filling defects in the basilar artery that represented the intra-arterial passage of clot[42]. Ropper with Koroshetz recently reported the nature of the underlying arterial pathology in 12 patients with posterior cerebral artery territory infarcts and brainstem symptoms[43]. Embolic donor sites that embolized to the posterior cerebral artery included the extracranial vertebral artery (5 patients) and intracranial vertebral artery (3 patients), while 3 patients had both extracranial and intracranial potential donor sites[43]. Basilar artery stenosis and occlusion can also serve as the nidus for distal embolization. Fresh

clot formed *in situ* is not organized or adherent to the arterial wall, so that the distal end often fragments discharging clot particles into the basilar artery branches. Castaigne *et al* noted the occurrence of embolization from basilar artery lesions[10], as did Pessin and colleagues[11]. However, in patients with basilar artery occlusion, it is difficult to distinguish between distal ischemia due to low flow, direct extension of propagated thrombus, and fragmentation of clot with embolism.

NON-ATHEROSCLEROTIC DONOR SITES

Vascular pathologies other than atherosclerosis can also serve as donor sites for embolism within the posterior circulation. Dissection is a very important lesion since this arterial pathology predisposes to luminal clot. Dissection of the extracranial vertebral artery can follow sudden neck movements or manipulation[22,44], or may be spontaneous, meaning that no unusual movement or injury is recalled by the patient[45,46]. The commonest site of dissection in the extracranial vertebral artery is the distal segment in which the vertebral arteries course around the upper cervical vertebrae after emerging from the foramina transversaria. The arteries are relatively fixed within the vertebral column, and are also anchored intradurally after they enter the cranium through the foramen magnum. Less often, tears occur in the proximal segment above the vertebral artery origins but before the arteries enter the vertebral foramina[45]. The initial lesion is a tear within the arterial wall. Bleeding into the wall produces a spreading 'dissecting' intramural clot. The clot can dissect through the intima, discharging fresh thrombus into the lumen. In other patients, the expansion of the arterial wall, or intimal flaps, lead to lumina compromise, decreased anterograde flow, and *in situ* formation of thrombus within the lumen. Fresh clot within the lumen is not organized or adherent, and often fragments and embolizes intracranially. Dissection into or through the adventitia leads to an aneurysmal pouch or localized extravascular hematoma (pseudoaneurysm). The most common symptom in patients with extracranial vertebral artery dissection is pain or discomfort. Often the pain is located in the occiput, neck or shoulder region. Headache is also common and is either limited to the occiput and posterior cranium or is described as generalized.

Neurological symptoms, when they occur, are almost always due to embolization of clot intracranially from the site of the dissection. Sudden stroke or TIAs may occur. The commonest recipient site is the intracranial vertebral artery. Ischemia usually affects the lateral medulla or the cerebellum, most often in posterior inferior cerebellar artery distribution[45,46]. Posterior cerebral artery

territory infarcts are rare, but I know of such occurring. Ultrasound examination using continuous wave Doppler to search for reversal of flow in the distal extracranial vertebral artery, and transcranial Doppler to assess changes in flow velocity in the intracranial vertebral artery segment, can often suggest the presence of dissection[47]. Magnetic resonance angiography and standard angiography by arterial catheterization show the arterial lesion which is most often characterized by a long string-like area of stenosis, or tapered occlusion, or irregularities with aneurysmal outpouchings.

Dissections also involve the intracranial vertebral arteries. Acute intracranial vertebral artery dissection causes subarachnoid hemorrhage when the tear breaks through the adventitia, and ischemia when the lumen is compromised by the intramural process[48]. Distal extension or embolization of clot is also common. Intracranial acute vertebral artery dissections often extend into the basilar artery and cause fatal brainstem and cerebellar infarction. Less well known are chronic intracranial vertebral artery dissections. These lesions are usually bilateral and are probably engrafted upon an abnormal vascular media as might be found in patients with fibromuscular degeneration, or hereditary disorders of connective tissue. Recurrent subarachnoid bleeding, or recurrent ischemia results. My colleagues and I reported one patient, a young nurse, who had many attacks of brainstem and posterior cerebral artery territory ischemia[48]. She had bilateral large dissecting aneurysms which contained filling defects representing clot. Her symptoms disappeared after a combination of aspirin and coumadin was prescribed, but not when each was given alone[48].

Large giant berry aneurysms and tortuous fusiform dolichoectatic aneurysms of the intracranial vertebral arteries and basilar artery can also harbor clot material which has the potential to embolize distally[49,50]. Recent investigations using transcranial Doppler ultrasound showed that peak and mean flow velocities were significantly reduced in patients with dolichoectatic posterior circulation arteries[47,50]. Pockets of slow flow, turbulence, and stagnation lead to thrombus formation within aneurysmally dilated segments. Thrombi can embolize or block the orifices of penetrating, circumferential, or distal branches.

Traumatic vascular occlusions affecting the intraosseous portion of the vertebral arteries can also serve as the source of intra-arterial emboli. Although I am not convinced that spondylitic bars or spurs or other rather stable cervical spine osseous lesions lead to arterial compromise[22], neck trauma with fractures and dislocations can cause acute vertebral artery disruption, dissection, and occlusion. Among a series of 10 patients 'locked-in' because of pontine infarction, 5 had neck injuries and a delayed onset of brainstem signs[51]. Four

patients in this series had cervical fractures, and 2 of these had documented traumatic vertebral artery occlusions in the neck[51]. In another report, a motor vehicle accident led to a traumatic distal extracranial vertebral artery dissection with subsequent basilar artery embolization[52]. A few years ago, I consulted on a young man with traumatic quadraplegia and neck fractures who developed a delayed embolus to the basilar artery with blindness and amnesia. No data are presently available on the frequency of vertebral artery occlusion or dissection in patients with severe neck injuries. The presence of paraplegia or quadraplegia makes it more difficult to detect additional weakness or ataxia from a pontine infarct.

Recently, I have become aware of positionally related thrombi that develop within the extracranial vertebral artery during surgery. Prolonged or unusual neck postures are known to be associated with posterior circulation infarction. Swimming[53], yoga[54], fitness exercises[55] and wrestling[56], have all been reported to precipitate vertebrobasilar territory infarction, but usually the mechanism has not been well documented. Sudden or unusual stretching can cause dissection. Alternatively, kinking or compression related to a prolonged period with the neck in an unusual position could cause a thrombus to form locally in a region of haemostasis. Then, when full motion is restored, the clot could embolize intracranially. Positional compromise could be facilitated or made possible by congenital anomalies, kinks, unusual vascular origins or courses, or loops, or by congenitally small or hypoplastic arteries. My colleagues and I have recently reported a group of patients in whom posterior circulation infarcts developed immediately after surgery or were delayed for up to 36 hours[57,58]. Most patients were either under 30 years of age or were older than 60. The surgery was most often orthopaedic, gynaecological or involved removal of skin lesions. All patients had endotracheal intubation and general anesthesia. The commonest loci for infarctions were the upper brainstem, cerebellum in the superior cerebellar artery territory, and the posterior cerebral hemispheres in the posterior cerebral artery territory. Only 2 patients had angiography: each had one small vertebral artery and intracranial filling defects within the distal vertebrobasilar system that represented emboli. No patient had known cardiac disease or vascular surgery[58]. I believe the mechanism is partial compromise of one vertebral artery, either during intubation or while anaesthetized, with formation of a thrombus and subsequent intra-arterial embolization. We are now engaged in studies using ultrasound in an attempt to study vertebral artery blood flow velocity changes during surgery.

EMBOLISM IN THE NEW ENGLAND MEDICAL CENTER SERIES

I have reviewed the evidence, drawn mostly from anecdotal cases or case series, concerning the importance of embolism as a cause of posterior circulation ischemia and infarction. Beginning about 2 years ago, my colleagues and I, especially Drs. Barbara Tettenborn, Michael Pessin, Dana DeWitt, Conrad Estol and Frank LaFranchise, began to collect a prospective series of consecutively studied patients with brainstem and cerebellar infarction. These patients have all been investigated as fully as judged clinically appropriate. All have had CT and/or MRI and all have had vascular investigations such as ultrasound and angiography, and more recently, magnetic resonance angiography. Most have also had cardiac testing. I included for analysis only patients in whom the data were sufficient to clarify the probable mechanism of the brainstem or cerebellar infarct[15].

In total, 88 patients have been collected. Table 1 shows the various stroke mechanisms and their frequencies. Cardiac origin embolism was diagnosed in 15 (17%) and intra-arterial embolism in 16 patients (18%). Table 2 shows the distribution of arterial occlusive lesions in patients with large artery haemodynamic compromise. As in prior series, the commonest site was the basilar artery. Table 3 enumerates the cardiac donor sites for embolism and the recipient arteries and Table 4 shows the donor and recipient sites among the intra-arterial embolism group. The responsible cardiac lesions were not different from those in most large series that include all brain emboli[26,27,28]. The most common recipient sites for both cardiac and intra-arterial emboli are the intracranial vertebral artery/posterior inferior cerebellar artery region and the more distal basilar artery/superior cerebellar artery/posterior cerebral artery region. The recipient sites may not be truly representative of the universe of posterior circulation emboli since I did not include in the series patients with infarcts limited to the posterior cerebral artery hemispheric supply.

Table 1 New England Medical Center Series - Ischemia mechanisms

Large artery occlusive disease	40	(46%)
Small artery disease	17	(19%)
Cardiac origin emboli	15	(17%)
Intra-arterial emboli	16	(18%)
	88	(100%)

Table 2 New England Medical Center Series - Large artery disease sites

Extracranial vertebral artery, origin	4
Intracranial vertebral artery, unilateral	6
Intracranial vertebral artery, bilateral	6
Intracranial vertebral artery and basilar artery	4
Basilar artery	20
	40

Table 3 New England Medical center Series - Cardiac source emboli

Donor lesions			Recipient sites	
Valve lesions		6	Intracranial vertebral artery/PICA	7
Mitral valve (stenosis and floppy)	(2)		Basilar artery	1
Aortic valve stenosis	(1)		Superior cerebellar artery	4
Nonbacterial thrombotic endocarditis	(1)		Top basilar artery	3
Prosthetic valve	(1)			
Ebstein's and atrial septal defect	(1)			
Atrial fibrillation		6		
Coronary artery disease		3		
Procedures		2		
Coronary angiography	(1)			
Coronary artery bypass graft	(1)			
		17	(15 patients)	

Table 4 New England Medical Center Series - Intra-arterial emboli

Donor sites		Recipient sites	
Extracranial vertebral artery - origin	6	Intracranial vertebral artery/PICA	6
Extracranial vertebral artery - positional	4	Basilar artery	3
Extracranial vertebral artery - dissection	3	Top basilar artery/superior cerebellar artery/posterior cerebral artery	10
Intracranial vertebral artery	3		18*
	16		

*16 patients but 18 sites.
PICA = posterior inferior cerebellar artery

CONCLUSIONS

I believe that the literature and my own experience show that embolism is an important cause of posterior circulation ischemia and infarction. Cardiac and intra-arterial emboli probably each account for at least 1/5th of all posterior circulation infarcts. The most common recipient sites are the posterior cerebral arteries, rostral basilar artery/superior cerebellar artery, and the intracranial vertebral artery/posterior inferior cerebellar artery areas. Some emboli block the basilar artery. The most frequent clinical syndromes reflect cerebellar and posterior cerebral artery hemispheric territory ischemia. The most important donor sites for intra-arterial emboli are the extracranial and intracranial vertebral arteries. Presently it is not known how often platelet and platelet-fibrin emboli arise from irregular ulcerative lesions at or near the origins of the vertebral arteries in the neck. Morphological studies using modern histopathological techniques to study lesions of the proximal innominate-subclavian-proximal vertebral artery regions are badly needed. Cardiac origin embolism is also important and probably 1 in 5 cardiac origin emboli go to the posterior circulation, paralleling the 1 in 5 posterior circulation infarcts that are cardio-embolic. Patients with posterior circulation ischemia should have evaluations similar to those ordered for patients with anterior circulation disease. Cardiac testing, ultrasonography, MRI and, in selected cases, MRI or standard angiography are needed to characterize the ischaemic aetiology to allow more logical selection of therapy for the individual patient with vertebrobasilar disease.

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SUPERIOR SAGITTAL SINUS THROMBOSIS

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SUMMARY

Seven cases of superior sagittal sinus thrombosis seen at Royal Prince Alfred Hospital over the 10 year period 1979 to 1989 have been reviewed. Diagnosis was confirmed by angiography, CT scan or autopsy. The average age was 33 years (16 to 47 years). Five of the patients were female and 2 male. On CT scan the 'empty Δ' sign, present in 4 cases, was the most specific diagnostic feature. The underlying causes included primary thrombocythaemia, homocystinuria, post-angiographic investiga-tion of an arteriovenous malformation, and oral contraceptives. In 2 cases no cause was found. Headache was the commonest and earliest symptom, being followed in frequency by convulsions and hemiparesis. Hemiparesis was the commonest sign observed, followed by papilloedema, cranial nerve palsies and impaired level of consciousness. Five of the patients developed signs and symptoms of raised intracranial pressure prior to the appearance of focal neurological deficits, mostly likely due to propagation of the thrombosis to cortical veins. There have been no controlled trials of therapy; however it is important to treat raised intracranial pressure rapidly and effectively, and although the role of anticoagulants remains controversial, their early use may be indicated when there is no radiological evidence of haemorrhage.

Superior sagittal sinus thrombosis is an uncommon form of stroke that is frequently overlooked. However, the general pathology and clinical picture of sinus thrombosis have been recognised since the 19th century. Ribes in 1825 was possibly the first to describe cerebral venous thrombosis in man[1]. In 1888 Sir William Gowers recognised the existence of aseptic intracranial venous thrombosis and in 1915 Holmes and Sargent described the syndrome of post-traumatic sinus thrombosis[2]. In the present study we have reviewed patients with the condition at Royal Prince Alfred Hospital over a 10 year period, to analyse the clinical and radiological features, aetiological factors, and the management and outcome.

METHODS

The medical records of 7 cases of superior sagittal sinus thrombosis at Royal Prince Alfred Hospital in Sydney over the 10 year period 1979 to 1989 were reviewed. The diagnosis was proven by angiography in all cases except one in whom it was established at autopsy.

RESULTS

CLINICAL FEATURES

The average age of the patients was 33 years, the youngest being a 16 year old boy, and the oldest a 47 year old woman. Five of the patients were female and 2 male (Table 1). Three patients were Noumean, another was born in Yugoslavia, while the remaining patients were born in Australia.

Table 1 Patient details

Case No	Sex/ Age	Time to diagnosis (days)	Underlying cause	Time taken to find cause (days)	Means of diagnosis
1	F45	Not diagnosed	Not known	-	Autopsy
2	F35	8	Thrombocythaemia	50	Angiography
3	F47	9	OCP	-	Angiography
4	F40	3	Not known	-	Angiography
5	F16	20	Homocystinuria	23	Angiography
6	F24	0	Homocystinuria	5	CT, Angiography
7	M24	1	Angiography of AVM	1	CT

Time to diagnosis = Time from admission (days) taken to arrive at diagnosis: OCP = oral contraceptive pill: AVM = arterio-venous malformation: CT = computed tomography

The underlying causes included primary thrombocythaemia (Case 2), homocystinuria (Cases 5 & 6), post-angiographic investigation of an arterio-venous malformation (Case 7), and oral contraceptives (Case 3). No cause could

be found in Cases 1 and 4 (Table 1). Cases 2 and 6 presented 9 days and 14 days postpartum respectively. In no patient was there evidence of infection.

The main symptoms and signs in the patients are summarised in Table 2. Headache was the commonest presenting feature and, in 5 of the 7 patients, was the initial symptom. The next most frequent symptoms were hemiparesis and convulsions. The commonest sign observed was hemi-paresis; other frequent signs were papilloedema and cranial nerve palsies, together with the non-specific features of an increased temperature and an alteration in the level of consciousness. No source of infection was found in any of the febrile patients. Five of the 7 cases had symptoms of increased intracranial pressure, followed by the appearance of focal neurological signs. Case 2 had a 2 day history of headaches prior to developing weakness and numbness. Case 3 had an acute onset of frontal headaches with nausea before noticing that she was dragging her left leg. Case 4 developed headaches and papilloedema 6 months prior to the onset of a hemiplegia. Case 5 developed drowsiness, papilloedema and photophobia 15 days prior to focal and generalised fits and a hemiparesis.

Table 2 Clinical features of superior sagittal sinus thrombosis

Symptoms		Signs	
Headache	6 (85%)	Hemiparesis	5 (71%)
Hemiparesis	3 (43%)	Papilloedema	4 (57%)
Focal epilepsy	3 (43%)	Oculomotor palsies	3 (43%)
Vomiting	2 (29%)	Somnolence, coma	3 (43%)
Generalised convulsion	2 (29%)	Fever	3 (43%)
Diplopia	1 (14%)	Aphasia	2 (29%)
Slurred speech	1 (14%)	Focal epilepsy	2 (29%)
Paraesthesiae	1 (14%)	Meningism	2 (29%)
Difficulties in speech	1 (14%)	Generalised epilepsy	1 (14%)
Photophobia	1 (14%)	Hemianopia	1 (14%)
Poor vision	1 (14%)	Sensory loss in limb	1 (14%)
Myalgia/arthralgia	1 (14%)	No signs	1 (14%)

RADIOLOGICAL FINDINGS

The angiographic findings are summarised in Table 3. Carotid angiograms were performed in 6 patients. Case 7 developed headaches after the first angiographic study of his arteriovenous malformation. Subsequently a CT scan showed a superior sagittal sinus thrombosis that was not present in the first angiogram. The thrombosis was attributed to dehydration together with anomalous venous drainage of the arteriovenous malformation (Fig 1).

Table 3 Radiological features of superior sagittal sinus thrombosis

Case No	Non-filling of SSS	Collaterals involved	Delayed venous filling	Other sinuses involved
1		Angiogram not done		
2	+	SMCV	+	Lateral, sigmoid
3	+	Cortical, deep cerebral	-	Right lateral
4	+	Deep cerebral	+	Lateral
5	+	Cortical	+	Right transverse
6	+	Cortical, tentorial, SMCV, EC	-	Internal CV, basal vein
7		Angiogram not done		

SMCV = Superficial middle cerebral vein: EC = extracranial anastomoses:
SSS = superior sagittal sinus: CV = cerebral vein

Five cases had involvement of other sinuses or veins, the most frequent being the lateral sinus. No mass effect was seen in any of the angiograms. Of the CT findings, the most frequent and specific sign was the 'empty delta (Δ) sign', which represents the image of thrombosis in the superior sagittal sinus (Fig 2).

TREATMENT AND OUTCOME

The treatment and outcome are summarised in Table 4.

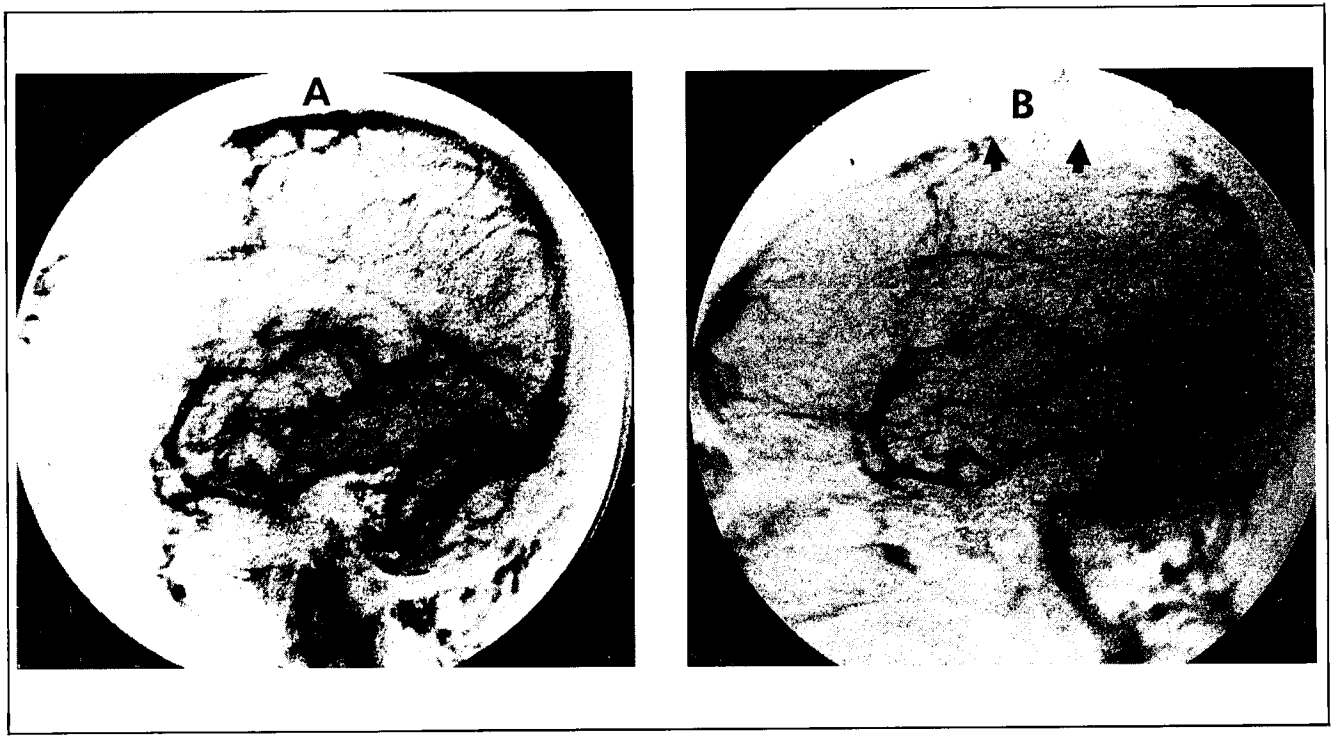

Fig 1 Case 4 A. Angiogram showing normally filling superior sagittal sinus
B. A later angiogram showing thrombosis of superior sagittal sinus (arrows) and partial thrombosis of straight sinus.

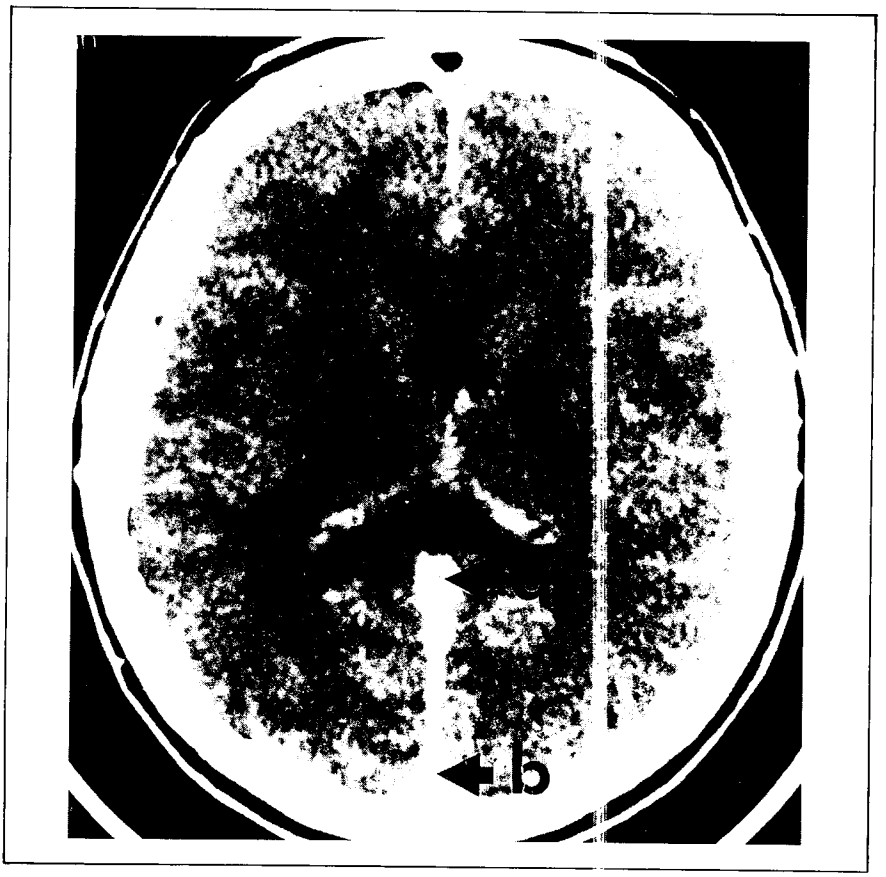

Fig 2 Case 6 CT scan with contrast showing non-filling at the junction of the vein of Galen and straight sinus (a) and at the confluence of the sinuses (b) - the 'empty Δ' sign

DISCUSSION

Frequency

The true frequency of superior sagittal sinus thrombosis is still unknown. Towbin[3] found that 9% of 182 consecutive adult autopsy cases had dural sinus thrombosis; the patients were mostly aged over 60 years and had associated pulmonary emboli and congestive heart failure. Scotti *et al*[4] found that 3.7% of angiograms in children demonstrated intracranial venous thrombosis. On the other hand, Ehlers and Courville[5] found only 16 cases of superior sagittal sinus

thrombosis in a series of 12,500 autopsies and Barnett and Hyland[6] encountered only 39 non-infective cerebral venous thromboses in 20 years. In a retrospective review in Melbourne, 46 proven cases were documented over a period of 20 years[7].

Table 4 Treatment and outcome

Case	S	Surgery	B	Ae	Anb	A'coag	Outcome
1	+	LPS	-	-	+	-	Death from coning
2	-	-	-	+	+	H&W	Mild residual crural weakness/paraesthesiae
3	+	HE	-	+	-	H&W*	Right homonymous hemianopia
4	+	LPS	-	+	-	H&W	Residual hemiplegia
5	+	LPS	-	+	+	H&W	Recovery
6**	+	Crt,LPS, IVC, CPS	+	+	-	H&W	Mild hemiplegia, right lower quadrantanopia, mild cognitive impairment, mild aphasia
7	+	-	-	+	-	-	Complete recovery

* = Heparin and warfarin used after patient developed pulmonary embolus and not for SSS thrombosis: ** = Patient intubated: S = Steroids: B = Barbiturates: Ae = Antiepileptics. Anb = Antibiotics: A'coag = Anticoagulants: LPS = Lumboperitoneal shunt: HE = Haematoma evacuation: CRT = Craniotomy: IVC = Intraventricular catheter: CPS = Cisterno-peritoneal shunt: H&W = Heparin and warfarin treatment simultaneously

Aetiology and Predisposing Factors

Although in many cases of venous sinus thrombosis no predisposing factors are found, a wide variety of diseases may be associated with the disorder, including infective and noninfective conditions. Sepsis, either due to direct extension from adjacent structure or arising from secondary spread from the transverse sinuses or cortical veins, used to be the commonest cause of sinus thrombosis. Superior sagittal sinus thrombosis may follow an ear or sinus infection and lead to an increase in intracranial pressure due to venous occlusion. This complication most commonly occurs in adolescents and children with otitis media. With the advent of antibiotics, it has become less common. Aseptic causes include trauma, pregnancy, dehydration, disseminated intravascular coagulation, polycythaemia, leukaemia, the nephrotic syndrome, systemic lupus erythematosus, sarcoidosis, and homocystinuria[8].

Clinical Features

The symptoms due to thrombosis limited to the dural sinuses are generally those of raised intracranial pressure[9]. Since the superior sagittal sinus drains spinal fluid, its occlusion may cause increased intracranial pressure, with headaches, somnolence, coma, vomiting and abducens nerve palsy. Patients may present with a picture identical to that of benign intracranial hypertension. When thrombosis spreads to the superior group of the superficial cortical veins, there is a syndrome of unilateral hemiplegia and convulsions, later extending to the other side of the body. Because of the localization of function in the cortex, the paralysis takes the form of crural monoplegia or, less commonly, paraplegia. Focal motor or sensory seizures are seen predominantly in the lower limbs. No predominance of lower limb signs was observed in our patients.

Russell suggested that, unless cortical vein thrombosis was present in addition to superior sagittal sinus thrombosis, intraparenchymal lesions and focal neurological deficits did not develop. In support of this contention, 5 of the patients in the present study showed a similar pattern of signs and symptoms. Each had manifestations of increased intracranial pressure followed by focal neurological signs. These events may be explained by the hypothesis that the signs of increased intracranial pressure were due to superior sagittal sinus thrombosis, and that focal neurological signs developed later as the thrombus propagated to the cortical veins. Further support is given to this argument by Case 1, who presented with signs of increased intracranial pressure one month prior to her death. One week before she died, she developed focal and generalised seizures, together with hemiparesis. Her autopsy revealed a thrombosed superior sagittal sinus of approximately one month's duration, and cortical vein thrombosis of approximately one
week's duration. The mortality of cerebral venous thrombosis is high, there being 29 fatalities (63%) in the Melbourne series of 46 proven cases[7].

Headache is usually an early symptom, as it was in our 7 cases. It is commonly unilateral, progressive, unresponsive to analgesics and correlates with the severity of the cerebral lesion. Other clinical features include a cortical sensory syndrome, aphasia (Cases 2 and 4), paralysis of conjugate gaze and urinary incontinence. In a few survivors bilateral choreoathetosis may result from infarction of the basal ganglia[2].

Cranial nerve palsies may develop if there is associated thrombosis of other cerebral venous sinuses. Spread of thrombus to the inferior petrosal sinus may produce a 6th nerve palsy. Extension into the jugular veins may involve the 9th,

10th and 11th cranial nerves, with swelling and tenderness of the neck (Vernet's syndrome of the jugular foramen). The presence of neck stiffness and photophobia are less common. The former was present in only 2 of our cases, and the latter in only one case.

Superior sagittal sinus thrombosis may rarely be complicated by pulmonary embolism. Crimmins *et al*[11] reported such an event in a 20 year old man who developed superior sagittal sinus thrombosis after sustaining a closed head injury. Four of our cases developed pulmonary embolism, postoperatively. Unfortunately, none had venography to exclude a deep venous thrombosis as the source. The diagnosis was made by lung scanning in 3 cases and at autopsy in the 4th case.

Diagnosis

Although cerebral venous thrombosis may be suspected, a definite diagnosis is usually not possible on clinical grounds alone. Hope of effective treatment hinges upon accurate and early diagnosis.

If an infection is present, there may be fever and leucocytosis. These features, together with an elevated erythrocyte sedimentation rate (>50mm/h) are frequently present even in the absence of infection.

ANGIOGRAPHY

Diagnosis of superior sagittal sinus thrombosis may be corroborated by angiography (Figs 1 and 3). Delayed views are necessary to allow for the slow filling of the venous system; in normal subjects the veins and sinuses fill in 2 to 4 secs following contrast injection, but in sinus thrombosis increased intracranial pressure slows the circulation so that the delay may be increased by 5 to 12 secs. It has to be remembered that hypoplasia or aplasia of the anterior ⅓ of the superior sagittal sinus is well recognised, especially in children, so that absence of filling of this portion of the sinus as an isolated finding is not always associated with pathology. The transverse sinus may also fail to fill because of an anatomical variation.

If angiography is not available, radionuclide scanning may be used to determine if the sinuses are occluded.

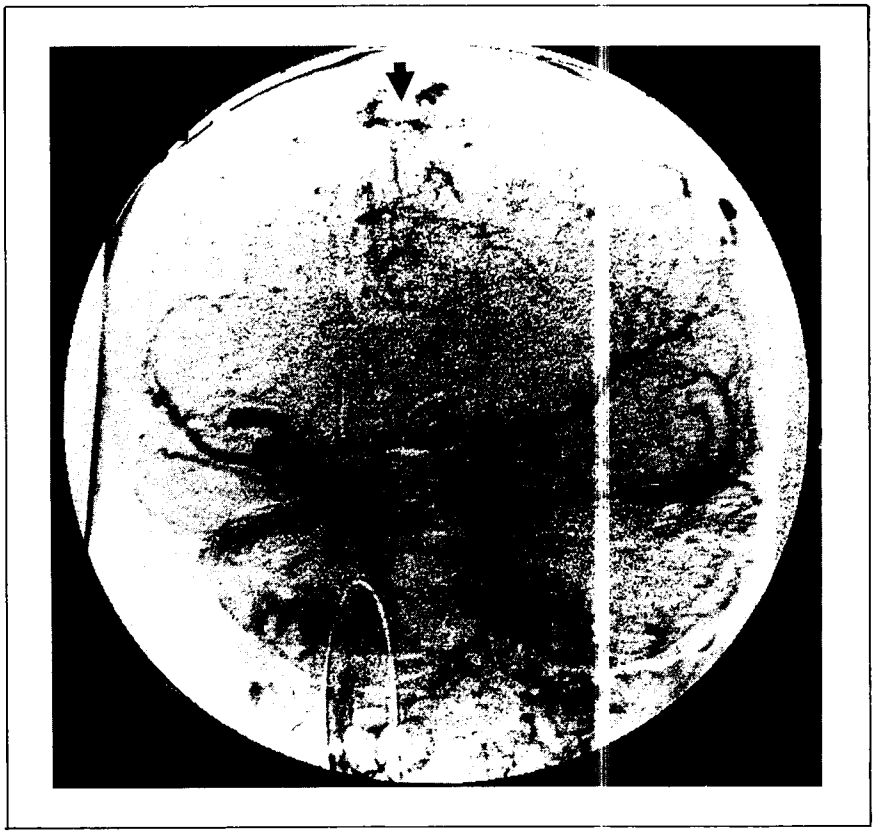

Fig 3 Case 6 Angiogram (AP view), confirming thrombosis of the superior sagittal sinus (arrow)

COMPUTED TOMOGRAPHY (CT)

CT may be quite specific in detecting superior sagittal sinus[13]. Wendling[14] was the first to diagnose dural sinus thrombosis by CT. Barnes and Winestock[15] were the first to describe the CT findings of superior sagittal sinus thrombosis, but emphasised the diagnostic value of dynamic radionuclide scanning. Later Buonanno and colleagues[16] demonstrated the 'empty triangle sign' (or 'empty delta (Δ) sign') in 2 of their 11 patients with superior sagittal sinus thrombosis. The occurrence of this sign has varied from 0 to 86% in large series[16,17,18,19]. It is seen along the course of the sinus only in the post-infusion scan, the empty triangle being the thrombus occupying the lumen of the sinus (Fig. 2). The outline of the triangle is due to contrast filling small fenestrated capillaries in the

walls of the sinus. Other hypotheses put forward as to the pathophysiology of the phenomenon include organisa-tion of the clot[14], blood-brain barrier breakdown[20] and dilatation of peridural and dural venous channels[16,17]. Virapongse *et al*[19] suggested that, since there is a high diagnostic accuracy for the empty delta sign, angiography is not needed for confirmation. However, some authors have failed to detect this sign despite careful examinations[21,22,23,24,25]. Shinohara *et al* suggested that the frequency of the appearance of the delta sign seemed to be higher in the subacute stage of the disease - i.e. 1 to 4 weeks after the onset of symptoms[25].

Other CT findings may include brain oedema manifested as diffuse low attenuation. This may sometimes be focal, making the differentiation from a tumour or infarct difficult. More characteristically, there are multiple parasagittal haemorrhages distributed in each hemisphere, diffuse gyral enhancement, small ventricles due to brain oedema, and sometimes cords of thrombosed veins[14].

Treatment

The treatment of superior sagittal sinus thrombosis is controversial. Surgery is not indicated because of the inherent risk of craniotomy and the difficulty of clot removal due to deep extension of the clot[26]. The main aims of therapy are to treat the primary cause, to reduce intracranial pressure, to control convulsions, and to prevent propagation of the thrombus.

When there is an infective cause, antibiotics should be administered until the thrombus recanalises. About half the cases of homocystinuria respond to large doses of pyridoxine orally. In pyridoxine-unresponsive homo-cystinuria, the use of acetylsalicylic acid (1 g daily) and dipyridamole (100 mg daily) has been suggested to prevent thrombosis[27].

Raised intracranial pressure is caused by impaired cerebrospinal fluid resorption. Diuretics, barbiturates, mannitol or steroids may be administered, but their use can be complicated by dehydration and hyper-coagulability[26].

Repeated lumbar puncture, which is not without risk, sometimes provides a temporary and effective means of reducing intracranial pressure until venous collaterals are established. Lumbo-peritoneal shunting and optic nerve or subtemporal decompression may help to save vision and lower the intracranial pressure.

If the cause of venous outflow obstruction cannot be remedied promptly, the

intracranial pressure must be monitored carefully. If it is not well-controlled, cerebral blood flow may be compromised, resulting in permanent damage. D'Avella *et al*[28] recommend intraventricular cannulation as a more accurate method of determining intracranial pressure than lumbar cerebrospinal pressure measurements. This method also allows drainage of cerebrospinal fluid when necessary.

The role of anticoagulants is controversial. Heparin may prevent the extension of the problems and its use is recommended by some authors[22]. However there is a risk of provoking haemorrhage particularly in the presence of haemorrhagic infarction. Kayenbuhl[12] found that cerebral haemorrhage was no more frequent in patients receiving anticoagulant therapy. Five of our patients were treated with anticoagulants without resulting complications. Their use should be avoided when a CT scan demonstrates significant haemorrhagic infarction.

Prognosis

One patient in our series of 7 cases died. Most of the published literature reports a mortality in the range of 40% to 60%[1,2,6]. The most important predictor of a poor prognosis is the rate of progression of the thrombosis. The early onset of convulsions and hemi-paresis signifies occlusion of cerebral veins which may lead to a rise in intracranial pressure or death.

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THE INFLUENCE OF AGE ON ATRIAL FIBRILLATION AS A RISK FACTOR FOR STROKE

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SUMMARY

To determine the influence of age on atrial fibrillation as a risk factor for cerebral infarction, the Austin Hospital Stroke Unit Register from 1977 to 1990 was reviewed. There were 2279 patients with cerebral infarction (excluding lacunar infarction syndromes) with a mean age of 68.3 years who were identified as subjects, and 800 patients with pseudostroke and lacunar infarction syndromes with a mean age of 64.7 years who were identified as controls. Data concerning potential risk factors for stroke (including sex, age, atrial fibrillation, cardiac disease, hypertension, diabetes, peripheral vascular disease and smoking) were analyzed using multivariate regression techniques.

It was found that atrial fibrillation was a significant risk factor for cerebral infarction (excluding lacunar infarction) for all age groups, after adjusting for the effects of other risk factors ($P<.001$). However, when age was stratified into four groups, the age-specific odds ratios for atrial fibrillation were not significantly different and no significant interactions between atrial fibrillation and age or other risk factors were found ($P>0.1$).

It was concluded that, although with increasing age atrial fibrillation becomes a more frequent cause of stroke, its potency as a risk factor does not increase correspondingly. There was no significant influence of age on the relationship between atrial fibrillation and cerebral infarction.

Atrial fibrillation is a common arrhythmia whose prevalence increases with age. Atrial fibrillation was found in 0.4% of persons over 16 years of age in an

American community[1]. The age-specific incidence rates for atrial fibrillation increased steadily from 0.2 per 1000 for ages 30 to 39 years to 39.0 per 1000 for ages 80 to 89 years[2].

One of the major problems for patients with atrial fibrillation is the increased risk of cerebral embolism[3,4]. Surprisingly, atrial fibrillation has been quantitated as a risk factor for stroke only in relatively recent times. The relative risk rates for atrial fibrillation have been variously reported as being from 1.3 to 7.5 in some epidemiological, clinical and autopsy studies[5,6,7,8,9].

It is well known to neurologists that the frequency of occurrence of atrial fibrillation increases with age in stroke patients. Does atrial fibrillation become a more potent risk factor for stroke with age? If so, the relative potency of atrial fibrillation as a risk factor for stroke in certain age groups may influence the management of patients with atrial fibrillation. For example, the benefits of anticoagulation may be more likely to outweigh the risk of stroke due to atrial fibrillation if the stroke risk were extremely high in the elderly.

METHODS

Subjects and controls

Data were extracted from the prospectively accumulated register of the Austin Hospital Stroke Unit from 1977 through to 1990. All patients with cerebral infarction, excluding lacunar infarction syndromes, were identified as subjects and all patients with pseudostroke or lacunar infarction syndromes were identified as controls for the purpose of the study. The diagnoses of cerebral infarction, pseudostrokes and lacunar infarction syndromes were made by neurologists on the basis of patients' past histories, clinical examinations, laboratory tests and CT head scans. The CT scan rates of stroke patients at the Stroke Unit increased from 49% in 1977 up to 93% in 1985. After that time, the CT scan rates remained at about 95%. Cerebral infarction was defined as a local neurological deficit of abrupt or rapid onset consistent with a lesion of vascular origin and which persisted for more than 24 hours or which resulted in death within 24 hours. Transient ischaemic attacks and lacunar infarction syndromes were excluded.

Data collection and analysis

The potential risk factors studied included sex, age, atrial fibrillation (AF), cardiac disease (HD), hypertension (BP), diabetes mellitus (DM), peripheral vascular disease (PVD) and current smoking (SMK). Data on these factors were collected using the defined criteria listed in Table 1. The data were analyzed using multivariate analysis

employing the standard logistic regression model of the "EGRET" Statistics Programme (Statistics and Epidemiology Research Corporation, Seattle, USA, 1990). Multivariate analysis of interaction terms followed that of single terms in the model, allowing consideration of the interactions between atrial fibrillation and age as well as other risk factors.

Table 1 Definitions of potential risk factors for the study

Sex	Male/Female
Age	Stratified at <=59, 60-69, 70-79, >=80 yrs
AF	Chronic, ECG confirmation
HD	Ischaemic, rheumatic, cardiomyopathy
HT	History of treated hypertension
DM	Pancreatic diabetes
PVD	Historical definition
SMK	Current smoking (>1 cig/d), yes/no

To study atrial fibrillation as a risk factor for cerebral infarction in different age groups, the data were further analyzed separately in four age-specific strata (aged at <=59 years, 60-69 years, 70-79 years and >=80 years).

RESULTS

The total admissions to the Austin Hospital Stroke Unit from 1977 to 1990 numbered 4346 patients. Amongst these, 2279 eligible subjects and 800 eligible controls were identified for inclusion in the study. The mean age of all admissions was 67.1 ± SD 12.0 years, the mean of the subjects 68.3 ± SD 11.8 years and of the controls 64.7 ± SD 12.4 years.

The most common form of pseudostroke encountered was due to migraine (31.0%). Other forms of pseudostroke diagnosed included: functional (10.7%), seizures (10.7%), tumours (10.7%), syncope (6.5%), metabolic disturbances (5.8%), transient global amnesia (3.6%), peripheral nerve disorders (2.6%), labyrinthine disturbances (2.1%), abscess (0.7%), multi-infarct dementia (0.7%), encephalitis (0.5%), and "others" (14.4%).

The atrial fibrillation prevalence rates were 3.24%, 4.42% and 3.88% in the patients with lacunar infarction syndromes, in those with pseudostroke and in the combined control group, respectively. There were no significant differences between these atrial fibrillation prevalence rates (χ^2=0.738; df=2; P>0.5).

Of the results of the multivariate analyses of the data, only the odds ratios for atrial fibrillation, cardiac disease and age were statistically significant (Table 2). The odds ratio for atrial fibrillation was 6.21 (P<.001). No significant interactions between atrial fibrillation and age or any of the other risk factors listed were found in the further analysis of the interaction terms in the model (P>0.1). Table 3 shows the overall and age-specific odds ratios for atrial fibrillation as a risk factor for cerebral infarction in the unstratified age group and the four age strata.

Table 2 Significant odds ratios of cerebral infarction in the results of multivariate regression

Term	OR	P-value	95% C. I.
AF	6.21	<.001	(4.26, 9.06)
HD	1.54	<.001	(1.21, 1.95)
Age	1.19	<.001	(1.09, 1.30)

Table 3 Odds ratios for atrial fibrillation in each age group

Group	Age(yrs)	OR	P-value	95% C. I.
Unstratified	15-100	6.21	<.001	(4.26, 9.06)
Stratum 1	<=59	6.07	<.001	(2.15, 17.14)
Stratum 2	60-69	7.19	<.001	(3.11, 16.63)
Stratum 3	70-79	5.78	<.001	(3.29, 10.18)
Stratum 4	>=80	6.56	<.001	(2.89, 14.89)

DISCUSSION

Selection of an appropriate comparison group is perhaps the most difficult and critical issue in the design of a case-control study. It was a carefully considered decision to select patients with pseudostroke or lacunar infarction syndromes as controls in the study reported above. There were 4 reasons for this decision. Firstly, the aim of the study was to determine the influence of age on atrial fibrillation as a risk factor for stroke. Hence, when selecting the control group,

we were most concerned that the pseudostrokes and lacunar infarction syndromes were independent causally from atrial fibrillation. Lacunar infarction syndromes are considered due to local in situ small vessel disease and are not related to any cardiac source of emboli. Other diseases causing pseudostroke have not been reported to be associated with atrial fibrillation. Furthermore, the atrial fibrillation prevalence rates in the controls were as low as those reported in other community-based studies[1,2,5,6,7,10]. Secondly, the critical requirement for controls in a case-control study is that the controls are comparable to the source population of cases. In this study, we used internal controls. The cases and controls were selected from the same Stroke Unit over the same period. The stroke diagnoses were made by the same neurologists under the same conditions and using the same criteria. Any exclusions made or restrictions employed in the identification of cases applied equally to the controls, and vice versa. Thirdly, the remote possibility that the intracerebral events in the subjects were responsible for the atrial fibrillation, and not vice versa, was controlled for in the study design: the controls also had intracerebral events and therefore would be likely to have had the same small increase in atrial fibrillation. Finally, the number of the controls was large enough for the study to have adequate statistical power.

The multivariate regression model was used in the study to take into account the effects of all potential risk factors simultaneously. After adjusting for the effects of other risk factors in the model, the odds ratio for atrial fibrillation as a risk factor for cerebral infarction was 6.21. This 6-fold increased risk found in the population studied is similar to reported levels in relevant community-based studies. As expected, because of the nature of the internal controls in the study, other risk factors had low odds ratios which barely reached statistical significance. This confirms that these risk factors had already been controlled for because of the intrinsic design of the study, in that a large proportion of the controls were stroke patients themselves, or lacunar infarction syndrome sufferers. Other potential risk factors in the study were not independent of the control diagnosis and therefore did not register significant odds ratios. However, the odds ratios for cardiac disease and age in the model were statistically significant, suggesting that the impact of cardiac disease as a risk factor was greater in the subject group than in the control group. The situation was similar with age. Again, it should be emphasized that although the odds ratios for sex, hypertension, diabetes, peripheral vascular disease and smoking were not significant, this does not mean that these are not significant risk factors for stroke. It merely suggests that there were no significant differences between the distributions of these factors in the subject group and the control group.

In the analysis of the four age strata, atrial fibrillation was associated with a remarkably constant risk of cerebral infarction (excluding lacunar infarction) in all age groups in the population studied. This finding is consistent with that of the Framingham study[2].

In the present study, the differences between the age-specific odds ratios for atrial fibrillation were not significant and no significant interactions between atrial fibrillation and age at any of the 3 stratified age levels were found ($P>0.1$). These findings suggested that, although atrial fibrillation became a more frequent cause of stroke with age, its potency as a risk factor did not increase correspondingly. Thus there was no significant influence of age on the relationship between atrial fibrillation and cerebral infarction. These findings should be confirmed in population-based studies.

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PRELIMINARY EXPERIENCE WITH ^{99m}Tc-HMPAO SPECT IN CEREBRAL ISCHAEMIA

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SUMMARY

To assess the sequential changes seen in cerebral blood flow using Single Photon Emission Computed Tomography with ^{99m}technetium-hexamethylpropylene amine oxime (^{99m}Tc-HMPAO SPECT) in acute ischaemic stroke, 35 patients were prospectively studied from June 1990- to March 1991. Scans were performed during the acute phase (1-7 days), sub-acute phase (8-21 days) and chronic phase of stroke (> 1 month). Nine patients underwent scans in all 3 phases, 15 patients had 2 scans, and 11 patients had one scan. The majority of infarcts were in the middle cerebral territory (15 patients), while 4 infarcts were in the posterior cerebral territory and two in the anterior cerebral territory. There was a total of 4 lacunar infarcts. Image analysis was by visual inspection and by semiquantitation using homologous regions of interest in opposite hemispheres. SPECT in the acute phase identified the final vascular territory affected in 19 of 27 patients. There were 8 patients in whom early SPECT predicted the vascular territory as seen on late CT scan when the early CT scan was normal. Hyperaemia or reperfusion in the involved vascular territiory was identified in 10 patients on scans performed during the sub-acute phase. Late SPECT scans showed perfusion defects greater than the infarct size seen on CT scan in the majority of patients. In all cases, the perfusion defect on the late SPECT scan was equal to or larger than the defect seen on the acute or sub-acute scan. Crossed cerebellar diaschisis was identified in 8 patients, and cortical/subcortical diaschisis in one patient. It is concluded that ^{99m}Tc-HMPAO in the acute phase is likely to be useful in predicting the topography of cerebral infarction earlier than CT scanning and may assist in the diagnosis of acute stroke. The changes of hyperaemia and reperfusion seen in the sub-acute phase may interfere with the interpretation of scans during this phase. The more extensive perfusion defect changes identifed in the chronic phase are believed to represent a persisiting ischaemic penumbra, or the changes of diaschisis.

Computerized tomography and magnetic resonance imaging provide structural localisation of infarcts in patients with ischaemic stroke. The role of functional

imaging in the diagnosis and management of patients with acute stroke is currently being evaluated. The potential value of this form of imaging lies in the early demonstration of affected vascular territories, in the demonstration of ischaemic and potentially salvagable tissue, in assessing the success of therapeutic interventions, and possibly in the early prediction of outcome after stroke.

We here describe our preliminary experience in examining the sequential changes that occur in cerebral perfusion in ischaemic stroke, using single photon emission computed tomography (SPECT) with ^{99m}technetium-hexamethylpropylene amine oxime.

PATIENTS AND METHODS

The period of this study was from June 1990 to March 1991. Patients were included in the study if they had the acute onset of a focal neurological deficit when the CT scan was normal, or showed cerebral infarction. Patients with cerebral haemorrhage, transient ischaemic attacks or pseudostrokes, and in whom informed consent could not be obtained, or the scan could not be performed because of the patient's medical condition, or because of technical difficulties, were excluded.

All patients underwent CT scanning on admission and between days 7 and 14. A detailed neurological assessment was performed on admission and the patients were reviewed daily. Routine investigations included biochemical and haematological tests and ECG. Patients also underwent appropriate investigations to determine the pathophysiology of their stroke, for example carotid duplex scanning, digital subtraction angiography, or echocardiography.

A SPECT scan was performed as early as possible after admission (preferably within 48 hours). In some cases, patients did not present for up to 10 days after the onset of their stroke, and in other cases, early imaging was delayed by acute medical problems. In the majority of instances follow-up scans were not performed on patients whose initial SPECT was normal. Also included in this study were several patients who had single scans only, 2 patients with internal watershed infarcts months earlier, and one patient with ill-defined subcortical ischaemia and ischaemic optic neuropathy. Four patients died, were lost to follow-up, or withdrew from the study, and therefore did not have late scans performed.

SPECT SCAN TECHNIQUE

All scans were performed in the Department of Nuclear Medicine at the Austin Hospital. Scans were performed within two hours of ^{99m}Tc-HMPAO injection using a rotating General Electric 400 AC Starcam camera. Sixty-four images were acquired over 360 degrees, with an acquisition time of 30 seconds per frame. Data were acquired on

a 128 x 128 matrix with a pixel size of 3.1mm. One pixel thick transverse slices were then created on a 64 x 64 matrix. The scans were interpreted by a neurologist and a nuclear medicine physician (not blinded). Image analysis was by visual inspection, and in certain cases by semi-quantitation, comparing homologous regions of interest.

RESULTS

Thirty-five patients were entered into the study. A total of 68 scans was performed. There were 20 male patients, and 15 female patients, with an age range of 33 to 80 years. The mean age of the patients was 64 years.

Subtypes of cerebral infarction studied

Middle cerebral artery territory infarcts were those most frequently studied (15 of 35 patients - Table 1). There were 4 lacunar and 2 anterior choroidal territory infarcts in the series. No cases of brainstem infarction were studied.

Table 1 Sites of infarction in patients studied

Artery territory		Number
Middle cerebral artery (MCA)		15
Total M.C.A. occlusion	2	
Superior division	6	
Inferior division	3	
Striatocapsular	4	
Anterior cerebral artery		2
Posterior cerebral artery		4
Thalamocapsular infarct		1
Anterior choroidal artery		2
Lacunes		4
Migrainous stroke		1
Internal watershed infarcts		4
Uncertain		2
Total		35

SPECT Scans Performed

There were 3 sub-groups of patients. The first sub-group includes 12 patients who were scanned in the acute (within 7 days), the sub-acute (8-21 days), and

the chronic (>1 month) phases. Three patients did not have late scans. One patient died, one patient was lost to follow-up and the other patient withdrew from the study. Twelve patients were included in the second sub-group. These patients underwent 2 scans, the first in the acute or sub-acute phase, and the second in the chronic phase. The third sub-group of 11 patients underwent a single scan only, performed in the acute, the sub-acute, or the chronic phase.

Acute phase (1-7 days)

Twenty-seven patients underwent SPECT scanning within the first 7 days of the onset of their strokes. The SPECT scan was abnormal in 20 of these patients, and predicted the final vascular territory involved (as determined by late CT topography) in 19 patients. Six of the remaining 8 patients had lesions which were beyond the resolution of the SPECT scan (3 patients had lacunar infarction, 2 patients had anterior choroidal artery infarction and one had migrainous infarction). All the abnormalities seen were those of hypoperfusion in the affected vascular territories. There were 12 patients in whom both the initial CT and SPECT were abnormal. In 10 of these patients, the perfusion defect on SPECT was more extensive than the CT topography. There were 8 patients in whom a perfusion defect was identified on the acute SPECT scan when the first CT scan was normal. In 7 of these patients SPECT identified the final vascular territory as determined by late CT topography. There were 2 patients in whom a lacunar stroke was identified on CT when SPECT was normal.

Sub-acute phase (8-21 days)

A total of 18 patients had a SPECT scan performed between days 8 to 21. In 4 of these patients, the SPECT was normal (1 patient with migraine, 2 with lacunes, and one unidentified stroke). Hypoperfusion was seen in 4 patients. Re-perfusion and hyperaemia were identified in 10 patients. Hyperaemia (defined as an increased cerebral blood flow when compared to the corresponding site in the opposite cerebral hemisphere, either by visual inspection or by semiquantitation) was identified in 6 patients, and evidence of re-perfusion in some or all of the affected vascular territory in 4 patients.

Chronic phase (> 1 month)

Twenty-three patients underwent scanning in the chronic phase. SPECT scanning was normal in 4 of these patients: in 3 patients, the first scan was normal, and a minor perfusion defect on the first scan was not present on the late scan in the other patient. In 17 of the remaining 19 patients, the perfusion defect on SPECT was more extensive than the final CT topography. The re-perfusion and/or hyperaemia seen in the sub-acute phase resolved in all patients. When comparing the changes on early SPECT with those on late SPECT (in the first

and second subgroups). The perfusion defect on late SPECT was equal to, or greater than the defect seen on early SPECT in all cases.

Remote effects

Hypometabolism in the contralateral cerebellar hemisphere was identified in 8 patients, which was interpreted as representing crossed cerebellar diaschisis, as described by Feeney and Baron[1]. In one patient with a thalamocapsular infarct, marked cortical hypometabolism was demonstrated throughout the entire cerebral hemisphere. This was interpreted as representing cortical-subcortical diaschisis[2].

DISCUSSION

The role of SPECT in the investigation and mangement of patients with ischaemic stroke is currently under evaluation, and is attracting much interest[3,4,5]. In this preliminary study, we found that SPECT in the acute phase (less than 7 days) may aid in the diagnosis of stroke, especially in the first 48 hours when CT is often normal, or shows partial changes in the affected vascular territory. Hayman[6] studied 17 patients with ^{123}IMP SPECT during the first 72 hours of stroke and found SPECT to be superior to CT in the first 48 hours, and equivalent to CT between 2 and 5 days in detecting cerebrovascular disease. In our study the SPECT scan was a fairly sensitive predictor of the final vascular territory affected during this time (except in the cases of lacunar stroke and anterior choroidal artery infarction). Early knowledge of the affected vascular territory may assist in the prediction of the pathophsiology of the infarct. This may direct the subsequent investigations performed and help determine therapeutic interventions.

During the sub-acute phase (days 8 to 21) re-perfusion and/or hyperaemia in and around the affected vascular territory was seen in some patients. This has been seen previously with positron emission tomography (PET)[7], ^{133}Xe[8] and with ^{99m}Tc-HMPAO SPECT[9], but not with 123IMP SPECT[10]. The mechanism of the hyperaemia during this period is unclear, although it probably represents re-perfusion through a previously occluded vessel, with disordered cerebral autoregulation leading to vasodilatation. PET studies have shown uncoupling of blood flow and metabolism (high blood volume and blood flow, low metabolic rate and oxygen extraction)[7]. Hyperaemia was not seen in the acute or chronic phase in any patients, although has been seen in the first 72 hours in other studies using ^{133}Xe[8] and ^{99m}Tc-HMPAO[9]. More studies are needed to determine the time sequence, and clinical significance of this phenomenon. The presence

of re-perfusion and/or hyperaemia during the sub-acute phase may provide misleading information concerning the extent of the affected vascular territory.

During the chronic phase, the perfusion defect was found to be more extensive than the final CT topography in the majority of cases, which may represent ischaemia and/or hypoperfusion around the cerebral infarct, or the presence of diaschisis[11]. It should be noted, however, that chronic ischaemia has not been demonstrated in similar clinical situations using PET techniques. This may suggest that diaschisis plays the more prominent role.

Thus, a potential role exists for SPECT scanning in the acute phase of stroke (especially within the first 72 hours), when it can aid in the diagnosis of stroke, and identify the affected vascular territory. More studies are needed to identify the sequential changes and the significance of hyperaemia, which may complicate the interpretation of scans during the sub-acute phase. This form of scanning has a potential role in studying patients in the recovery phase of stroke, and in assessing the success of therapeutic interventions.

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MECHANISMS AND CLINICAL FEATURES OF INTERNAL WATERSHED INFARCTION

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SUMMARY

The mechanism of internal carotid watershed cerebral infarction is not well understood, but the phenomenon has been described in association with carotid occlusive disease, and more recently with distal middle cerebral artery occusion beyond the origin of the lenticulostriate branches. The clinical correlates of these changes have not yet been described.

We present 5 patients in whom acute internal watershed infarction had occurred, and correlate the clinical, neuropsychological and ^{99m}Tc-HMPAO SPECT (Single Photon Emission Computed Tomography using ^{99m}technetium-hexamethylpropylene amine oxime) cerebral perfusion findings. Four patients had distal middle cerebral artery occlusion demonstrated on angiography, and one showed profound hemispheric depression in cerebral perfusion with only a small area of infarction.

We have concentrated on the mechanism of distal middle cerebral artery occlusion to describe the "arc" of the watershed zone created. We propose that internal watershed infarcts can further be subdivied into anterior and posterior subtypes, outline the vascular territories involved, and propose an overall classification of cerebral watershed infarction.

Watershed infarcts occur along the borderzone between two main cerebral arterial territories. In the cerebral circulation, 3 types of unilateral watershed infarcts are recognised, viz. (i) anterior watershed, (ii) posterior watershed, and (iii) internal or subcortical watershed infarction[1].

The present paper is concerned with internal watershed ischaemia, which accounts for up to 18% of anterior cerebral circulation watershed infarctions[2,3].

The mechanism of this subtype of infarction is not well understood, although the phenomenon has been described in relation to internal carotid occlusive disease in the majority of cases[4]. More recently[3,5], it has been described in association with distal middle cerebral artery occlusion, beyond the origin of the lenticulostriate branches. The clinical correlates of these changes have not yet been described.

We here describe 5 patients with internal watershed infarction, 4 of whom had middle cerebral artery occlusion demonstrated on angiography. The clinical features (including the neuropsychological assessment) are briefly presented, along with computerized tomography (CT), digital subtraction angiography and, in 3 cases, cerebral perfusion studies using ^{99m}Tc-HMPAO SPECT (Single Photon Emission Computed Tomography using ^{99m}technetium-hexamethylpropylene amine oxime). We have concentrated on the mechanism of middle cerebral artery occlusion to further subdivide this category of cerebral infarction and outline the vascular territories involved.

PATIENTS AND METHODS

Five patients with unilateral internal watershed infarction were selected from the Austin Hospital Stroke Register[6], 4 of whom had distal middle cerebral artery occlusion demonstrated on digital subtraction angiography. All patients underwent CT scanning on admission and between days 7 and 14. CT criteria for internal watershed ischaemia are as described by Demasio[7] and Wodarz[1]. All patients underwent digital subtraction angiography, and 3 underwent late SPECT cerebral perfusion studies. Neuropsychological and speech therapy assessments were performed on 4 patients. The late outcome is described in all patients, ranging between 6 months to 7 years. Electroencephalography (EEG) was performed in 2 patients.

PATIENT DETAILS

Case 1

A 47 year old man had the cerebrovascular risk factors of hypertension and smoking. He also had classical migraine. He described the progressive onset over 24 hours of right tongue and hand paresthesiae, followed by right hemiparesis, right hemianaesthesia to all modalities, expressive and receptive dysphasia, and right-sided neglect. CT on day 1 was normal and when repeated on day 8 showed total internal watershed infarction. Digital subtraction angiography showed middle cerebral artery occlusion at the bifurcation, with preservation of the early temporal branch, which arose proximal to the occlusion. Collateral circulation was demonstrated between the anterior and posterior cerebral arteries. Single photon emission tomographic scanning (SPECT) at 2 years post-infarction showed global hypoperfusion over the territory of the left middle cerebral artery. This

patient gradually improved over the next 6 months. At this time, he had persisting word-finding difficulty and right-sided weakness - face 4/5, arm 3/5, leg 4/5.

Case 2

A 54 year old woman had a past history of hypertension and smoking. She presented with 2 episodes of fluent dysphasia and right facial weakness. The first episode lasted for 2 hours, followed several hours later by the second episode. CT on day 1 was normal, and on day 8 revealed anterior internal watershed infarction. Digital subtraction angiography revealed occlusion of the middle cerebral artery beyond the lenticulostriate branches. Collateral circulation was demonstrated over the cortical middle cerebral arterial territory. When reviewed at 12 months, the patient showed mild disinhibition and cognitive inflexibility, but she had a good recovery of speech and no facial weakness.

Case 3

A 75 year old man had a past history of hypertension, smoking, peripheral vascular disease and ischaemic heart disease. He presented with fluent dysphasia (moderate receptive and nominal deficit), which had evolved slowly over 2 weeks. CT scan showed a localised corona radiata infarct on the left side. Digital subtration angiography revealed an occluded mid-portion of the left middle cerebral artery beyond the lenticulostriate branches. A high-grade right internal carotid stenosis and an occluded right subclavian artery were also present. SPECT scanning revealed some minor ischaemic changes in the territory of the left inferior division of the middle cerebral artery. The patient gradually improved over the next 6 months, with almost complete resolution of his deficit. At 2 years post ictus he had occasional word-finding difficulty and a nominal deficit.

Case 4

A 31 year old woman was 8 weeks pregnant and had a past history of hypertension, smoking and classical migraine. She presented with the acute onset of expressive and receptive dysphasia with right face, arm, and leg weakness. CT showed an anterior internal watershed infarct. Digital subtration angiography revealed middle cerebral artery occlusion at the bifurcation into the 2 terminal branches. She made a steady improvement over the next 6 months. She had several seizures toward the end of her pregnancy and required anticonvulsant medication. She had persisting right-sided weakness but was able to walk unaided. She also had a residual expressive deficit, but good comprehension.

Case 5

A 55 year old man had a history of non-insulin dependent diabetes mellitus, hypertension, smoking, obesity, and a transient ischaemic attack 2 years earlier (details not clear). He presented with malaise and nausea, then left leg, followed by left arm and facial weakness developing over 24 hours. This was associated with decreased sensation to light touch on the left, left sensory and visual neglect, and a left homonymous hemianopia with macular sparing. CT on day 1 showed a small infarct in the posterior corona radiata, and on day 9 a posterior internal watershed infarct. Digital subtraction

angiography was performed on day 13 and revealed only minor atheromatous disease at the origins of both internal carotid arteries. SPECT scans were performed on days 1, 16 and 58 and revealed posterior parieto-occiptial ischaemia. This was more extensive in the early and late studies with some improved flow to the cortex on the subacute scan, suggesting an element of re-perfusion. Depression of perfusion to the basal ganglia was also noted, especially on the subacute and late scans. On review at 6 months, he had a residual left hemiparesis (3/5), with a persisting left hemianopia.

DISCUSSION

The results presented above reaffirm the mechanism of distal middle cerebral artery occlusion leading to internal watershed ischaemia, as previously described[3,5]. The clinical features and outcomes in our patients are presented briefly, with 4 of our 5 patients demonstrating dysphasia and neuropsychological deficits in spite of the subcortical locations of the infarcts.

One patient had infarction in the complete internal watershed zone, 3 in the anterior internal watershed zone, and the 5th in the posterior watershed borderzone. From the results of CT topography, the type of middle cerebral occusion seen on digital subtraction angiography, and the perfusion defects seen on SPECT scan, we can hypothesize possible mechanisms for internal watershed ischaemia and outline a proposed classification of watershed infarcts (Table 1).

Table 1 Proposed classification of watershed infarcts

1.	Anterior external watershed infarcts
2.	Total internal watershed infarcts (confluent)[8] - anterior internal watershed - posterior internal watershed
3.	Partial internal watershed infarcts (single perforators)[8] - anterior partial internal watershed - posterior partial internal watershed
4.	Posterior external watershed infarcts

Total internal watershed infarct

Complete infarction in the internal borderzone results from occlusion of the middle cerebral artery, beyond the lenticulostriate branches, and proximal to the 2 terminal divisions. Collateral circulation from the anterior cerebral and posterior cerebral arteries supplies the majority of the territory of the occluded superior and inferior divisional branches. Infarction is then restricted to the subcortical white matter, normally supplied by both the terminal branches of the lenticulostriate vessels and the medullary branches of the 2 terminal divisions.

Anterior internal watershed infarct

The anterior internal watershed infarct resulted from occlusion of the middle cerebral arterial trunk. We postulate that collateral circulation from the posterior cerebral artery supplied the territory of the occluded inferior division, with incomplete collateral circulation over the territory of the occluded superior division.

Posterior internal watershed infarct

Posterior internal watershed infarction may result from occlusion of the inferior division of the middle cerebral artery, with the extent of ischaemia being dependent on the collateral circulation between the posterior cerebral artery, the superior division of the middle cerebral artery and the anterior choroidal and lenticulostriate arteries.

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REGIONAL CEREBRAL BLOOD FLOW AND RECOGNITION MEMORY IN ELDERLY NORMALS: POTENTIAL APPLICATION TO ALZHEIMER'S DISEASE

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SUMMARY

Regional cerebral blood flow, a physiological measure of brain function, has been used for the assessment of cognitive dysfunction in Alzheimer's disease.

A number of studies have found diminished temporo-parietal regional cerebral blood flow (RCBF) in Alzheimer's disease patients at rest and have differentiated these patients from normal subjects with a high degree of sensitivity. However the majority of the Alzheimer's disease patients have been in the moderate to severe stages of the disorder. Few studies have assessed RCBF in the early stages of Alzheimer's disease. With increasing emphasis now being placed on the early detection of such patients we chose to examine RCBF during a task which made demands on those cognitive processes which are impaired in the early stages of the disease, *viz.* a recognition - memory task. Using a 32-channel RCBF system, we examined 20 normal control subjects over the age of 60 years and 10 patients with early to moderate Alzheimer's disease. RCBF was examined during a task of recognition - memory, and also at rest. Normal subjects showed a global increase in RCBF, with marked left frontal activation, as compared with when at rest. Resting perfusion was decreased in the Alzheimer's subject, and there appeared to be a greater degree of intersubject variability in flow during activation.

No reliable test is available to diagnose Alzheimer's disease during life, so that a definitive diagnosis can be made only on post-mortem examination. Clinicians must rely on a constellation of clinical features, neuropsychometry and tests of exclusion to arrive at a diagnosis of "probable" Alzheimer's disease[1].

Lack of an objective diagnostic test may partly reflect our inadequate knowledge of the underlying nature and mechanism of the brain dysfunction in Alzheimer's disease. It has been well established that physiological changes antedate the symptomatology of Alzheimer's disease[2]. It therefore seems logical to study the physiological changes in brain function underlying this disease at their earliest possible stage. In addition to elucidating the pathophysiology of Alzheimer's disease, this might lead to the development of a reliable diagnostic test for the disorder. Distinguishing the early stages of Alzheimer's disease from other diseases such as depressive pseudo-dementia can be difficult and the misdiagnosis rate is high[3]. This has significant implications for the treatment of these disorders, since the latter disorder is amenable to antidepressant therapy whereas such therapy may exacerbate cognitive slowing if administered to patients with Alzheimer's disease[4]. Although no drug therapy has been of proven benefit in Alzheimer's disease this situation may well change in the future, in which case an objective means of assessing the response to treatment would be necessary. In this regard, the ability to diagnose the disorder (and potentially to intervene) before neuronal death has occurred, would be essential. Finally, the development of a reliable test to aid in clinical diagnosis may help differentiate the various sub-types of disorder that are thought to comprise Alzheimer's disease[5].

Several techniques with varying combinations of capacities for spatial and temporal resolution have been applied to the study of the brain in Alzheimer's disease. Electroencephalograms assess temporal changes in electrical activity and have demonstrated an increase in slow-wave activity (particularly theta frequency), while a delayed processing time of discrete stimuli has been found in long latency event-related potential components[6]. Radio-isotope based techniques such as regional cerebral blood flow (RCBF), single photon emission computed tomography (SPECT) and positron emission tomography (PET) have revealed diminished cerebral blood flow and metabolic activity, particularly in the temporo-parietal regions[7]. The technique for measuring RCBF is based on a well-researched and proven mathematical model and is a reliable and quantifiable method for the measurement of cortical perfusion. Although the spatial resolution in PET (6-8mm) is superior to that in RCBF (20-30mm), the ability to distinguish gray from white matter blood flow is superior in the latter[8]. Furthermore, RCBF is cheaper than PET scanning. These factors have ensured an ongoing role for RCBF measurement, despite the emergence of the newer techniques of emission computed tomography.

Although most studies of RCBF have examined brain function at rest, there is evidence to suggest that there is more variability in RCBF at rest than during

a specific activation task[9]. Brain activity at rest does not reflect subtle changes in higher centre functions such as memory, which are associated with the early stages of Alzheimer's disease. To our knowledge, only one study of RCBF during a memory-activation task has been undertaken in Alzheimer's disease. This study compared RCBF in Alzheimer's disease cases and age-matched elderly normals at rest and during a test of Word Pair Learning and Recall (before and after treatment with pyritinol). Alzheimer patients showed a significantly greater number of regions activated during the activation task, although the performance of the Alzheimer patients was significantly poorer than the controls[10].

The aim of the present study was to examine brain dysfunction using RCBF measurement in patients with mild Alzheimer's disease compared with age-matched controls at rest and during a recognition memory test. Previous research, including work from the authors' own group[11], has demonstrated that patients in the early stages of Alzheimer's disease may show a decrease in RCBF at rest. It was anticipated that patients with Alzheimer's disease would show a greater and more regionally specific decrease in RCBF during a memory recognition task than controls, since the activation task would place a processing load on the dysfunctional memory-related neuronal networks in Alzheimer's disease. We anticipated that these changes would be most evident in the temporo-parietal regions at rest and, in accordance with models of recognition-memory[12], greater in the fronto-temporal regions during recognition-memory, compared to age-matched controls.

METHODS

All subjects underwent screening to exclude any significant medical, neurological or psychiatric history, particularly a history of respiratory disease or of drug or alcohol abuse. Handedness was assessed in each subject using the Edinburgh Laterality Questionnaire. All subjects were right-handed. All subjects were required to give informed consent.

Twenty normal volunteers aged 60 years or over (mean age = 70.1 years) were recruited from the community. These subjects fulfilled the following criteria: (i) a score in the "nil depression" range of the Zung Depression Inventory[13]; (ii) a score of 26 or greater on the Folstein Mini-Mental State Examination (MMSE) for screening of cognitive function[14]. Ten patients in the early stages of Alzheimer's disease were recruited from a community referral base. The patients were assessed by a neurologist and a psychiatrist and fulfilled the NINCDS-ADRDA criteria for "probable" (n=5) or "possible" (n=5) Alzheimer's disease[1]. Patients were graded as mild using CDR criteria[15]. Patients did not

fulfil the DSMIII-R criteria for depression[16] and scored less than 7 on the Hachinski Ischaemia Scale[17]. A neuropsychologist assessed the extent of cognitive decline in each patient, using a comprehensive neuropsychological battery. Each patient underwent investigation, including a cerebral CT scan, for other possible causes of dementia. Where possible, a history was also obtained from a family member or associate of the patient.

RCBF was measured using the Xenon-133 intravenous technique. A 32 channel cerebrograph monitored the uptake and clearance of the Xenon-133. Surface markings for positioning of the detectors were the external auditory meatus and the nasion. A template was used to ensure accurate positioning. A 30 second background count was taken prior to the first measurement of RCBF. A 5 minute remaining activity count was taken prior to the second measurement of RCBF. Each participant underwent 2 measurements of RCBF: (i) during a resting baseline condition, and (ii) during a task of recognition memory. The Initial Slope Index (ISI) was the chosen index of perfusion, as it is the most reliable parameter for the measurement of RCBF in pathological conditions where the blood-brain barrier may be disturbed and the partition coefficient for Xenon-133 is not known. ISI values were corrected to pCO_2 (40mm Hg). An initial 5 minute "dummy-run" was undertaken to acclimatise each subject to the experimental situation. Conditions were equivalent to those at rest, except that cold saline was administered instead of Xenon-133.

The memory task consisted of the recognition of 36 pre-learned target words randomly intermixed with 89 distractor words of equal frequency. A button press response (with the middle finger of each hand) was required when the subject recognised a target word. A separate comparative measure of RCBF was also undertaken while the subjects were at rest with their eyes closed.

RESULTS

In the normal group there was a global increase in perfusion during the memory activation task, as compared with when at rest. Perfusion was greatest in the left frontal region during the recognition memory task (Fig 1).

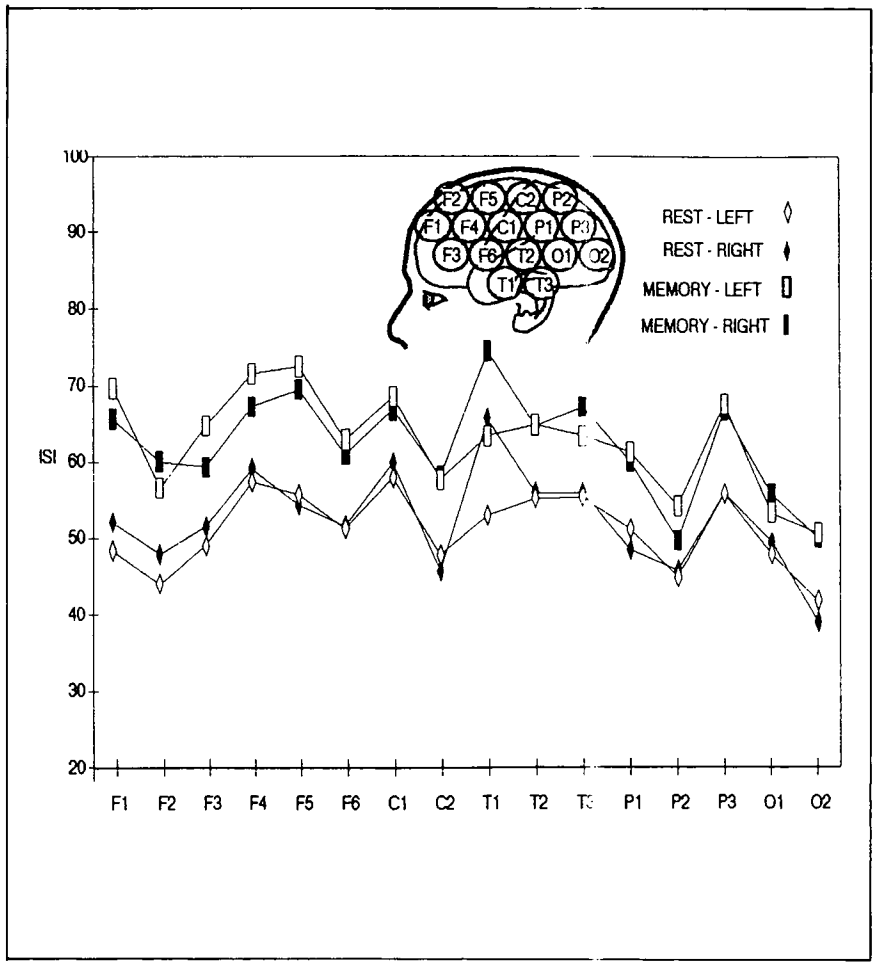

Fig 1 The hemispheric distribution of RCB in 20 elderly normals at rest and during a visual recognition task

The patients with mild Alzheimer's disease demonstrated a global reduction in perfusion at rest, compared with normals (Fig 2).

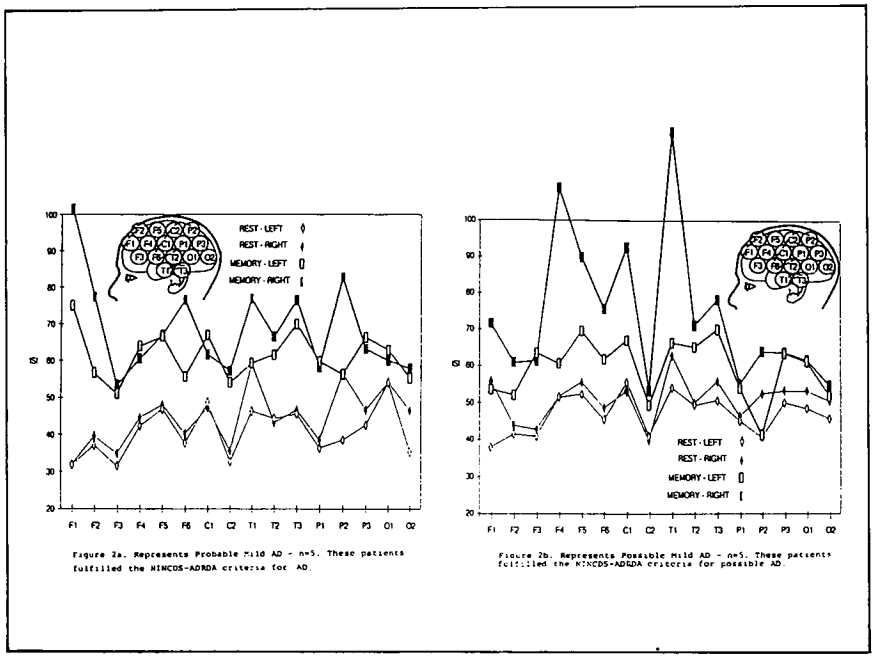

Fig 2 Hemispheric ISI distribution during a visual recognition memory task and resting baseline condition in mild Alzheimer's disease. RCBF at rest is lower than control subjects. Activation is comparable in both patient groups on the average, with both showing larger hemispheric differences than controls.

In these patients preliminary assessment showed a greater hemispheric variability between individuals in RCBF during activation, as compared with the normal controls. Example of 2 Alzheimer's disease patients are shown in Figs 3 and 4.

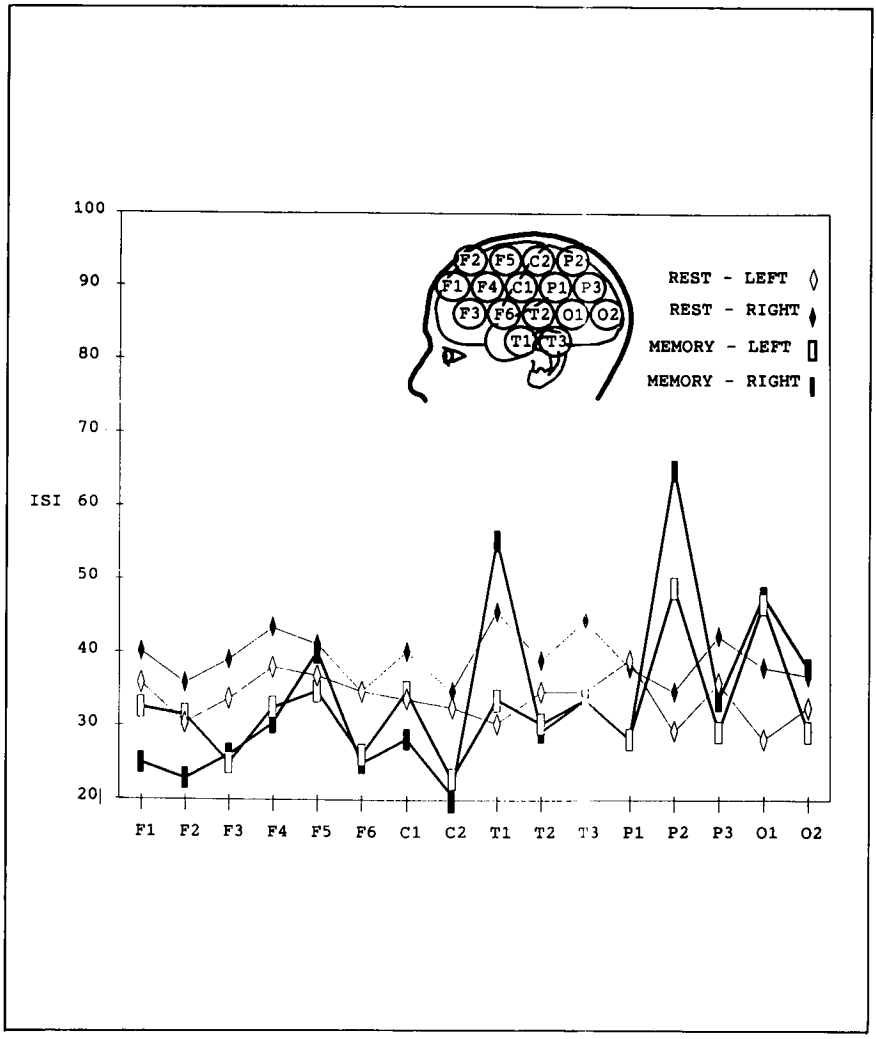

Fig 3 Male, 71 yrs. Neuropsychometric examination revealed impoverished processing of recent memory and difficulty learning novel information. These results were considered in reference to the subject's deterioration of personality and intellect and are consistent with the diagnosis of Alzheimer's dementia. Psychiatric examination found no evidence of depression. Neurological assessment concluded the patient was in the mild stages of Alzheimer's dementia.

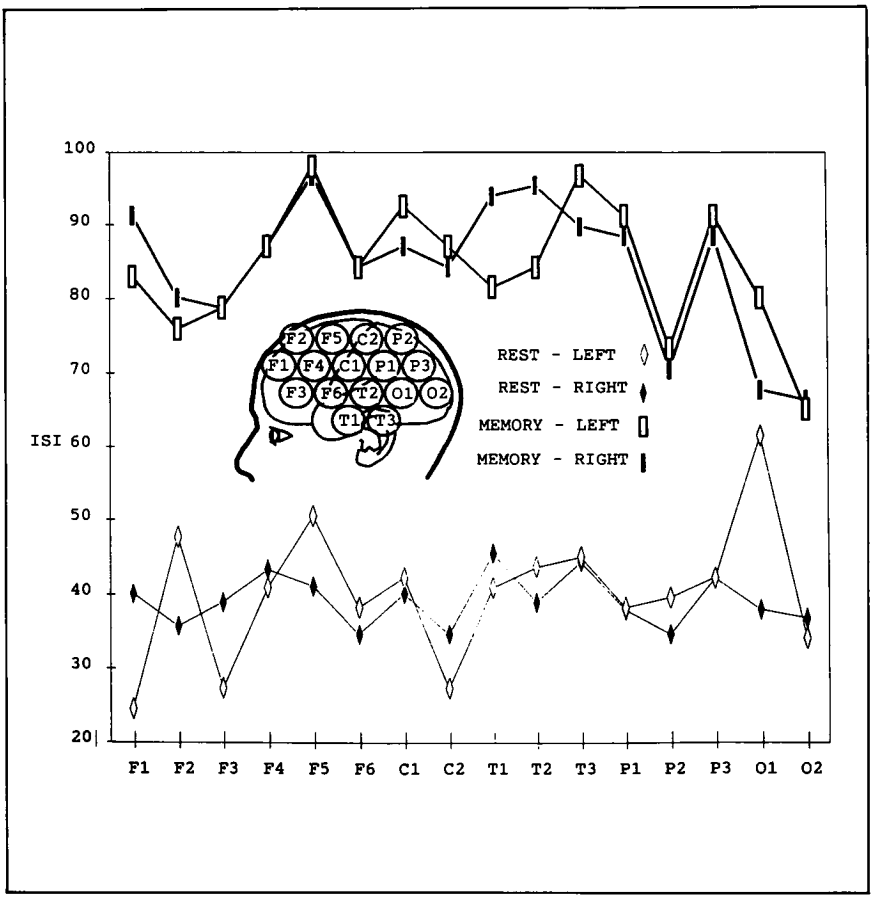

Fig 4 Female, 76 yrs. Neuropsychometric examination revealed impairment of functions mediated by the frontal lobes. CT investigation showed the brain structure was normal for age. Psychiatric assessment showed no evidence of depression. Neurological examination concluded the patient had mild Alzheimer's dementia.

The RCBF during the activation task in the group with early dementia was asymmetrical, with a reduced flow in the left hemisphere. However, no consistent topographical pattern within the hemispheres could be demonstrated. Table 1 sets out the mean RCBF in the 2 groups at rest and during the memory-activation task.

Table 1 Mean RCBF (left and right hemisphere) for normals, Alzheimer's disease "probable" and Alzheimer's disease "possible" subjects during a memory activation task

	NORMALS n = 20	AD "prob" n = 5	AD "poss" n = 5
Activation ISI			
Left	61.4 (15.4)	58.2 (21.6)	58.9 (9.7)
Right	62.0 (15.1)	64.6 (22.9)	74.3 (16.1)
Rest ISI			
Left	50.1 (9.1)	40.8 (8.1)	45.9 (12.6)
Right	52.2 (11.0)	44.7 (6.9)	51.0 (13.1)

DISCUSSION

The findings in the normal controls showed a consistent increase in RCBF during the memory activation task, with increases in the flow in the left frontal and right parietal regions, as compared with the resting function. Although relatively few in number, the data from patients with early Alzheimer's disease demonstrated a diminished RCBF at rest compared with the normal controls: this is similar to the findings in the moderate-severe stages of the disease[16]. The preliminary findings in the patient group during memory-activation suggest a failure to activate in the left hemisphere. There was more variability in RCBF in the early dementia group than in age-matched controls. This greater variability may reflect the heterogeneity of Alzheimer's disease and consideration of individual data obtained both at rest and during memory activation is therefore essential in attempting to define a pattern of RCBF in this patient group. For example, one patient, a 72 year old male with a mild global impairment on neuropsychometric testing, showed relatively little change in RCBF between rest and memory-activation (Fig 1). In contrast a 79 year old female with predominantly frontal changes on neuropsychometric testing demonstrated a marked increase in RCBF during the activation task (Fig 2). Detailed analysis will be undertaken subsequently to examine each individual patient's RCBF in relation to his or her clinical symptomatology and neuropsychometric profiles. At this stage it seems possible that the activation task may provide additional information to that derived from RCBF at rest. Further longitudinal analysis in an increased number of patients with early dementia will help to determine the nature and value of this information.

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COLOUR DUPLEX FLOW IMAGING IN CAROTID ARTERIAL DISEASE: CORRELATION WITH INTRA-ARTERIAL DIGITAL ANGIOGRAPHY

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SUMMARY

Colour duplex flow imaging is a highly accurate form of non-invasive assessment of the extra-cranial carotid circulation. This method is precise in characterising the degree of carotid stenosis, when compared with intra-arterial digital subtraction angiography. The accuracy of colour duplex in defining mild (1-30%), moderate (31-70%) and severe (71-99%) stenosis was 96%, 95% and 98%, respectively. Sensitivities and specificities were greater than 90% in each category, while positive and negative predictive values ranged from 96% to 100%.

The addition of colour flow imaging to conventional carotid duplex ultrasound represents a significant advance in non-invasive testing. It constitutes a powerful investigation for the diagnosis and physiological assessment of extra-cranial cerebrovascular disease. The technique is becoming a new 'gold-standard', comparable with angiography.

In the study here reported, the accuracy of colour Doppler was evaluated in relation to intra-arterial digital subtraction angiography (DSA) of carotid vessels.

METHODS

Patients undergoing evaluation for symptomatic carotid arterial disease were assessed with colour doppler flow imaging and, if clinically indicated, intra-arterial DSA. The clinical presentations were either carotid territory transient ischaemic attacks (TIA), completed stroke or amaurosis fugax.

Non-invasive testing was performed on an Acuson 128 instrument. The carotid vessels were scanned longitudinally with both anterolateral and posterolateral probe positions being used to obtain optimum images. Transverse images of the external and internal carotid vessels were also obtained. Pulsed doppler - frequency spectra were recorded from the proximal internal carotid arteries and from the flow stream above and below any area of suspected stenosis.

The criteria used in doppler spectrum analysis of diameter stenosis are set down in Table 1.

Table 1 Pulsed Doppler spectrum analysis related to internal carotid stenosis

Degree of stenosis	Peak systolic velocity
Mild (1-30%)	<110 cm/sec
Moderate (31-70%)	110-200 cm/sec
Severe (71-99%)	>200 cm/sec (peak diastolic >100 cm/sec)

Biplanar DSA of carotid arteries was performed following intra-arterial injection of contrast. The degree of stenosis of promixal internal carotid arteries was assessed by a neuroradiologist who was blinded to the non-invasive test results.

RESULTS

Sixty carotid vessels from 30 patients were studied with both procedures. Overall, 57 studies (95%) were in perfect agreement. Three occlusions were correctly characterised by both colour Doppler and DSA, while there were no psuedo-occlusions in the series. Both studies identified 15 normal vessels.

Table 2 records the accuracy of colour duplex in the 3 grades of stenosis determined by DSA.

Table 2 Accuracy of colour Doppler in relation to DSA

Degree of stenosis	Negative		Positive				Predictive value		
	True	False	True	False	Sensitivity	Specificity	Positive	Negative	Accuracy
Mild (1-30%)	44	1	14	1	93%	96%	93%	96%	96%
Moderate (31-70%)	40	1	17	2	94%	95%	90%	97%	95%
Severe (71-99%)	48	1	11	0	92%	100%	100%	98%	98%

DISCUSSION

Approximately 10% of strokes are preceded by transient ischaemic attacks[1]. If a patient suffers a TIA and has a severe carotid stenosis (defined as a greater than 70% luminal narrowing), carotid endarterectomy has been shown to reduce the risk of subsequent stroke[2]. Thus accurately identifying symptomatic patients with severe carotid stenosis is important. The ideal test would have no associated risk and would have 100% sensitivity and specificity. Intra-arterial angiography has previously been the gold-standard for defining such vascular lesions, but it is not without risk. The reported risk of stroke in this situation has varied widely, ranging from 12% to 1.3%, but it is never insignificant, and carotid surgery carries its own risk[3]. In addition, angiography provides little information about the arterial wall and may fail to detect the small but important blood flow which may occur through a near occlusion.

B mode ultrasonography allows visualisation of the arterial wall and lumen: when combined with continuous-wave Doppler ultrasound, it provides a measurement of luminal narrowing. The addition of colour-flow imaging facilitates tracking of the carotid arteries, thus enhancing the accuracy of the study[4]. Low-velocity flow is more readily detected, allowing better differentiation between high grade stenosis and actual occlusion. Colour also enables more accurate velocity measurements, by identifying the axis of flow[5].

In the present study, colour-flow Doppler imaging compared well with angiography, obtaining a positive predictive value of 100% for the clinically important category of severe carotid stenosis. Moreover, the negative predictive value was acceptable at 98%, with only one case being miscategorised. Sensitivity and specificity were high for the recognition of all categories of stenosis, with specificity attaining 100% for the severe stenosis subgroup. Colour-flow Doppler imaging appears to be an accurate tool for evaluating carotid artery stenosis, and is comparable to intra-arterial digital subtraction angiography.

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PATTERN OF MEMORY DEFICITS IN A CONTROLLED PSYCHOMETRIC STUDY OF THALAMIC HAEMORRHAGE

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SUMMARY

Twelve patients with unilateral thalamic haemorrhages were assessed psychometrically. The results were compared with control subjects matched for sex, age and years of education. The pattern of deficits and preserved abilities cannot be explained in terms of semantic/episodic distinction, but could be interpreted as manifestations of disconnection between the frontal and temporal systems.

The thalamus has been considered one of the sites responsible for amnesia in the Wernicke-Korsakoff syndrome[1,2]. Some authors have argued that thalamic lesions can be associated with amnesia in the absence of concurrent disease of the mammillary bodies[3].

In a report of a stab wound to the brain, it was argued that the patient suffered from anterograde amnesia, especially for verbal material, as the result of dysfunction of the left thalamus[4]. Though rather extensive assessment was carried out, the role of the thalamus remained inconclusive because the fencing foil involved also traversed both the cortex and the sub-cortex. Another case of profound anterograde memory impairment for verbal material was associated with a small infarct in the left dorso-medial nucleus of the thalamus, but the patient also had a history of mental illness[5]. Anterograde amnesia for both verbal and non-verbal material was also reported in a patient with bilateral thalamic lesions[6].

The concept of a memory circuit has been proposed, linking the hippocampal formation, mammillary bodies and certain thalamic nuclei into a pathway

necessary for normal memory functioning[7], with a possibly different functional emphasis for specific areas[8]. However, others have argued that a specific site need not represent a discrete functional entity[9]. Some have considered that diencephalic amnesia is a disconnection syndrome between the frontal and the temporal lobes[10]. In the light of these arguments, the investigation of the effect of thalamic lesions could provide relevant information. In fact, there have been attempts to examine the memory functioning of patients with thalamic haemorrhages[11,12,13,14].

In particular, detailed psychometric assessment was carried out on a female patient with a predominantly right thalamic haemorrhage[13]. Anterograde amnesia for both verbal and visual material was prominent and persisted over the 3-year follow-up period, despite full orientation and good concentration. Four patients with bilateral thalamic infarctions were found to develop deficits in anterograde verbal and visual learning and retrograde amnesia, but motor learning was preserved[15]. The pattern of preserved learning abilities was described in a severely amnesic patient after bilateral thalamic infarction[16]. However, no controlled psychometric group study on unilateral thalamic lesions has been conducted so far. The present controlled study was therefore undertaken to delineate possible cognitive deficits in unilateral thalamic haemorrhage.

SUBJECTS AND METHODS

SUBJECTS

Patients with an episode of acute stroke due to unilateral thalamic haemorrhage were selected, confirmation of the diagnosis by computed tomography (CT) being obtained in all cases. Those with additional lesions on CT were excluded. Twelve patients were recruited. The clinical and CT features of these patients are summarized in Table 1.

The control subjects were volunteers from a Senior Citizens' Club. They were matched for sex, age and education with the patients. Those with stroke, vascular disease, neurological disorders or alcoholism were excluded. The age and education level of the patient and control groups (Table 2) did not show significant intergroup differences. All patients and control subjects were right-handed.

Table 1 Clinical and CT features of patients

Case	Sex	Age (yrs)	Side of lesion	Site of lesion	Size of haematoma (mm^3)	Size of haematoma & oedema (mm^3)	Mass effect	Intra-ventricular bleeding	Time of psychometry (months)*	CBRS
1	M	65	R	H	9.9	34.8	++	-	21	C
2	M	61	R	H	13.4	24.0	+	+	17	C
3	M	57	R	H+Lo	12.2	18.9	+	+	26	A
4	M	46	R	H+Lo	4.3	13.1	+	-	12	A
5	M	66	L	H+Lo	5.0	10.3	+	-	13	A
6	M	67	R	H+Lo	4.8	11.7	+	-	23	A
7	M	59	L	H	1.8	13.6	+	-	29	A
8	F	62	R	H+Lo	6.7	16.4	+	-	12	C
9	F	58	R	Lo	7.5	15.3	+	+	21	C
10	F	65	L	H+Lo	7.5	15.3	+	+	18	A
11	F	64	L	H+Lo	1.4	1.6	+	+	67	C
12	F	57	L	H	4.3	18.4	+	-	41	C

A = independent self-care with no marked behavioural impairment; C = medium dependency with moderate impairment; CBRS = Clifton Behavioural Rating Scale; F = female; H = high thalamic; L = left thalamic; Lo = low thalamic; M = male; R = right thalamic; + = present; ++ = marked; - = absent; * since acute stroke

Table 2 Subject characteristics - sex, age and education

		Patient Group	Control Group
Sex Ratio Males:Females		7:5	7:5
Age (years)	Mean	60.6	63.0
	Range	46-67	56-69
	SD	5.8	4.4
Education (years)	Mean	2.7	4.5
	Range	0-9	0-9
	SD	3.3	3.8

PSYCHOMETRIC METHODS

The Clifton Behavioural Rating Scale (CBRS)[17] was administered to obtain an estimation of the patient's overall adjustment to daily life including self-help, locomotion, socialization, communication and occupation. The scores obtained can be converted into grades, representing different levels of disability and dependency.

For the assessment of cognitive abilities, the following instruments were chosen because when taken together, they provided qualitative and quantitive information regarding the subject's ability in relation to attention, verbal reasoning, spatial reasoning and verbal and non-verbal material:

(i) the Wechsler Adult Intelligence Scale (WAIS): Comprehension, Similarities, Picture Completion and Block Design[18]

(ii) the Wechsler Memory Scale (WMS): Information, Orientation, Mental Control, Passage Immediate Recall, Passage 5-minute Delayed Recall, Digits Forward, Digits Backward, Associate Learning and Visual Reproduction[19]

STATISTICAL METHODS

To determine whether there were significant differences in terms of test performance between the patient and the control groups, analysis of covariance (ANOCOVA) was employed. The effect of the thalamic lesion in the test scores was assessed after the effect of the covariate of the number of years of education was partialled out. Furthermore, the group difference in the test scores between patients with right and left thalamic lesions was evaluated with a 't' test. Raw scores were used in all analyses. The significance level was set at $p = 0.01$.

RESULTS

The means and standard deviations of the dependent measures for patients and controls are summarized in Table 3. ANOCOVA applied to the data showed that the patients obtained significantly lower scores on a number of tests than the controls. On the WAIS, patients performed significantly worse on the Block Design [$F(2,22) = 16.15$, $p<0.01$]. On the WMS, patients were markedly less proficient on the Immediate Passage Recall [$F(2,22) = 16.28$, $p<0.01$] and also on the Delayed Passage Recall [$F(2,22) = 21.79$, $p<0.01$]. Performance on the other tests, however, did not differentiate the 2 groups in the present study. Furthermore, no significant differences were found between the 7 patients with right-sided and the 5 with left-sided lesions. Thus, the results offered little support for functional asymmetry at thalamic level.

Table 3 The dependent measures in patients and control subjects

	Patient Group		Control Group	
	Mean	Standard deviation	Mean	Standard deviation
WAIS				
Comprehension	11.4	4.1	13.2	3.8
Similarities	5.3	5.7	4.3	3.2
Picture completion	5.8	4.0	5.2	2.2
Block design*	18.1	7.1	25.6	4.0
WMS				
Information	4.4	1.6	5.2	1.6
Orientation	5.7	0.5	5.9	0.3
Mental Control	3.1	1.7	3.9	1.3
Passage recall (immediate)*	6.5	4.4	11.3	2.4
Passage Recall (delayed)*	4.0	4.1	10.3	3.0
Digits forward	6.3	1.4	7.3	0.9
Digits backward	3.3	1.4	3.4	1.3
Visual reproduction	3.4	2.2	5.3	1.7
Associate learning	8.3	3.2	9.8	1.7
WMS total score	40.9	12.1	52.1	8.0

* = statistically significant difference ($p<0.01$) between groups

DISCUSSION

The purpose of this controlled psychometric study was to investigate the cognitive deficits of unilateral thalamic haemorrhage. It was found that the thalamic lesion group obtained significantly lower scores on the Block Design of the WAIS and the Passage Recall of the WMS. Functional asymmetry, however, was not demonstrated.

Our finding of impairment in visual-spatial organization ability is consistent with the understanding of the thalamus as the 'way station' for all sensory pathways to the cerebral cortex[20]. As such, it participates in most of the exchanges between the higher and lower brain structures, and between sensory and motor components at the same structural level of processing - the cerebral cortex[21]. However, based on the present results alone, it was not possible to specify whether sensory reception, central neural interpretation or motor reproduction was most affected.

As for memory functioning, the results indicated that the thalamic lesion group was impaired in recalling passages but was relatively unimpaired in recalling paired association and digits. The results also suggested that there was no impairment in maintaining access to semantic knowledge systems, as in general everyday and abstract reasoning. Tulving has drawn a distinction between 'semantic' and 'episodic' memory, the former consisting of the relatively permanent pool of knowledge held in common by a culture and the latter comprising memory for specific events, which can be considered as a record of events unique to the individual[22]. Our findings, however, could not be easily explained by this distinction, since performance involving episodic memory in learning passages and paired associates were differentially impaired. The 'disconnection syndrome' appears to offer a more feasible interpretation. Warrington and Weiskrantz have proposed that the amnesic subject suffers from a disconnection between the cognitive mediational memory systems in the frontal lobe and semantic knowledge in the temporal lobe[10]. This model would explain the relatively intact semantic memory store of the thalamic lesion group. It would also explain the differential impairment in recalling passages in the present study in that the task places a high demand for mediational cognitive strategies as compared to remembering digits and paired associates. Such mediational cognitive strategies would involve active organisation and chunking of the material to be remembered.

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A CLINICAL AND PATHOLOGICAL STUDY OF PROGRESSIVE SUPRANUCLEAR PALSY

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SUMMARY

The clinical features of 26 patients diagnosed as progressive supranuclear palsy are reviewed. The atypical findings were the relatively low frequency of visual complaints (23%) and of significant dementia (20%). As well, the characteristic eye signs, supranuclear ophthalmoplegia of vertical gaze, occurred some years after the onset of the inital symptoms in a small but substantial number (31%), which significantly delayed the diagnosis, in one case by as long as 18 years.

The pathological studies on 2 of the clinical cases and an additional 6 cases showed the characteristic pattern of involvement of particular subcortical and brainstem nuclei. In particular, significant degeneration of the pedunculopontine tegmental nucleus was confirmed. Degeneration of the pedunculopontine tegmental nucleus may well play an important role in the motor disability in progressive supranuclear palsy.

Progressive supranuclear palsy was first defined as an entity with characteristic clinical and pathological features by Richardson, Steele and Olszewsky in 1964[1], even though isolated case reports had appeared in the literature as early as 1904[2].

The typical combination of clinical signs include supranuclear ophthalmoplegia predominantly in the vertical plane but later in all directions, axial rigidity mainly but not always in extension, pseudobulbar palsy, and extrapyramidal signs. Less constant features are pyramidal tract involvement and dementia[3].

The pathological findings are unique, with neurofibrillary tangles, nerve cell loss, gliosis and granulovacuolar degeneration in specific nuclei of the brainstem[1,3,4].

Antiparkinsonian and other medications have been used in this condition with little success[4]. The usual course is a relentless progression over 4 to 7 years during which the patient becomes immobile, bedridden and anarthric[1,3,4,5].

We describe the clinical features of 26 patients who were diagnosed and observed over a 13 year period. Eight cases were examined pathologically.

METHODS

Thirty-one clinical case records were reviewed with the provisional diagnosis of progressive supranuclear palsy from the Flinders Medical Centre and Repatriation General Hospital. Five were excluded because the clinical features documented were insubstantial. Further information was obtained by contacting the general practitioners who had continued the management of some of the cases.

Eight cases were studied pathologically, including 6 from the Institute of Medical & Veterinary Science. Neuropathological assessment was undertaken using standard neuropathological techniques and several cortical, subcortical, brainstem and cerebellar nuclei were examined. In addition the pedunculopontine tegmental nucleus was studied using immunoperoxidase techniques, namely ubiquintin, tau, phosphorylated and non phosphorylated neurofilament protein.

RESULTS

CLINICAL CASES

There were equal numbers of males and females. The average age of onset of the initial symptoms was 63.1 years (range 43 to 76). The average period between the onset of symptoms and the diagnosis was 4.6 years (range 12 months to 18 years). There were 15 deaths. In the 10 where an exact date of death could be determined, the average length of survival from onset of symptoms was 7.1 years.

Presenting Clinical Features (Fig 1)

The most common primary initial complaint was that of recurrent falls (11/26, 42%). In a further 5 cases (20%) falls were also a feature on presentation, albeit less prominent than other symptoms. In 3 others (12%) a gait disturbance, namely, slowness and hesitancy, without falls was the main presenting complaint. Visual symptoms, including diplopia and inability to open the eyes, were present in 6 (23%). Personality changes such as irritability, apathy, forgetfulness and slowness in thought were relatively common early features and present in just over a third of cases (38%). Two cases presented with speech disturbances, in particular, dysarthria and hesitancy. One patient presented with dysphagia. In 4 others, speech and/or swallowing disturbances were also a problem, but of secondary concern. In the remaining 3 cases, the symptoms were those of immobility and slowing down. Two cases noted a minor resting tremor.

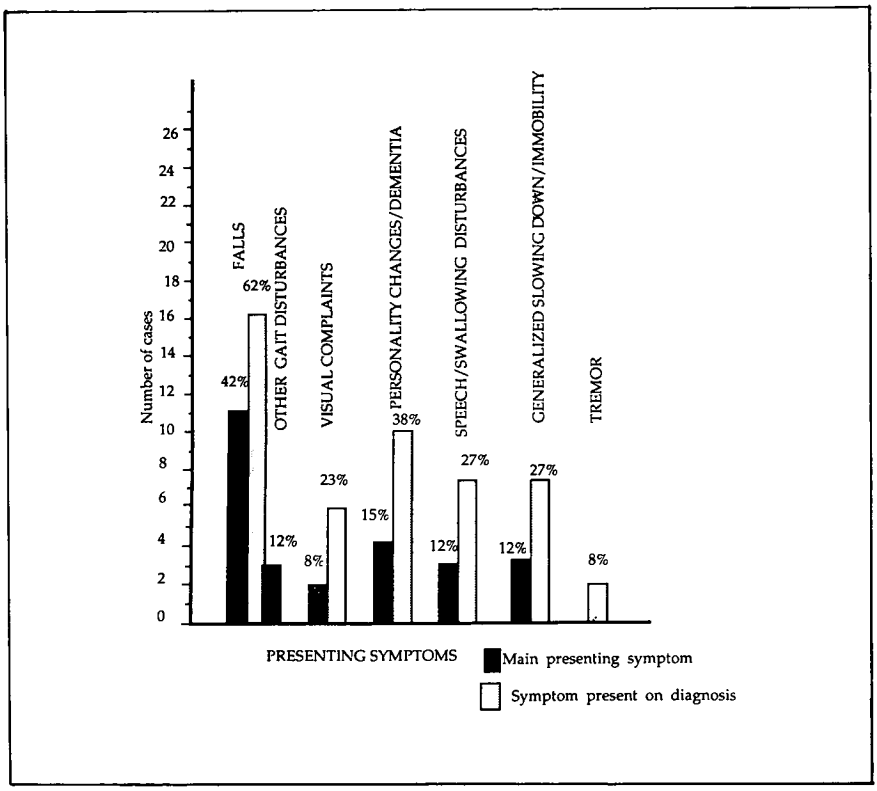

Fig 1 Frequencies of particular symptoms

Signs On Presentation (Fig 2)

Supranuclear ophthalmoplegia of vertical gaze, the hallmark of this entity, was present eventually in all cases. Axial rigidity was moderate to severe in 22 cases (85%), mild in 2 (8%), and absent in one. Corticobulbar signs with a brisk jaw jerk, dysarthria and/or slow tongue movements were present in 24 cases (92%). Pyramidal features such as brisk reflexes and upgoing plantar responses were seen in 19 cases (73%). Extrapyramidal signs such as limb rigidity and bradykinesia were present in 18 (70%). While forgetfulness and slowness in thought were relatively common complaints, only in 5 cases was there a significant dementia, and in 3 others dementia was present but considered of mild to moderate degree.

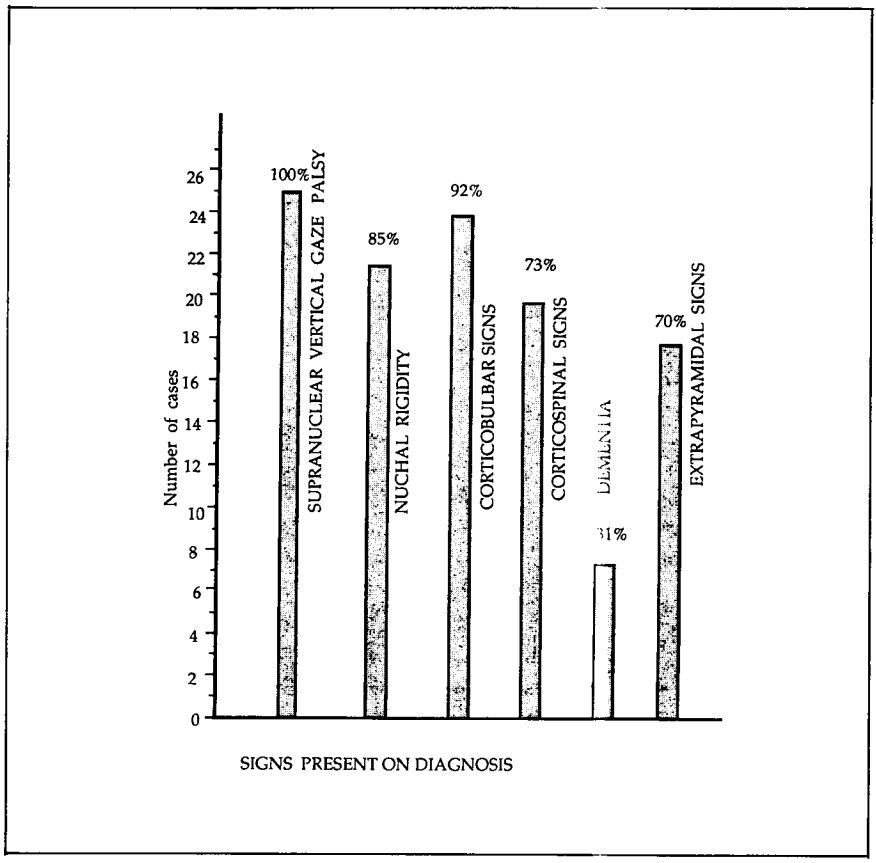

Fig 2 Frequency of occurrence of various signs at the time of diagnosis

Atypical Cases

In 8 cases (31%), the diagnosis was delayed by 6 or more years after the onset of symptoms. Four of these had been seen by neurologists and the characteristic eye signs and axial rigidity were absent during this period. In one particular case, as will be described below, the diagnosis was not made until 18 years after the onset of symptoms, despite regular neurological review. In one case two siblings had Parkinson's disease.

CASE REPORT

A 67 year old woman was initially seen about 21 years previously because of a history of recurrent falls. Initially they would occur when stepping over uneven ground such as gutters and steps. She would tend to fall backwards or to her left. There was no warning, and no loss of consciousness. Repeated neurological examinations over the next several years were considered normal. There was no abnormality of her gait.

Over a period of 18 years she had increasing falls, coming to occur weekly and then daily. She incurred a number of limb fractures and soft tissue injuries over the years as a result. Numerous investigations including CT head scans, Holter monitoring, EEG and tests assessing autonomic function were all normal. In 1988, 18 years after her first falls, she was reviewed because of visual blurrings, deterioration in handwriting, short term memory problems and intermittent dysarthria with choking. Examination then revealed paucity of movements generally, supranuclear ophthalmoplegia in the vertical direction, a mildly brisk jaw jerk, brisk limb reflexes with an upgoing left plantar response and normal axial tone. There was no significant dementia.

Computed tomography and magnetic resonance imaging of the head were performed and were normal. She was living alone in her own home until this time but subsequently required hostel accommodation. Two years later she was transferred to a nursing home bed because of the frequency and severity of falls but there was little progression of other findings. She is currently still alive and requires two people with her to walk.

PATHOLOGY

Eight cases were studied pathologically. Neuronal loss, gliosis, granulovacuolar degeneration and neurofibrillary tangles were typically present in the globus pallidus, subthalamic nuclei, substantia nigra, locus coeruleus, periaqueductal grey matter and dentate nuclei. The frontal and occipital cortex, hippocampus, thalamus and the Purkinje cells of the cerebellum were either mildly affected or not affected at all (Table 1).

Immunohistochemistry staining for the tau has been used to demon-strate neurofibrillary tangles successfully in Alzheimer's disease[6]. While neurofibrillary tangles of progressive supranuclear palsy are ultrastructurally different[7], they nevertheless show strong positive immunostaining with the tau antibody.

The pedunculopontine tegmental nuclei area (PPTg) was studied in detail (Table 2).

DISCUSSION

Early studies of progressive supranuclear palsy had shown a male predominance[1,3]. It has been pointed out that early reports were from a Veterans hospital, which may been at least one reason for the male bias[8]. More recent reports have shown a more even sex distribution[9,10,12], similar to that of our cases.

It is generally agreed that the onset of the initial symptoms is at or after the sixth decade, although it is not unusual to have people present in their forties[4]. Steele's review of the literature in 1972 recorded a mean age of onset of 55 years[3]. In Kristensen's review in 1984[5] the mean age was 59.6 years. More recent reports have had mean ages of 62.9 and 63.5 years, which are similar to our results[8,10].

Table 1 Assessment of neurofibrillary tangles, neuronal loss and gliosis in selected areas of the cerebrum, brain stem and cerebellum in the 8 cases studied pathologically

Site	Case number							
	1	2	3	4	5	6	7	8
Cerebral cortex	+	0	+++	0	+	0	0	0
Striatum	=	0	++	++	+	+	0	+
Pallidum	+++	+++	+++	+++	+++	++	+++	++
Thalamus	+	+++	+	NA	+	+	+	+
Subthalamic nuclei	++	+++	+++	NA	+++	+++	++	++
Nucleus basalis	+	+	++	++	++	++	+	+
Red nuclei	++	+++	++	++	++	+++	+	++
Substantia nigra	+++	+++	+++	+++	+++	+++	+++	+++
Locus ceruleus	+++	++	++	++	++	++	+	++
Tegmental raphe nuclei	++	++	++	++	++	+	+	+
Pontine nuclei	++	+	++	++	++	+	+	+
Inferior olives	++	+	+	++	+++	++	+	+
Purkinje cells	0	0	0	0	0	0	0	0
Dentate nuclei	+++	++	+++	+++	+++	++	++	+++
Dorsal vagal nuclei	+	+	+	+	+	+	+	+

NA = not available; 0 = absent; + = mild; ++ = moderate; +++ = severe in relation to the assessment of neuronal loss, gliosis and neurofibrillary tangles

Table 2 Pedunculopontine nucleus in progressive supranuclear palsy - assessment of neurofibrillary tangles, neuronal loss and gliosis in the nucleus in the 8 cases studied pathologically

	Case number							
	1	2	3	4	5	6	7	8
NFTs	+++	+	++	+++	+	++	++	++
Neuronal loss	++	+++	++	++	++	++	+	++
Gliosis	++	++	+	++	+	+	+	+

NFTs = neurofibrillary tangles

The presenting clinical features were mostly in keeping with previous reports[1,3,4,8,9,10,11]. Disturbance of balance and falls were characteristic early symptoms in about one-half of the cases. Unexpectedly, visual complaints were infrequent symptoms, a finding which is not readily explained. It is unlikely that patients presenting with visual symptoms would have been referred to other centres for confirmation of the diagnosis as both hospitals from which cases were derived had an ophthalmological unit attached to them.

Significant dementia was also relatively low in frequency. Steele's original report[1] emphasized that while dementia was a recognised association it usually remained mild, although some cases have been documented with a severe dementia. Other reviews have concluded that dementia is an inconstant finding[5]. The absence of characteristic cortical types of apraxias such as agnosia, agraphia and constructional deficits made Albert classify the mental disturbances as a 'subcortical dementia'[15]. This highlights the idea that, rather than a primary loss of intellectual capacity, deterioration is secondary to impaired timing and activation of pathways which may involve brainstem connections. This is supported by findings from others who concluded that psychological assessments involving verbal and memory tests did not reveal significant problems but visually based tests were impaired, suggesting that the associated oculomotor disorder contributes to the mental changes[14].

The presence of a resting tremor has been regarded as a very unusual finding in progressive supranuclear palsy[1,3,12,15]. The idea of it never occurring has

probably been dismissed and one recent review gave an occurrence rate of 12-16%[16]. Two of our 26 cases had a resting tremor and it was considered by the patients as a trivial problem.

It should be emphasized that a diagnosis, during life, based solely on a combination of clinical signs may be incorrect. It has been reported recently that a case of diffuse Lewy body disease was diagnosed as progressive supranuclear palsy before death because of the presence of supranuclear ophthalmoplegia[17]. The dementia in this case, interestingly, was consistent with diffuse cortical involvement. Two cases of idiopathic Parkinson's disease have been reported as having typical ocular features of progressive supranuclear palsy which was transient and occurred during an intercurrent illness[18]. Conversely, the diagnosis can be unduly delayed if the characteristic eye signs occur late, as was the case in a small but substantial number of our patients[19,21]. More subtle oculomotor disorders such as derangement of the quick component optokinetic nystagmus[20] and poor pusuit eye movements[15] occur earlier and should be looked for when progressive supranuclear palsy is considered.

The pathological findings were similar to those previously shown[1,5]. Abnormalities in the pedunculopontine tegmental nucleus have recently been described in idiopathic Parkinson's disease[22,24]. Zweig et al[23] and Hirsch et al[24] have pointed out that this area shows significant degeneration in Parkinson's disease as well as progressive supranuclear palsy, although not in Alzheimer's disease[25]. Our pathological studies confirmed this finding. This group of nuclei contain the principle hindbrain cholinergic nuclei (excluding those of the cranial motor nuclei)[22]. While their anatomical connections and functional role in humans are poorly understood, studies in experimental animals have shown a central link between forebrain and hind brain motor control[26]. It is therefore probable that these nuclei serve a primary function of movement regulation in humans and the characteristic degeneration seen in progressive supranuclear palsy and Parkinson's disease may explain the significant motor disorders of these conditions.

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ATAXIA TELANGIECTASIA PRESENTING AS AN EXTRAPYRAMIDAL MOVEMENT DISORDER AND OCULAR MOTOR APRAXIA WITHOUT OVERT TELANGIECTASIA

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SUMMARY

Ataxia telangiectasia may present with few, if any, of its typical extra-neurological manifestations, but the combination of an extrapyramidal movement disorder,ocular motor apraxia with head thrusting and cerebellar incoordination is characteristic. In this sporadic case there was no overt immune dysfunction, oculo-cutaneous telangiectasiae were inconspicuous and the neurological presentation was atypical with dystonia predominating over cerebellar incoordination. The uncontrollable and disabling involuntary movements, which have not to our knowledge been described in ataxia telangiectasia before, showed a partial response to moderately large doses of benzhexol, but were refractory to all other medications. Treatment in the future is to be with increasing doses of benzhexol until the dystonia is controlled or larger doses cannot be tolerated.

Ataxia telangiectasia is an autosomal recessive disorder predominantly involving the immune and central nervous systems and thought possibly due to defective genetic recombination[1]. The gene for ataxia telangiectasia has been localized to chromosome 11q22-23[2], but its identity and function remain unknown. Neurological symptoms typically appear at age 12 to 18 months and often before the oculo-cutaneous telangiectasiae and other extra-neurological manifestations. Progressive cerebellar ataxia due to degeneration of the Purkinje and granule cells[3] typically overshadows the ocular motor apraxia with head thrusting[4,5] and choreo-athetosis[3] also being seen in most or all cases. Presentation may be as a progressive movement disorder[3] and oculo-cutaneous

telangiectasiae may be absent or inconspicuous[3]. The other extra-neurological manifestations are variable, but include selective immunoglobulin deficiencies (Types A and E), impaired cell-mediated immunity, lymphopenia, recurrent sinopulmonary infections, a predisposition to lymphoreticular malignancy and increased spontaneous and irradiation-induced chromosomal translocations[3]. Elevation of α-foeto-protein and/or carcinoembryonic antigen is also typical, but variable[3]. The diagnosis can be made when the characteristic neurological manifestations are present in combination with at least some of the other typical abnormalities. We describe a patient with sporadic ataxia telangiectasia without apparent immune dysfunction, inconspicuous oculo-cutaneous telangiectasiae and a debilitating, jerking dystonia with the typical ocular motor apraxia. To our knowledge this type of movement disorder has not been described previously in ataxia telangiectasia. Significant relief from the involuntary movements was obtained with high dose benzhexol ('Artane').

CASE HISTORY

The patient presented at 28 years of age because of incapacitating involuntary movements. There was no family history of neurological, immune system or malignant disease and he had an uneventful gestation and birth. He was well, other than for possible excessive drooling noted from birth, but could not walk at 18 months. At that age he could stand leaning against support, at which time dystonic posturing of the left foot occurred. At 2 years he could walk clumsily, was generally uncoordinated and involuntary movements affected both left limbs. Thereafter the involuntary movements spread to involve all the limbs and the face and axial musculature as he became progressively more dysarthric and poorly coordinated. He attended primary and secondary school, was an average student, but passed in all years. At 18 he could walk only with a frame and by 20 he was wheelchair bound and without functional upper limb movements. Throughout, increasingly gross involuntary movements have occurred at rest, but have always been exacerbated by attempted use of his limbs. There has been no symptomatic limb weakness or sensory loss. Treatment with various benzodiazepines, haloperidol and tetrabenazine had been without effect.

Examination was remarkable only for the presence of inconspicuous oculo-cutaneous telangiectasiae (Fig 1) and his neurological abnormalities. Eight years after he last walked he was generally wasted, without fasciculations, and, he could move all 4 limbs voluntarily and with apparently normal power. At rest his neck was held in torticollis to the left; there was hypertrophy of the right sternomastoid. Often violent, jerking dystonic movements of all 4 limbs, the neck and the trunk occurred frequently at rest and were typified by co-contraction of agonist and antagonist muscles resulting in forced limb extension. Occasional finer choreiform movements of the digits and facial musculature were also seen. Action, anticipated use of a limb, or maintenance of limb posture in

space precipitated similar dystonias of greater amplitude and with overflow to the other limbs and the axial and facial musculature. Speech was s urred and its normal rhythm and cadences disrupted. Tongue movements were apraxic. Marked apraxia of voluntary eye movements, pursuit and saccades, in all directions wa invariably accompanied by head thrusts. Vergence eye movements were impaired. F rmal testing of coordination was impossible. The remaining neurological examination was normal.

Fig 1 Scleral oculo-cutaneous telangiectasiae (arrow) seen in both eyes

Investigation (Table 1) found gross elevation of α-foe oprotein at 168 KU/l, but revealed normal immune function apart from an equivoca ly low immunoglobulin E. Severe cerebellar atrophy in the absence of abnormalities o the basal ganglia or other cerebral structures was demonstrated by magnetic resonance i naging (Fig 2). The clinical impression of ocular motor apraxia with increased sacc dic latency and saccadic hypometria was confirmed by electrooculography.

Table 1 Outline of investigations

α-foetoprotein	168 KU/l (normal range < 11 KU/l)
carcinoembryonic antigen	1 ng/l (normal range <10 ng/l)
Immunoglobulin	G 14.7 g/l (normal range 6.0 - 14.3 g/l)
"	M 1.6 g/l (" " 0.3 - 1.8 g/l)
"	A 1.0 g/l (" " 0.65 - 3.4 g/l)
"	E < 10 g/l (" " 0 - 210 g/l)
Normal	- lymphocyte count
	- lymphocyte subtypes
	- copper studies
	- vitamin E
	- pyruvate and lactate
	- EEG
	- chest and sinus X-rays
	- chromosomal studies

α-foetoprotein was elevated, but carcinoembryonic antigen and immune function were essentially normal. Chromosomal fragility was not demonstrated, but the effects of irradiation were not studied.

A trial of L-dopa was without effect. High dose benzhexol (36 mg/day with an increasing regimen) has resulted in a marked, but incomplete, improvement in the dysarthria and involuntary movements, but has not altered the ocular motor apraxia or the generally poor coordination.

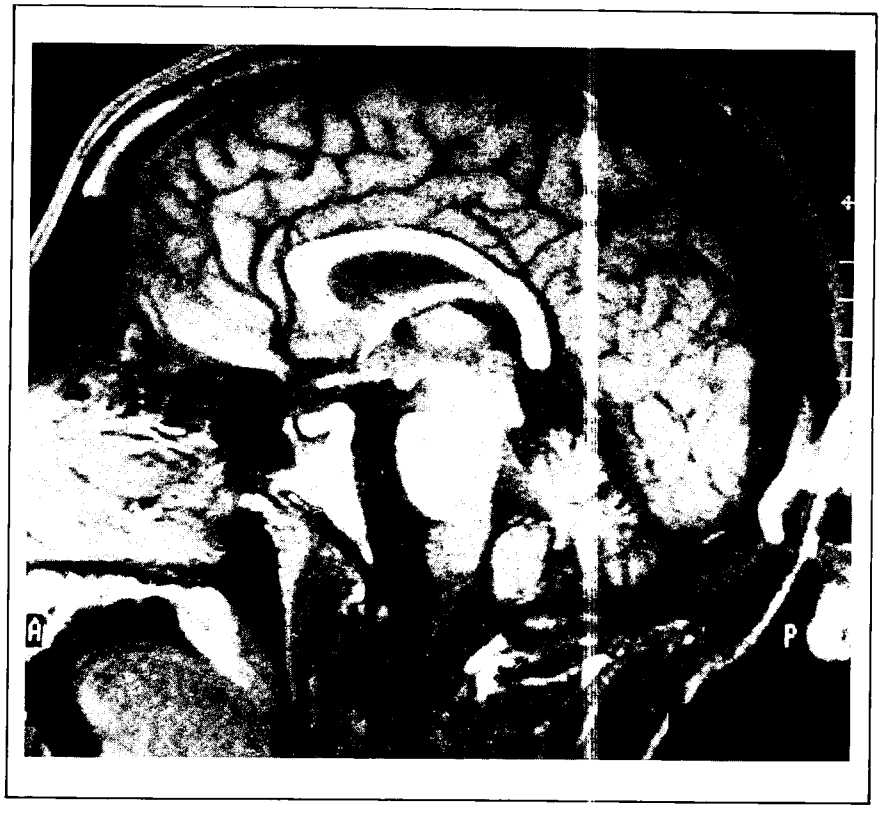

Fig 2 Sagittal T_1-weighted MRI demonstrating marked cerebellar atrophy

DISCUSSION

The characteristic neurological features of ataxia telangiectasia are the age of symptomatic onset at 1 to 1.5 years, cerebellar ataxia, choreoathetosis and ocular motor apraxia with head thrusting. The ocular motor apraxia is characterised by increased voluntary saccadic latency in the vertical and horizontal planes[4,5,6,7], saccadic hypometria with normal saccadic velocity[4,5] and the use of head thrusts to enable refixation[4,5,6,7]. Similar disruption to involuntary saccades has been described[4,5]. Optokinetic nystagmus and smooth pursuit may be absent or impaired[4,5], stimulation of the vesibulo-ocular reflex induces deviation of the eyes in the direction of the slow phase[4,5] and suppression of the vestibulo-ocular reflex is impaired[4,5]. The disorder can be discriminated from other cerebellar

degenerations by the demonstration of increased saccadic latency and saccadic hypometria and head thrusting which are not seen in pure hereditary cerebellar ataxia[8].

In this patient cerebellar ataxia was seen mainly as a dysarthria, congenital drooling and a history of clumsiness preceding dystonia in at least some limbs. MR imaging confirmed the presence of marked cerebellar atrophy. The cerebellar contribution to his motor dysfunction was overshadowed by a severe jerking dystonia affecting all the limbs and the axial musculature which was responsive to high dose benzhexol. This striking extrapyramidal disorder occurred in the absence of gross involvement of the basal ganglia on MR imaging. To our knowledge such a dystonia and its successful treatment have not been described before.

The extra-neurological features of ataxia telangiectasia are known to be variable[1,9] and in their absence diagnosis depends upon demonstration of the typical neurological deficits. Oculo-cutaneous telangiectasiae may be subtle or absent[1,9], spontaneous chromosomal translocations may not be found[1] and immune function may normal[1]. In this patient no immune system abnormality other than an equivocally low immunoglobulin E level could be demonstrated. The strong clinical grounds for diagnosis were confirmed by gross elevation of α-foetoprotein levels in the absence of another cause.

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FAMILIAL SPASTIC PARAPLEGIA: AN ELECTROPHYSIOLOGICAL STUDY OF CENTRAL SENSORY CONDUCTION PATHWAYS

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SUMMARY

An electrophysiological assessment has been performed studying somatosensory, visual and auditory pathways in clinically affected and unaffected members from 4 pedigrees with the autosomal form of 'pure' familial spastic paraplegia (n=32). In some members from 2 families, testing of all 3 sensory pathways showed abnormal results, even in those clinically unaffected. In another family, some had abnormal somatosensory and visual pathways, with no involvement of the auditory pathway. In a further family, the somatosensory and brainstem auditory pathways were abnormal, with sparing of the visual pathway.

These findings indicate that the neuronal degeneration in familial spastic paraplegia extends beyond the spinal cord and involves the visual and auditory pathways. The differences between families, and the asymptomatic abnormalities in clinically unaffected members, suggest diversity in the expression of the genetic defect.

Familial spastic paraplegia (FSP) in its 'pure' form is characterized by spasticity of the lower limbs and variable posterior column dysfunction[1,2,3,4]. There may be associated features such as extrapyramidal manifestations, optic atrophy, retinal degeneration, cerebellar ataxia, dementia, and amyotrophy, in which case the term "complicated spastic paraplegia" is used[5].

In this study electrophysiological techniques have been used to examine the involvement of visual, auditory, and somatosensory pathways in the autosomal dominant form of 'pure' FSP, in order to explore the extent of asymptomatic involvement of central sensory systems.

MATERIALS AND METHODS

PATIENTS

All clinically affected patients from the 4 pedigrees had autosomal dominant progressive spastic paraparesis with an onset in the 2nd or 3rd decade of life, and with variable posterior column dysfunction (Fig 1). There were no cranial nerve disturbances or other neurological abnormalities. All affected and unaffected members from the 4 pedigrees were examined by one of the authors.

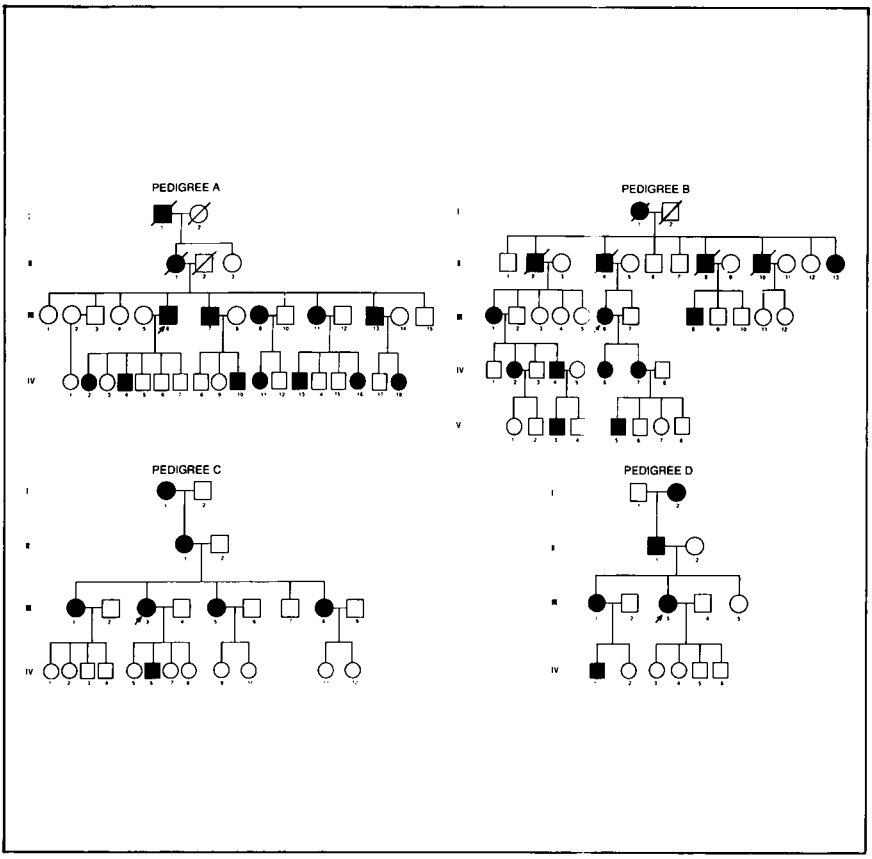

Fig 1 Pedigrees A, B, C and D with autosomal dominant familial spastic paraplegia. (Closed-in symbol = clinically affected).

ELECTROPHYSIOLOGICAL TECHNIQUES

Visual Evoked Potentials (VEPs)

Full field VEPs were recorded in the dark using a Philips video monitor and a Medelec MS6 system with filters set at 0.32-800 Hz, and with an analysis time of 200 msec. Using automatic artefact rejection, 128 monocular responses per trial (minimum of 2 trials per study) to a full-field black and white checkerboard pattern stimulus (horizontal half-width of field size 16° 16', check size 52') reversing at 2 Hz, were recorded from 0z referenced to Cz (10-20 system). A response was regarded as abnormal if the absolute latency of the first major positivity, or the interocular latency difference, exceeded our 3.0 standard deviation upper limit of normal (SD ULN), with vision corrected for distance where necessary. Where the interocular latency difference was greater than the 3.0 SD ULN, the eye with the longer latency was considered abnormal. Borderline VEPs were those where the latencies fell between the 2.5 and 3.0 SD ULN. Sixty volunteers (aged 19-69 years) were tested to establish our reference range.

Brainstem Auditory Evoked Potentials (BAEPs)

Auditory evoked potentials were recorded using a Medelec MS6 with the CK63 click stimulator and Teca HS3 shielded earphones. The stimuli were 0.1 msec monaural 70 dBHL and SL rarefaction clicks, provided at a frequency of 10 Hz - the contralateral ear being masked with white noise, 30 dB below the stimulus level. Responses were recorded, using 10 mm silver/silver chloride disc electrodes, from the ipsilateral mastoid placement referenced to Cz. A bandwidth of 500 Hz - 1.6 kHz was used, with an analysis period of 10-15 msec. Using automatic artefact rejection, 1000-5000 responses were averaged per trial, a minimum of 2 trials being performed per ear. Contralateral responses to rarefaction stimuli and ipsilateral responses to condensation stimuli were recorded where necessary to assist with wave identification. Abnormal responses were documented in the absence of peripheral hearing loss, and with a normal wave I, and when a prolonged I-III, III-V or I-V inter-peak latency exceeded the 3 standard deviation upper limit of normal (SD ULN). Normal reference ranges for females and males were determined in our laboratory on 36 volunteers (aged 18 to 56 years).

Somatosensory Evoked Potentials

Somatosensory evoked potentials were recorded using the same Medelec MS6 with the Medelec constant voltage stimulator. The median nerve was stimulated at the wrist (cathode proximal), using a large bipolar stimulating electrode (2.5 cm) to produce a barely visible twitch of the thenar muscles. Responses were recorded with 10 mm silver/silver chloride disc electrodes placed at Erb's point (EP), over the second cervical vertebra (C2) and between the C_3 and P_3 positions of the 10 - 20 International EEG system for the right median, and the C_4 - P_4 positions for the left median nerve, all referenced to Cz. The stimuli were square wave electrical pulses of 0.1 msec duration, delivered at a rate of 3 Hz for the clavicular, 2 Hz for the spinal and 3-5 Hz for the cortical responses. The bandwidth was 8.0 Hz - 3.2 kHz and the analysis time 20 msec for clavicular and spinal responses, and 0.32 Hz - 1.6 kHz and 100 msec respectively for the cortical responses. A minimum of 256 (EP and C_2) and 512 (cortical) responses were

averaged using automatic artefact rejection, with two or more trials being performed per placement.

The posterior tibial nerve was stimulated at the ankle, immediately behind the medial malleolus (cathode proximal), with the same stimulating electrode to produce a barely visible twitch of digit one. Responses were recorded from the popliteal fossa (P.F.) with a Medelec sensory electrode (2 cm), between the 12th thoracic vertebra (T12) and the 1st lumbar vertebra (L1) referenced to the contralateral anterior superior iliac spine with the silver/silver chloride disc electrodes, and from Cz to FPz with similar disc electrodes. Stimuli were square wave electrical pulses of 0.1 msec duration, delivered at a rate of 1 - 2 Hz. A bandwidth of 8.0 Hz - 3.2 kHz and an analysis period of 50 msec were used for the popliteal fossa and lumbar potentials and 0.32 Hz - 3.2 kHz and 100 - 150 msec respectively for the cortical potentials. A minimum of 256 responses were averaged using automatic artefact rejection, with at least 2 trials being performed per placement.

Recorded absolute latencies to median stimulation were the N9 (clavicle), N13 (C2) and N20 (cortical); interpeak latencies were determined as N9 - N13 and N13 - N20 (or N9 - N20 where N13 was not recorded). Posterior tibial responses included the absolute latencies N8 (P.F.), N21 (T12/L1) and P40 (cortical) and the interpeak latency N21 - P40. Abnormal responses were documented as those where the cortical N20 or P40 absolute or interlimb latencies (peripheral conduction normal), or N13 - N20 or N21 - P40 interpeak latencies (for upper and lower limbs respectively) were outside our 3SD ULN established on 22 volunteers (aged 21 to 48 years).

RESULTS

Pedigree A (Table 1)

The SEP interpeak latencies for patient III-6 were within the reference range, but the interlimb latency for N21 - P40 was prolonged at 3.6 msec (reference range 0.1 - 1.4 msec). In patient III-7 the spinal response was absent to right posterior tibial nerve stimulation, the cortical P40 response having a latency of 40 msec. No spinal responses were recorded from III-13 and the absolute latencies for the P40 were right 43 msec and left 45 msec. This interlimb difference of 2 msec was also outside the reference range. The cortical responses for IV-18 were poorly defined after left posterior tibial nerve stimulation and the right N21 - P40 latency was abnormal. The interpeak latencies for IV-5 were normal but the N21 - P40 interlimb difference was 1.5 msec and thus abnormal. The N21 - P40 interpeak latencies for patients IV-6, IV-7, IV-9 and IV-17 fell outside the reference range, with IV-7 also having an abnormal interlimb difference of 3 msec. Patient IV-10 had prolonged P100s in both eyes (Fig 2). Patient IV-18 had a P100 falling just outside the reference range. Two asymptomatic members had broad, ill-defined and prolonged P100 responses (IV-

6 and IV-17). The interpeak latencies for the BAEPs were normal.

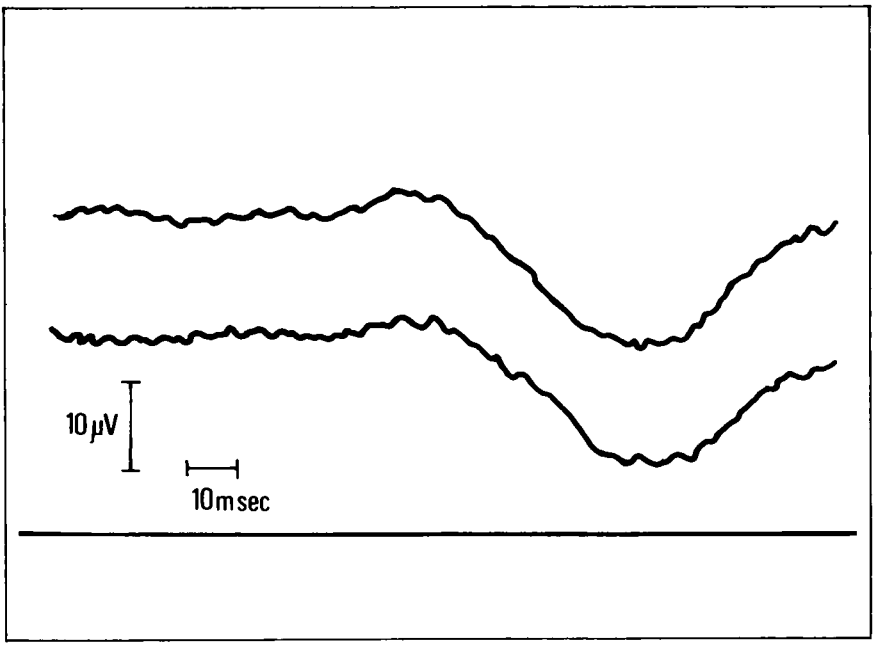

Fig 2 VEP from the right eye in the symptomatic member IV 10 from Pedigree A. The response is broad and prolonged.

Pedigree B (Table 2)

No cortical responses were seen after bilateral posterior tibial nerve stimulation in III-6. There was also bilateral prolongation of the N13 - N20 latencies. In IV-1 the left N21 - P40 was prolonged, as was the interlimb latency difference. The N13 - N20 latencies were bilaterally abnormal in IV-4. In IV-7 no spinal or cortical responses were found after right median stimulation. In V-1 the interpeak latencies were normal but the interlimb difference of 4 msec lies outside the reference range (0.1 - 1.4 msec). Only the asymptomatic member V-2 had an abnormal unilateral N21 - P40 latency. The VEP's were normal except for V-3 and V-4. Three members had abnormal interpeak latencies for BAEPs, indicative of defective central sensory conduction (III-6, IV-1, IV-4).

Pedigree C (Table 3)

Spinal and cortical responses from posterior tibial nerve stimulation were absent bilaterally in III-3, with preservation of popliteal fossa responses. The

remainder of the SEP studies in this family were normal. IV-6 had a unilateral prolongation of the P100. All other VEP studies in this family were normal. Two symptomatic members (III-1 and III-3) and one asymptomatic member (IV-4) had abnormal BAEPs.

Pedigree D (Table 3)

Spinal and cortical responses from median and posterior tibial nerve stimulation in III- 3 were absent, with normal peripheral nerve conduction. The SEPs in asymptomatic members were normal. The VEPs were normal. The BAEPs were also normal except in the symptomatic member (Fig 3).

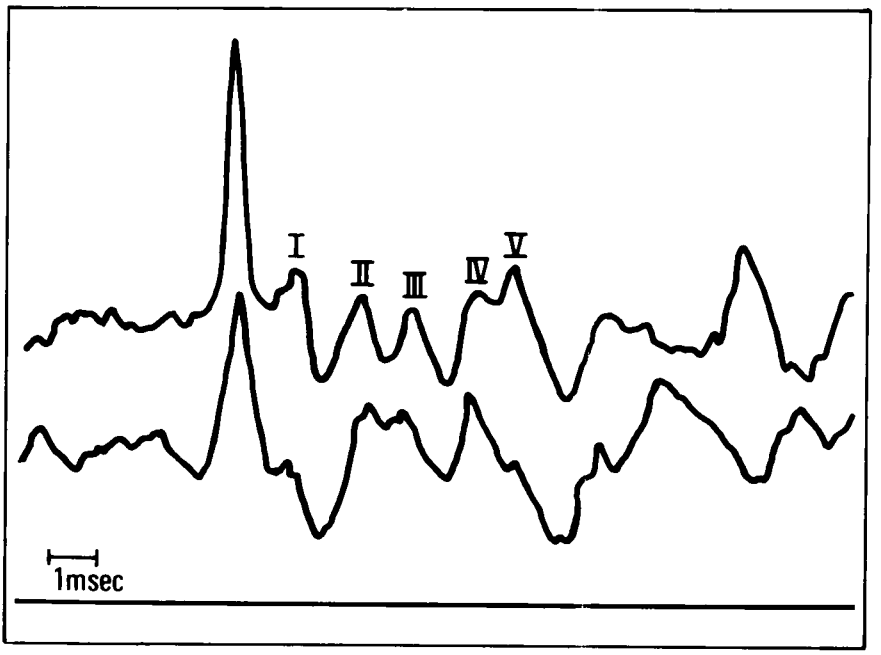

Fig 3 BAEP from the left ear from the affected member III-3 from Pedigree D. The interpeak latencies between waves I-III and I-V are prolonged, indicating a disturbance in the central auditory conduction pathway.

Table 1 Somatosensory, visual, auditory evoked potentials (msec) in FSP: Pedigree A

		Interpeak Latencies Upper Limbs		Lower Limbs			Interpeak Latencies (Ipsilateral)		
		N_9-N_{13}	N_{13}-N_{20}	N_{21}-P_{40}	VA	P_{100}	I-III	III-V	I-V
Affected									
III-6 M, 50	R	3.3	6.4	20.0*	6/5	105	2.50	1.86	4.36
	L	3.7	5.8	16.4	6/5	110	2.56	1.48	4.03
III-7 M, 46	R	4.2	5.4	-*	6/9	113	2.00	1.96	3.96
	L	4.3	4.4	17.0	6/5	113	2.04	1.70	3.74
III-13 M, 39	R	4.6	5.5	-*	6/12	114	2.00	2.11	4.11
	L	4.7	4.9	-*	6/5	114	2.07	2.00	4.07
IV-2 F, 24	R	3.8	4.9	17.0	6/4	125	2.23	1.76	3.99
	L	4.1	4.6	16.5	6/4	123	2.37	1.79	4.16
IV-4 M, 22	R	4.1	5.7	19.7	6/5	114	2.00	1.85	3.85
	L	4.2	5.3	20.9	6/4	116	2.25	1.75	4.00
IV-10 M, 15	R	3.3	6.4	19.0	6/4	133*	2.09	1.51	3.60
	L	3.3	6.2	19.5	6/18	138*	2.32	1.44	3.76
IV-18 M, 11	R	3.7	6.0	28.0*	6/5	128	1.98	1.54	3.52
	L	4.0	5.8	-*	6/5	129*	2.07	1.58	3.65
Unaffected									
IV-5 M, 13	R	3.5	5.2	18.5*	6/5	119	2.10	2.10	4.20
	L	3.6	5.6	20.5*	6/5	116	2.10	2.00	4.10
IV-6, M, 11	R	3.4	6.2	25.0*	6/5	134*	2.04	1.89	3.93
	L	3.1	6.6	24.0*	6/5	130*	2.01	2.01	4.02

		Interpeak Latencies Upper Limbs		Lower Limbs			Interpeak Latencies (Ipsilateral)		
		N9-N13	N13-N20	N21-P40	VA	P100	I-III	III-V	I-V
Unaffected (Cont)									
IV-7 M, 9	R	2.7	6.2	21.0*	6/5	127	2.10	1.84	3.94
	L	2.7	6.3	24.0*	6/9	125	2.27	1.82	4.09
IV-9 F, 17	R	4.1	5.6	20.5	6/6	114	2.07	1.78	3.85
	L	4.2	5.5	N.D.	6/12	119	2.16	1.68	3.84
IV-17, M, 12	R	2.5	5.7	22.0*	6/6	147*	2.05	1.60	3.65
	L	2.5	6.7	23.0*	6/4	150*	2.15	1.41	3.56
Reference Ranges:	F,R	4.2	7.6		*Right eye VEP*		*Female BAEP*		
(Upper Limit 3SD)	F,L	4.7	8.1		(F & M)				
	M,R	5.1	7.6		≤ 35 yrs	99-129	1.70-	1.45-	3.40-
	M,L	5.1	7.7		> 35 yrs	100-128	2.45	2.45	4.40
	F&M	R		20.4					
	F&M	L		21.4	*Left eye VEP*		*Male BAEP*		
					≤ 35 yrs	103-127	1.70-	1.35-	3.60-
					> 35 yrs	101-129	2.70	2.55	4.70

* = Abnormal result - see text

ND = Not done

VA = Visual acuity, given uncorrected unless specified c (= corrected)

Table 2 Somatosensory, visual, auditory evoked potentials (msec) in FSP: Pedigree B

		Interpeak Latencies Upper Limbs		Lower Limbs			Interpeak Latencies (Ipsilateral)		
		N_{9}-N_{13}	N_{13}-N_{20}	N_{21}-P_{40}	VA	P_{100}	I-III	III-V	I-V
Affected									
III-6 F, 75	R	3.1	11.7*	-*	6/12c	116	2.2	2.1	4.3
	L	2.9	13.9*	-*	6/12c	113	2.0	2.6*	4.6*
IV-I7 F, 18	R	3.6	6.6	20.0	6/4	115	2.50	1.98	4.60*
	L	4.2	7.0	22.0*	6/5	113	2.20	2.47*	4.67*
IV-4 M, 36	R	4.6	8.2*	ND	6/4	120	2.40	2.80*	5.20*
	L	4.7	7.9*	ND	6/4	122	2.40	2.60*	5.00*
IV-7 F, 48	R	-*	-*	ND	6/12	115	2.00	2.15	4.15
	L	4.8*	9.5*	ND	6/12	115	2.15	2.35	4.36
V-3 M, 11	R	ND	ND	ND	6/4	141*	2.18	2.15	4.33
	L	ND	ND	ND	6/5	138*	2.25	1.91	4.16
V-5 M, 25	R	3.8	6.1	18.5	6/4	120	2.37	2.20	4.57
	L	3.8	7.5	20.5	6/4	117	2.10	2.20	4.36

		Interpeak Latencies Upper Limbs		Lower Limbs			Interpeak Latencies (Ipsilateral)		
		N9-N13	N13-N20	N21-P40	VA	P100	I-III	III-V	I-V
Unaffected									
V-1 F, 25	R	3.2	5.8	15.0	6/4c	118	1.88	2.14	4.12
	L	3.2	5.4	19.0	6/4c	117	2.05	2.00	4.05
V-2, M, 11	R	2.9	6.0	20.3	6/5	116	2.09	2.10	4.19
	L	3.2	6.0	28.0*	6/5	114	2.27	1.93	4.20
V-4 M, 8	R	ND	ND	ND	6/4	138*	1.99	1.78	3.77
	L	ND	ND	ND	6/4	138*	2.05	1.88	3.93
V-7 F, 22	R	3.6	5.5	19.3	6/5	126	2.02	1.98	4.00
	L	4.0	5.2	19.0	6/5	126	1.93	1.93	3.86
Reference Ranges:	F,R	4.2	7.6		*Right eye VEP*		*Female BAEP*		
(Upper Limit 3SD)	F,L	4.7	8.1		(F & M)				
	M,R	5.1	7.6		≤ 35 yrs	99-129	1.70-	1.45-	3.40-
	M,L	5.1	7.7		> 35 yrs	100-128	2.45	2.45	4.40
	F&M	R		20.4					
	F&M	L		21.4	*Left eye VEP*		*Male BAEP*		
					≤ 35 yrs	103-127	1.70-	1.35-	3.60-
					> 35 yrs	101-129	2.70	2.55	4.70

* = Abnormal result - see text
ND = Not done
VA = Visual acuity, given uncorrected unless specified c (= corrected)

Table 3 Somatosensory, visual, auditory evoked potentials (msec) in FSP: Pedigrees C & D

		Interpeak Latencies Upper Limbs		Lower Limbs			Interpeak Latencies (Ipsilateral)		
		N_9-N_{13}	N_{13}-N_{20}	N_{21}-P_{40}	VA	P_{100}	I-III	III-V	I-V
PEDIGREE C									
Affected									
III-1 F, 22	R	5.6	7.1	ND	6/4c	120	2.40	2.30	4.70*
	L	5.7	6.6	ND	6/9c	118	2.30	2.00	4.50*
III-3 F, 26	R	3.3	7.3	-*	6/4	112	1.92	2.42	4.48*
	L	4.1	6.8	-*	6/4	113	2.06	2.30	4.22
IV-6 M, 27	R	4.1	6.0	19.0	6/4	128	2.10	2.10	4.20
	L	4.1	5.9	19.0	6/4	130*	2.00	2.20	4.40
Unaffected									
IV-3 M, 18	R	3.5	7.0	ND	6/4	120	1.95	2.38	4.33
	L	3.6	7.1	ND	6/4	120	2.05	2.30	4.35
IV-4 M, 21	R	4.3	6.2	17.0	6/5	120	2.40	2.50	4.90*
	L	4.0	6.1	16.5	6/5	120	2.18	2.37	4.55
IV-5 F, 22	R	3.2	6.3	16.5	6/4	115	1.90	1.81	3.71
	L	3.1	5.8	17.0	6/4	112	2.01	1.79	3.80
IV-8 F, 21	R	2.7	5.5	16.3	6/4	107	2.10	1.85	3.95
	L	2.6	6.2	15.3	6/4	109	2.06	1.90	3.96

		Interpeak Latencies Upper Limbs		Lower Limbs			Interpeak Latencies (Ipsilateral)		
		N9-N13	N13-N20	N21-P40	VA	P100	I-III	III-V	I-V
PEDIGREE D									
Affected									
III-3 F, 58	R	-*	-*	-*	6/4	111	2.45	2.18	4.63*
	L	-*	-*	-*	6/4	110	2.64*	2.45	5.09*
Unaffected									
IV-3 F, 37	R	3.1	6.0	15.1	6/4	119	1.90	1.95	3.85
	L	3.3	6.1	15.0	6/5	118	1.89	1.85	3.84
IV-4 F, 35	R	3.2	6.5	16.5	6/4	100	1.96	1.84	3.80
	L	3.0	6.5	16.0	6/5	99	1.90	1.85	3.75
Reference Ranges:	F,R	4.2	7.6		*Right eye VEP*		*Female BAEP*		
(Upper Limit 3SD)	F,L	4.7	8.1		(F & M)				
	M,R	5.1	7.6		≤ 35 yrs	99-129	1.70-	1.45-	3.40-
	M,L	5.1	7.7		> 35 yrs	100-128	2.45	2.45	4.40
	F&M	R		20.4					
	F&M	L		21.4	*Left eye VEP*		*Male BAEP*		
					≤ 35 yrs	103-127	1.70-	1.35-	3.60-
					> 35 yrs	101-129	2.70	2.55	4.70

* = Abnormal result - see text

ND = Not done

VA = Visual acuity, given uncorrected unless specified c (= corrected)

DISCUSSION

We have demonstrated electrophysiological abnormalities of the somatosensory, visual, and auditory pathways in clinically affected and unaffected members from 4 families with the autosomal dominant 'pure' FSP (Table 4). In one family (Pedigree A) abnormalities of somatosensory responses were associated with abnormal visual responses, but normal brainstem auditory studies. In family B, abnormal SEPs in affected and unaffected members were found with abnormal visual and auditory studies. Abnormal SEPs, VEPs and BAEPs were demonstrated in affected members from Pedigree C, with only one unaffected member having an abnormal BAEP. The affected member studied from Pedigree D had abnormal SEPs and BAEPs, with unaffected members having normal studies.

Table 4 Summary of abnormal evoked potential studies in FSP

PEDIGREE	SEP	VEP	BAEP
A.			
Affected (n = 7)	4	2	0
Unaffected (n = 5)	5	2	0
B.			
Affected (n = 6)	4 (n = 5)	1	3
Unaffected (n = 4)	2 (n = 3)	1	0
C.			
Affected (n = 3)	1	1	2
Unaffected (n = 4)	0	0	1
D.			
Affected (n = 1)	1	0	1
Unaffected (n = 2)	0	0	0

Our data suggest a phenotypic spectrum of central sensory pathway involvement in FSP and support the concept of FSP being a heterogeneous neurodegenerative disorder, with involvement of the visual and brainstem

auditory pathways in addition to the corticospinal and sensory tracts of the spinal cord. This phenotypic variation probably contributes to some of the different electrophysiological findings reported in the literature, as do the small number reported, the clinical heterogeneity, and the age-dependent penetrance. Happel *et al*[6] found abnormal VEPs in clinically affected but not in unaffected members. Livingstone *et al*[7] obtained normal VEPs in dominantly inherited cases, but abnormal responses in some sporadic cases. Most of the 13 patients studied by Pedersen and Trojaborg[8] had normal visual, auditory and somatosensory studies; 4 of their patients had various combinations of abnormalities of VEP, BAEP and SEP testing. The BAEPs were found to be normal by Cassandro *et al*[9] and Rossini *et al*[10]. Abnormal SEP's in affected and unaffected members have also been shown by Dimitrijevic *et al*[11].

FSP has been classified amongst the spinocerebellar degenerations[12]. Its aetiology and pathogenesis are unknown, and its true nosology is yet to be defined. Neuropathological studies are limited and are consistent with an axonal degeneration of the long ascending and descending tracts of the spinal cord[13,14,15,16,17]. Our results show that the axonal degeneration is not necessarily confined to the long tracts of the spinal cord, but also involves axons of the visual and auditory pathways. Our study also shows that clinically unaffected members of a FSP family may have evidence of subclinical involvement in the somatosensory, visual and auditory pathways. It is possible that such persons may in time develop clinical features of spastic paraparesis.

In conclusion, our results show that electrophysiological abnormalities extend beyond the somatosensory pathways of the spinal cord and involve the visual and auditory pathways in the autosomal dominant form of 'pure' familial spastic paraplegia. This indicates that neuronal degeneration is more widespread in the central nervous system than has been recognised previously. The variation in the extent of neuronal degeneration within and between families suggests two possible mechanisms: (i) variable expression of a single gene, or (ii) multiple gene effects. Molecular genetic studies are in progress to elucidate these hypotheses.

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LITHIUM NEUROTOXICITY

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SUMMARY

Lithium is potentially toxic to many parts of the central and peripheral nervous systems. Clinical lithium neurotoxicity may appear at any time during therapy and probably often goes unrecognised, at least for a time. Acute lithium toxicity has a mortality of 15%, and 10% of survivors suffer permanent neurological sequelae that are largely unpredictable though persons with the longest and most clinically severe intoxication are probably at highest risk. Even rapidly effective treatment with haemodialysis will not always protect against permanent residual neurological deficits. Lithium may also produce neurotoxic syndromes which develop chronically.

There is a large variation among patients in relation to what constitutes a toxic serum lithium level. Both acute and chronic toxicity can occur with therapeutic range serum lithium levels. Failure to appreciate this fact may lead to delays in diagnosis and treatment, placing the patient at risk of permanent neurological damage or death. The diagnosis of lithium intoxication is largely clinical though the EEG may help if typical though non-specific EEG changes are present. If available, the red cell:plasma lithium ratio may be a sensitive indicator of intoxication. Prompt and effective treatment is indicated once the diagnosis of lithium intoxication is made. Prevention of intoxication, which requires the active involvement of both the doctor and patient, is crucial.

Lithium was first introduced into psychiatry by Cade in 1949[1], for the treatment of bipolar affective disorder, and is accepted as the treatment of choice for acute mania and for maintenance treatment of that disorder[2,3]. Lithium is also used to treat chronic cluster headache. However, despite its undoubted efficacy[4] lithium is a potentially toxic substance. It appears that the extent of its toxicity is probably underestimated and that many cases go unrecognised[5]. The most troublesome toxicity is neurological[5]. A recent editorial[6] stated that the side

effects of lithium are not disabling, and that intake of the drug does not produce any irreversible or untreatable consequences, despite considerable evidence to the contrary dating back at least to 1972[7].

The exact mechanism by which lithium produces its clinical effects is not known[2], nor is the basis of its neurological toxicity[8]. Numerous potential mechanisms have been postulated, based upon the observed effects of the drug on transmembrane ionic concentrations, enzyme systems and neurotransmitter transport[2].

The recent presentation of a patient with chronic lithium neurotoxicity, which went unrecognised for 2 years, prompted the present review.

CLINICAL MANIFESTATIONS

Clinical toxicity may appear at any time during the course of lithium treatment, even after many years of stable uncomplicated therapy[5,9]. The toxic syndromes can be categorized as either acute or chronic, according to the tempo of their onset.

ACUTE TOXICITY

Acute lithium intoxication can produce a wide variety of effects in both the central and peripheral nervous systems[2]. The manifestations of acute neurotoxicity have been well documented[10,11,12] and are outlined in Table 1. A patient may remain clinically acutely intoxicated well beyond the time of disappearance of lithium from his or her serum[11]. Hansen and Amdisen[11] noted that those with the longest period of intoxication prior to cessation of lithium intake took the longest time to recover. The explanation may be that lithium is cleared from the brain more slowly than from the blood[15,16]. Consistent with this are the observations that EEG changes persist after lithium has been cleared[2,11], and that the patient's clinical state may continue to worsen for up to one week after lithium intake is ceased[11,17,18]. Of particular concern in acute lithium intoxication is the development of an acute organic brain syndrome or a delirium which can progress to coma, associated with which in one study there was an overall mortality rate of 15%[11].

Table 1 Manifestations of acute lithium neurotoxicity#

1. *Encephalopathy*

- Depressed level of consciousness - ranging from apathy through confusion to coma
- Seizures
- Psychosis - with delusions, hallucinations
- Affective disorders

2. *Motor*

- Pyramidal - spasticity, hyperreflexia, clonus, extensor plantars
- Extrapyramidal - Parkinsonism
  - rigidity
  - opisthotonus.
  - oculogyric crises
  - choreoathetosis
  - neuroleptic malignant-like syndrome
- Cerebellar - limb ataxia, staggering gait, dysarthria, intention tremor
- Neuromuscular - muscle weakness
  - peripheral neuropathy with weakness, areflexia, flaccidity
  - fasciculations
  - myoclonus
  - coarse, irregular tremor
  - myopathy

3. *Brainstem signs*

- Nystagmus (vertical and horizontal)
- Lid lag and lid retraction
- Anisocoria
- Conjugate gaze palsies
- Opsoclonus

#Compiled from references 2,9,10,11,12,13,14

Fortunately most patients with lithium intoxication do survive and Schou[12] stated that those who do, recover completely, without sequelae. Others have also indicated that the side effects of lithium are transient and resolve once use of the drug is ceased[6,9], and have stated that lithium alone does not cause permanent damage[3]. However, numerous cases of persisting neurological dysfunction following episodes of acute lithium neurotoxicity have been reported[3,9,18-29]. Such events have been estimated to occur in 10% of patients[11]. The residual damage is most often to the cerebellum[22,30], resulting in gait and limb ataxia, intention tremor, nystagmus and dysarthria. Several cases have had cerebellar atrophy demonstrated on pneumoencepha-lography, CT scan, or MRI scan[9,19,20,22,23,29].

Schou[17], in his review of 40 cases of long-lasting sequelae of acute lithium intoxication, observed that cerebellar features were often absent in the acute phase, and only became apparent as the acute phase resolved. Some patients continued to worsen over several weeks. Cerebellar dysfunction may persist as an isolated consequence of acute intoxication[23,24], but this is thought to be rare[20]. More often it is the dominant manifestation of a more diffuse encephalopathy[9], the features of which may include pyramidal (spasticity, hyperreflexia, extensor plantars), or extrapyramidal (rigidity, dyskinesias, Parkinsonism) signs, cognitive dysfunction including dementia, and minor brainstem signs[7,9,21,22]. Additional peripheral nervous system dysfunctions may include a myopathy and a peripheral neuropathy[22]. A sensorimotor polyneuropathy, which may be severe, can develop acutely during lithium intoxication[5,31], or may only become apparent following recovery[9,26,27,28,29]. Electrophysiological and pathological evidence point to a process of axonal degeneration[5,26,27,28,29,31]. Recovery over weeks to months is the usual outcome[29,31].

It is not possible to predict with confidence which patients suffering acute lithium neurotoxicity will develop continuing neurological sequelae[22] and an individual variation in sensitivity to the cation may be important[9]. Those who do develop sequelae appear to have the same clinical manifestations during the acute phase as those who do not[22]. In one review[9] no definite risk factors for the development for permanent sequelae could be identified, including age, psychiatric diagnosis, concomitant treatment and duration of lithium therapy. In addition, the dose of lithium and the serum lithium level were no higher than in those without sequelae. Schou[22] found a female preponderance amongst those with long-lasting sequelae but this may have simply reflected the sex ratio of his patients on lithium treatment[9], and the small number of cases studied. It is thought likely that those with more severe intoxication are at a greater risk of permanent sequelae[7,10,11], and others have stated that those who develop coma are likely to be left with some permanent damage[2]. A longer duration of lithium intoxication prior to treatment may be another risk factor[10,11]. Some improvement in the sequelae can be expected over the first 6 to 12 months, but significant improvement thereafter is rare[22]. In general, a varying degree of spontaneous recovery does occur, though complete recovery is uncommon[30]. Some cases do not improve at all[30]. As already stated, the polyneuropathy tends to recover, in contrast to the other sequelae[29,31]. A variety of drugs has been tried with no convincing benefit, but speech therapy, physiotherapy, and general rehabilitative measures may help recovery of function[22,30]. Schou[22] reported that, after recovery, 3 patients were able to take lithium again without a reduced tolerance or any exacerbation of their neurological sequelae.

Acute lithium intoxication may occur shortly after starting therapy, or during the course of stable maintenance treatment[9]. Aside from accidental or intentional overdose, precipitating factors include (i) incidental medical illness, especially if febrile, (ii) dehydration, (iii) renal failure, (iv) a low salt diet, (v) drug interactions e.g. diuretics, nonsteroidal anti-inflammatory agents, (vi) a low food intake and (vii) major surgery. These factors usually produce intoxication by reducing the renal lithium clearance, leading to lithium retention and a rise in serum lithium levels. In circumstances where the serum level does not rise, another mechanism may be operating, as will be discussed later. Sometimes no obvious precipitant can be identified[22]. Some risk factors, other than those causing lithium retention, which may predispose a patient to developing lithium neurotoxicity, have been identified. They include concomitant drug use, the psychiatric diagnosis and symptomatology and the presence of pre-existing organic brain disorders. These will be discussed in more detail later. Age and sex do not seem important[32].

CHRONIC TOXICITY

Tremor has long been recognized as a chronic neurotoxic effect of lithium and has been reported in 44 to 80% of patients[9]. The tremor is a fine, rapid, non-Parkinsonian one which may be due to an exacerbation of a pre-existing essential tremor or to the unmasking of a familial tremor[33]. Other extrapyramidal syndromes which have been recognized as chronic side effects of lithium treatment include cogwheel rigidity, with a reported incidence ranging from 5 to 60%,[34,35,36] and a Parkinsonian syndrome which is thought to be uncommon[21,36,37]. Neither the tremor nor the extrapyramidal syndromes are improved by anticholinergic drugs[34], and may in fact be worsened by them[37].

Less well recognized chronic lithium-induced neurotoxic syndromes affect other areas of the nervous system[30]. The existence of such syndromes has been questioned[38]. Lewis[39] reported a case in which a progressive cerebellar disorder was not recognized as being caused by lithium for 6 months. Neuropsychological testing also revealed the presence of cognitive dysfunction. Both the cerebellar disorder and the cognitive dysfunction resolved 10 days after ceasing lithium. Other cases of lithium-related cognitive dysfunction detected by neuropsychological testing have been reported[40].

Nystagmus, including vertical nystagmus, has been seen in acute lithium intoxication[9,12,14,27,41] and as part of the residual sequelae[3,7,19,22,23]. Several cases of chronic isolated downbeating nystagmus, occurring without an episode of

acute toxicity, have been reported[42,43]. The nystagmus persisted despite the cessation of lithium, and one patient responded to valproate[43]. A post-mortem examination of a patient who developed downbeating nystagmus following acute lithium intoxication showed neuronal damage in the regions of the nuclei prepositus hypoglossi and the medial vestibular nucleus[41]. Experimental damage to these areas in rhesus monkeys has produced downbeating nystagmus[41].

Subclinical effects on both the peripheral and central nervous systems have been reported in patients receiving chronic lithium maintenance therapy[44,45,46], as well as in normal volunteers receiving lithium[46]. The abnormalities reported in these studies included slowing of peripheral motor and sensory conduction velocities with reduction in action potential amplitudes, prolongation of interpeak latencies in brainstem auditory evoked responses, and prolongation of central conduction times measured by somatosensory evoked potentials. In one study the mean nerve conduction velocity was found to correlate inversely with the serum lithium level[44]. Lithium's ability to modify the impulse conductivity of excitable cell membranes and synaptic transmission may be responsible for these changes[44].

Other presentations of chronic lithium neurotoxicity include benign intracranial hypertension[47], a 6th cranial nerve palsy (probably due to raised intracranial pressure)[48] and a myopathy[30]. Additional neurological effects of lithium include a potentiation of the muscle relaxing effects of neuromuscular junction blocking agents used in anaesthetics[2], leading to prolonged recovery from the use of these agents[49]. This interaction may be due to the ability of lithium to inhibit or reduce acetylcholine synthesis in the presynaptic axon terminal[50]. A myasthenia gravis-like illness, thought to have been induced by lithium and responding to anticholinesterases, has been reported[51]. There is some suggestion that lithium may aggravate epilepsy, though there are also reports to the contrary[8].

PATHOLOGY

Although toxic demyelination has been suggested as the mechanism underlying the permanent neurological sequelae of lithium intoxication[30], the evidence points more in the direction of neuronal or axonal injury. Pathological studies of sural nerves from patients developing a polyneuropathy after acute lithium intoxication showed axonal degeneration[26,27,28,29]. The occurrence of cerebral[22] and cerebellar atrophy[9,19,20,22,23,29] on neuro-imaging in patients with neurological sequelae after acute lithium intoxication suggests that neuronal loss has occurred. A post mortem study of the brain of a patient who died from acute lithium poisoning

showed neuronal degeneration and dropout, with replacement gliosis and axonal swelling[41].

DIAGNOSIS

The diagnosis of lithium intoxication is primarily a clinical one, but may be aided by measurement of serum lithium levels and the EEG appearance.

SERUM LITHIUM LEVELS

Acute lithium toxicity is usually associated with high serum lithium levels, and had previously been assumed to occur only with serum levels above 2mmol/l[12], but numerous reports of toxicity occurring with therapeutic range levels have appeared[10,13,17,23,25,32,37,52,53,54,55,56,57]. The lowest recorded level associated with toxicity is 0.48mmol/l[58]. Cases of chronic lithium intoxication with normal serum levels of the cation have also been reported[33,34,39,48]. Failure to appreciate this has led to delay in diagnosis[39] which may, in cases of acute intoxication, place the patient at risk of permanent neurological sequelae or of death.

Possible explanations for the occurrence of neurotoxicity with therapeutic range serum lithium levels have been discussed in the literature. The most controversial point is the role of drug synergism, particularly the combined used of lithium and neuroleptics[32]. Cohen and Cohen's[14] report of 4 cases suggesting the incompatibility of lithium and haloperidol has been much debated[59], with evidence subsequently being presented that the combination is safe[60,61]. Other neuroleptic agents of the phenothiazine family have since been implicated[2], as have drugs with anticholinergic and antihistaminic properties[9], tricyclic antidepressants[4], and the anticonvulsants phenytoin [62] and carbamazepine[63]. Spring and Frankel[64] suggested that there may be 2 types of neurotoxicity produced by the interaction between lithium and neuroleptics. The first is a 'pure' lithium toxicity syndrome of delirium, seizures and EEG changes, but with no significant extrapyramidal symptoms. The second is a largely extrapyramidal syndrome, which could occur with haloperidol alone, which is similar to the neuroleptic malignant syndrome and which resembles the cases reported by Cohen and Cohen[14]. Spring and Frankel[64] postulated that neuroleptics other than haloperidol, for example phenothiazines, may predispose a patient to the neurotoxic effects of lithium and that lithium and haloperidol act synergistically on dopaminergic pathways to produce extrapyramidal syndromes. They cited the difference between the effects of haloperidol and phenothiazines on red blood cell lithium concentrations in support of this concept. Phenothiazines,

particularly thioridazine, enhance red blood cell lithium levels *in vitro*, by an increase in passive leak diffusion, whereas haloperidol and tricyclic antidepressants do not[65].

The following clinical and experimental evidence supports the hypothesis that lithium has an effect on dopaminergic pathways: (i) lithium alone may produce a Parkinsonian syndrome[21,66] and it enhances the Parkinsonian effects of neuroleptics[37], (ii) lithium aggravates the symptoms of idiopathic Parkinson's disease[67], (iii) lithium may cause quiescent tardive dyskinesia to reappear[68] and may either improve[69] or worsen[70] existing tardive dyskinesia, (iv) lithium reduces hyperkinesia in patients with choreic syndromes and in those patients with Parkinson's disease whose levodopa treatment has induced dyskinesias[67], (v) lithium has been reported to cause choreoathetosis in a patient with no history of tardive dyskinesia[54], (vi) lithium inhibits striatal dopamine synthesis in rats[71] and (vii) lithium may accelerate synaptosomal reuptake of dopamine[72].

Spring and Frankel[64] concluded that there did exist a potential for interactions between lithium and neuroleptics, but the issue seems not fully resolved. The same neuroleptic malignant-like syndrome described by Cohen and Cohen[14] in patients receiving combined lithium and haloperidol treatment has been seen in those taking lithium alone[73]. Psychiatric patients managed with lithium may well require additional treatment with other psychotropic agents and anticholinergic drugs, and the potential for interactions between the drugs must be recognised[9]. As this potential for interaction is not limited to the drugs discussed above, the combined use of other drugs with lithium should be carefully assessed, and kept to a minimum[9].

Severe degrees of certain psychiatric symptoms may lower a patient's threshold of lithium tolerance, leading to toxicity at therapeutic range serum lithium levels. West and Meltzer[53] described 5 acutely toxic patients with normal serum lithium levels, who had higher global ratings of psychotic symptomatology and anxiety prior to becoming toxic than did 30 patients who did not develop toxicity. They suggested that patients in the acute manic phase who are markedly anxious or psychotic may be more vulnerable to lithium toxicity. This suggestion must be reconciled with the clinical experience that some patients with bipolar affective disorder tolerate higher doses of lithium while manic than when euthymic[74]. It has also been suggested that susceptibility to lithium neurotoxicity may depend on the type of psychiatric illness suffered. Patients with schizophrenia or schizoaffective disorders may be at higher risk than those with bipolar affective disorder[10,58]. However Prien *et al*[75] could find no evidence to support this view.

Patients with pre-existing organic brain disorders may be predisposed to lithium toxicity[13,17]. Supporting evidence comes from case reports in which neurotoxicity has developed with therapeutic range serum lithium levels in severely disturbed hyperactive children[76], and in patients with a history of epilepsy[17], tardive dyskinesia[54,68] and probable multiple sclerosis[5]. However, Aminoff and Marshall[77] found no increased toxicity in patients with Huntington's disease treated with lithium. Patients with baseline EEG abnormalities[76] or with EEG abnormalities developing after a single 750mg dose of lithium[78], have been found likely to develop more severe EEG changes and clinical neurotoxicity during chronic lithium therapy, even with serum lithium levels that may be within the therapeutic range.

The development of an acute intercurrent medical illness in a patient previously stable on lithium maintenance therapy may also sensitize the patient to the ion, causing toxicity without altering serum lithium levels[32]. The concept of variable tolerance to lithium is further supported by reports of patients with very high serum lithium levels and only moderate clinical toxicity[11]. Plasma lithium levels have been found not to correlate with clinical neurotoxicity or EEG changes[58].

The pathophysiological basis for the variation in individual tolerance to lithium may be related to the intracellular:extracellular lithium concentration ratio. This ratio appears to be partially under genetic control[79], but is also subject to acquired influences. Steady state concentrations of lithium are higher in the brain than in the serum[2]. Patients who concentrate lithium intracellularly more than the average, particularly in the brain[2,56], may be more susceptible to lithium neurotoxicity[10]. It is not practicable to measure the intracellular concentrations of lithium in the nervous tissue where the ion exerts its neurotoxic effects, but animal studies show a good correlation between brain levels and red blood cell levels, greater than that which exists between brain and plasma lithium levels[80]. The red cell lithium concentration is usually expressed as a percentage of the plasma level. This red cell:plasma ratio has been found to fluctuate with the phases of bipolar affective disorders[81], and as previously mentioned is increased by phenothiazines[65]. Therefore, if red cell levels more accurately reflect brain lithium levels, it is possible that patients developing neurotoxicity with normal serum lithium levels might have relatively higher red cell:plasma lithium ratios[32,65,81].

Some clinical evidence supports this theory. Elizur *et al.*[81] reported a patient who developed acute lithium intoxication during a hypomanic relapse of a bipolar affective disorder. The plasma lithium level was within the therapeutic range at

1.1mmol/l, but the red cell:plasma lithium ratio was markedly elevated at 61.6% (control values are in the order of 30% to 40%). The neurotoxicity regressed when the patient became euthymic, and the red cell:plasma ratio fell to 30%. Four weeks later lithium toxicity reappeared during another manic relapse, and the red cell:plasma ratio had risen to 54.8%. The plasma lithium levels were said to have remained virtually unchanged. In general, these workers found red cell:plasma lithium ratios fell rather than rose in acute mania. The case they reported illustrates how it is possible for clinical lithium neurotoxicity to develop and remit, paralleled by relevant changes in the red cell:plasma lithium ratio, whilst plasma lithium levels are stable and are within the therapeutic range. Although not routinely available, red cell:plasma lithium ratios may be sensitive indicators of impending lithium toxicity[80,81], and may be more useful diagnostically in cases of suspected lithium neurotoxicity where the serum lithium levels are not elevated.

Generally speaking, patients may be at risk of lithium neurotoxicity either because of increased retention of lithium leading to raised serum levels of the cation, or because of an individual sensitivity to or lower tolerance for lithium. The serum lithium level is of only limited value in making the diagnosis of lithium neurotoxicity[32], as it may not be an accurate reflection of the brain levels of lithium, and it cannot take into account an individual's sensitivity to the ion. The clinical signs of toxicity are a better guide[18].

OTHER DIAGNOSTIC MEASURES

The CSF is usually normal in acute lithium intoxication[9], though an elevated protein and pleocytosis have been reported in some cases[25]. The EEG usually shows characteristic changes[9,11,22] which include a slowing of the dominant rhythm, progressing to θ and δ activities and disorganization of the background rhythm. Widening of the frequency spectrum occurs and some slow synchronous bilateral paroxysms of δ activity may appear[82]. Patients with chronic lithium intoxication may also show EEG slowing which reverses upon recovery[39]. The EEG abnormalities correlate with the neurological effects[49,78], and the correlation is better than that between lithium serum levels and clinical neurotoxicity[49]. Apart from the impracticalities of serial EEG recordings, the EEG changes are too non-specific and too difficult to quantify to be of practical value in the routine monitoring of patients[32]. However, baseline EEG abnormalities may suggest a potential susceptibility to neurotoxicity and may prompt a more cautious introduction of lithium therapy[32]. Furthermore, it can be difficult at times to distinguish the psychiatric manifestations of lithium intoxication from those of the underlying psychiatric illness[53], and the development of the typical

EEG changes would increase the possibility of a lithium-induced encephalopathy[32,52].

TREATMENT

Serum lithium levels may continue to rise after lithium intake is ceased, with worsening of the clinical state[18,55]. This is likely to be a result of redistribution of lithium from tissues which have accumulated the ion[2,18]. Therefore simply ceasing lithium intake may be insufficient to relieve toxicity[2] and saline diuresis to get rid of the ion is considered ineffective[11]. The only effective way of eliminating lithium from the body quickly is by dialysis[11]. Haemodialysis rapidly and effectively lowers serum lithium levels, though prolonged (12 to 16 hour) treatments are recommended, as serum lithium levels tend to rise again afterwards[7]. This rebound effect is produced by the redistribution of lithium, as mentioned above. Unfortunately, neurological sequelae may still develop despite the rapid lowering of serum lithium levels by haemodialysis[7]. While there are no guarantees of improved outcome, it makes sense to minimize the duration of the patient's exposure to toxic levels of the ion[22]. Furthermore, renal impairment may be present[7,11,22], either as the cause or result of lithium intoxication. If so, it would delay lithium clearance[12]. Aggressive treatment with haemodialysis is therefore recommended[2,7,11,24]. Some suggest that peritoneal dialysis is a suitable alternative[7], whilst others consider it much less effective[4,11]. Naturally, any aggravating factors such as dehydration, sodium depletion or acute illness should be treated, and any drugs with the potential for adverse interactions with lithium should be withdrawn or avoided. The treatment of chronic lithium neurotoxic syndromes may require no more than the cessation of the drug for resolution[39,47].

PREVENTION

Preventing the development of lithium neurotoxicity requires the active participation of both the patient and doctor, and includes the following measures: (i) careful selection of patients for treatment - i.e. use of the drug should be restricted to those in whom there is a definite indication[10], (ii) awareness by the treating physician of the different serum levels required for management of acute mania, and for maintenance therapy - lower levels are required for maintenance[10], (iii) awareness of those patients who may be at special risk of neurotoxicity, which requires a thorough pre-treatment assessment, including a check on renal function[10], (iv) knowledge of the side effects of lithium[7], particularly the features of the acute and chronic neurotoxic syndromes, (v) awareness by the treating

physician and the patient of the factors and circumstances which may precipitate intoxication, particularly with respect to drug interactions[9,10] and acute illness, (vi) education of the patient regarding potential side effects, and the need to present early, should these manifestations develop[10], (vii) regular clinical assessments and serum lithium levels[5,10,11], supplemented by EEGs where necessary[5], and red cell:plasma lithium levels if available, should be carried out. (A therapeutic serum lithium level should not lead to complacency[5], as the treating physician should be aware of the possible occurrence of lithium neurotoxicity with normal serum lithium levels), and (viii) prompt withdrawal of lithium, correction of aggravating and precipitating factors, and referral for dialysis if appropriate once the diagnosis of toxicity is made[7].

Prevention is critical, because of the not inconsiderable mortality rate of 15%, and because of the risk of permanent neurological damage from the ion.

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THE CHRONIC FATIGUE SYNDROME: A REAPPRAISAL AND UNIFYING HYPOTHESIS

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SUMMARY

The chronic fatigue syndrome is one of the most common medical problems in Western countries. Research work in virology, immunology, metabolic medicine and psychiatry in this area is reviewed and a disease model proposed. The chronic fatigue syndrome can be considered as a continuum ranging from cases with chronic viraemia on the one hand to instances of frank psychiatric illness on the other. In the majority of patients the fully evolved syndrome may involve an interaction of premorbid factors (psychological, immunological), environmental trigger factors (virus) and enhancing factors (emotional response to illness). A Venn diagram is a convenient way of expressing this concept.

The sensation of difficulty in maintaining a physical or mental effort, i.e. the sensation of fatigue, is an ubiquitous one experienced to some degree by everyone. At times it may be an appropriate response to emotional or physical stress, such as the post-event fatigue of the long distance athlete; at other times the fatigue is inappropriate to the environmental stress to which the individual has been subjected. Fatigue of this latter type, in which maximum voluntary strength is usually maintained must be distinguished from the exercise impairment which is seen in patients with myopathic or neuromuscular disorders. Fatigue occurs as a result of many everyday stresses including lack of sleep, sustained emotional concentration and unaccustomed physical work. When it is encountered it is a signal to the individual that rest is needed. Persistent fatigue which interferes with the ability to work efficiently and to enjoy normal recreational activities is a common problem encountered in family medicine. In one study, 21% of 500 unrelated patients seeking primary medical care suffered from severe fatigue with a median duration of 14 months[1]. A lesser incidence of fatigue was found in an earlier (1978) USA National Ambulatory Medical

Care Survey which preceded widespread public awareness of the fatigue syndrome[2]. This survey suggested that fatigue was responsible for 2.6% of consultations with general practitioners and 4% of visits to internists. Patients with persistent fatigue are often referred to a neurologist because of a concern that they may have a central nervous system or a myopathic disorder. The purpose of the present review is to examine recent evidence considering possible aetiological factors in chronic fatigue of uncertain cause and to present a unifying aetiological hypothesis.

HISTORICAL BACKGROUND

The scientific and industrial revolutions have improved living conditions in Western countries enormously, with the result that the environmental stresses faced by most individuals today are considerably less than those which confronted their 19th century forebears. It is not surprising, therefore, that chronic fatigue was recognised by medical authorities in the past. C.M. Beard used the term "neurasthenia" to describe patients with excessive weariness[3] and Janet, writing some year later in France, described a group of patients with psycasthenia, which he considered a form of neurosis[4]. Controversy existed from the earliest days as to whether this was an organic or a functional problem. The neurasthenic reaction was discussed by Mayer Gross *et al.* in the chapter on personality disorders and neurotic reactions in their classic text book of psychiatry[5], but the authors commented that neurasthenia seldom arose as a primary condition.

This concept of persistent fatigue as a post-infectious complication dates back to the 1940s. Brucella infection was sometimes followed by prolonged fatigue, the chronic brucellosis syndrome[6], and some patients recovering from influenza in the 1950s pandemics complained of persisting loss of energy[7]. In both these situations there was some evidence that emotional factors may have contributed to the ongoing symptoms[6,7].

Several outbreaks of severe persistent asthenia occurred in an epidemic fashion in the 1940s and 1950s in different parts of the world and were described under many different names (Iceland disease, Royal Free disease, benign myalgic encephalomyelitis). The Royal Free outbreak was particularly noteworthy in that a large number of medical and nursing staff were affected by an acute illness with fever, lymphadenopathy, patchy anaesthesia and unusual muscle spasms which led to the temporary closure of the Royal Free Hospital Group. This acute illness was followed by protracted fatigue in many staff members. The outbreak was reported by members of the hospital staff in the British Medical Journal[8].

A Lancet editorial, suspecting the presence of an encephalitic disorder, coined the term "benign myalgic encephalomyelitis"[9]. Many of the outbreaks reported at that time occurred in communities where poliomyelitis was rife and have subsequently been attributed to poliomyelitis phobia[10]. There is no doubt that in other outbreaks, such as that at the Royal Free Hospital, the presence of physical findings including fever and lymphadenopathy suggested an infective illness, at least in the initial stages. Patients with some symptoms in common with those encountered in the epidemics, mainly prolonged sensations of fatigue, were subsequently considered as suffering sporadic instances of a similar syndrome. In the 1970s re-examination of the medical records of the Royal Free outbreak by a psychiatric team led to the recognition that most of the neurological signs documented in the files, including unusual patterns of sensory loss and atypical muscle spasms, could readily be explained as hysterical phenomena. This led McEverdy and Beard to propose that the Royal Free outbreak and other like it were a form of epidemic hysteria[11,12]. This view led to a polarisation of opinion between those who considered that the epidemics had a purely physical basis and those who favoured a psychiatric explanation, and there was little emphasis on the possibility of a multi-factorial basis for the disorder. The presence of features suggestive of a viral infection early in the piece, and of a hysterical illness in the later stages was remarked on, however, by one early investigator[13]. Epidemics of chronic fatigue have been less common in recent years but still occur, as evidenced by an outbreak of a similar illness in the Lake Tahoe (Nevada) area.

CHRONIC FATIGUE SYNDROME - PROBLEMS OF DIAGNOSIS AND DEFINITION

Chronic fatigue evidenced by feelings of exhaustion after physical work, as well as by varying degrees of mental tiredness, has become increasingly common as a sporadic presentation in Western countries. Fatigue is a relatively non-specific symptom which can follow a large number of well-defined physical and psychiatric ailments but, even after detailed investigation, a group of patients remains with no distinct basis for their symptoms. The existence of a chronic fatigue syndrome, possibly related to viral infection, has received wide publicity in the lay press and many patients are aware of this entity even before consultation with an internist or a neurologist. Where a free choice medical system exists, patients may seek repeated opinions until they find a physician sympathetic to their own view of their illness. Consumer-orientated medicine of this type may lead to a view of an illness in the community that does not accord exactly with the available scientific information, a situation which has arisen in relation to the chronic fatigue syndrome.

The ill-defined nature of fatigue as the basis for a syndrome has led to considerable confusion in the literature and has resulted in attempts to formulate a working case definition. The CDC group has suggested criteria which involve the persistence for over 6 months of disabling fatigue for which there is no alternative physical or psychiatric explanation (major criteria). In addition, the patient must have either 6 of 11 minor symptomatic criteria and 2 of 3 signs or 8 of 11 minor symptoms[14]. The symptoms include mild fever measured by the patient or chills, sore throat, painful lymphadenopathy (cervical or axillary), muscle weakness, myalgia, exercise intolerance, headaches, arthralgia, neuropsychological complaints, sleep disturbance and an acute onset of symptoms. The signs comprise low grade fever, pharyngitis and cervical or axillary lymphadenopathy[14]. The time course of the minor symptoms must parallel that of the fatigue state.

Although this case definition represents an improvement over the loose criteria used previously, problems arise from the fact that all of the minor criteria and the first major criterion are non-specific and do not in themselves distinguish a true idiopathic fatigue syndrome from other conditions that may induce chronic fatigue, especially psychiatric illness. The crucial criterion is the second major one, which involves the exclusion of other physical or psychiatric diagnoses. It is a weakness of the approach that the methodology to be used to exclude psychiatric illness is not clearly set out. Where a structured interview technique such as the diagnostic interview schedule of the NIH has been used to exclude significant psychiatric illness, the percentage of patients presenting with chronic fatigue who have a significant psychiatric disorder has been found to be very high and the proportion with an idiopathic chronic fatigue syndrome small (6 of 135 patients with fatigue in one study)[15]. This approach involves the major difficulty that it does not readily allow for the patients where both psychiatric and physical facets may contribute to the condition. It encourages a division of sufferers into mutually exclusive non-organic and organic categories, and this may be inappropriate[16].

VIRAL HYPOTHESIS

Considerable work has been reported linking a chronic fatigue syndrome to infection with several common viruses. Interestingly, in studies of patient groups who are clinically very similar, American researchers have concentrated on and found some evidence to implicate the Epstein Barr (EB) virus while British research has largely concentrated on Coxsackie B virus studies.

The EB virus is a good candidate as a cause of the chronic fatigue syndrome,

given the long recognised development of asthenia in some patients with proven glandular fever, and the tendency for other Herpes viruses to produce chronic infections. Several studies have demonstrated raised antibody levels to EB virus, including antibodies to EB viral capsid antigens, in fatigue patients[17,18,19,20].

The evidence that EB virus is the sole cause of the chronic fatigue syndrome is not compelling. In one large study, mean antibody titres to several EB virus antigens tended to be higher in patients than in normal controls, but the differences generally were not statistically significant[21]. EB virus infection is almost ubiquitous in the adult population and the results of serological studies need to be interpreted with great caution. The finding of elevated titres of antibodies active against EB virus desoxynuclease and DNA polymerase, which are expressed only during viral replication, in a group of patients with prolonged illness, suggests that a small subset of patients may have ongoing EB virus infection[22]. Several of these patients went on to develop lymphoma, a development not typical of the idiopathic fatigue syndrome[22]. Elevated rubella antibody titres have been reported in one study in 20 patients with ill-defined fatigue syndromes (including depression and fibrositis). The author suggested that the introduction of a more potent strain of rubella vaccine (FA27/3) in 1979 may account for the increase in numbers of chronic fatigue patients in the 1980s, especially women[22]. Elevated titres of antibodies to Coxsackie B virus have been found in the chronic fatigue syndrome[23] and a London group has reported positive enterovirus cultures from faeces in 22% of chronic fatigue patients as opposed to 7% of controls. This finding was associated in the majority of patients with detection of enterovirus-specific IgM antibodies[24]. Use of an enterovirus group-specific monoclonal antibody directed against VPI polypeptide revealed positive results in 51% of patients[24], but further work has suggested that this is not a significant finding. Although there is convincing evidence of viral infection at the onset in some patients with the chronic fatigue syndrome, with several different viruses being implicated, there is no convincing evidence of persistent viral infection at this stage. Diagnostic labels like chronic EB virus syndrome are often inappropriate.

IMMUNOLOGICAL ABNORMALITIES

Abnormalities in both cellular and humoral immune mechanisms have been identified in the chronic fatigue syndrome. A reduction in immunoglobulin levels, especially affecting IgA levels, has been reported in a small percentage of cases[17], with reduction in IgG subsets and preservation of IgA levels in most cases in another study[25]. Total, helper and suppressor T cells levels were reduced in an Australian study where impaired cellular immunity in patch testing and a

statistically significant reduction in phytohaemagglutinin-induced lymphocyte transformation was found in fatigue patients, as opposed to controls[25]. A deficiency in natural killer cells in the chronic fatigue syndrome has been reported by one group[26]. It has been suggested that mitogen stimulated lymphocytes in the chronic fatigue syndrome synthesise less lymphokines than in controls[27]. Circulating immune complexes are found in about ⅓ of patients with the chronic fatigue syndrome, using a C1Q binding assay.

In one study an atopic tendency has been documented in over 50% of chronic fatigue subjects[28]. The significance of much of the immunological data reported is not clear in that while there is no doubt that definite immunological abnormalities exist in cases of the chronic fatigue syndrome, a direct relationship of these findings to the pathogenesis of the fatigue has not been established. Subtle immunological changes, including reduced T cell numbers and impaired T cell function, are well recognised in depressive illness[29], while the interaction between the psyche and the immune system is not completely understood. The immune abnormalities are relatively minor and unlikely to be pivotal in the syndrome.

METABOLIC FINDINGS

Exercise intolerance is a common finding in metabolic myopathies, especially mitochondrial disorders[30]. As a result, the suggestion has been raised that impaired cellular energetics may underlie the chronic fatigue syndrome. Abnormalities in phosphorus NMR studies in one patient with the chronic fatigue syndrome have indicated excessive intracellular acidosis with exercise[31]. Further studies have shown this finding to be inconstant in chronic fatigue patients and to not always differentiate fatigue from non-fatigue patients. Initial studies suggesting impaired state III respiration in isolated skeletal muscle mitochondria in the chronic fatigue syndrome[32] have not been supported by a larger study where both respiratory complex assays and assay of all glycolytic enzymes were within normal limits[33]. There is no convincing evidence that disordered muscle intermediary metabolism plays any role in the fatigue of the condition.

NEUROPHYSIOLOGICAL STUDIES

Single fibre EMG studies represent a sensitive tool for detecting abnormalities in either neuromuscular transmission or sarcolemmal conduction. Abnormalities in single fibre EMG studies were reported in 30 of 40 chronic fatigue syndrome patients in one study[34]. Our group found abnormalities in less than 10% of cases in a study utilising an age and sex matched control group[35]. These findings

support the existence of a physical problem, at least in a sub-group, but cast little light on the pathogenesis of the syndrome as a whole.

PSYCHIATRIC ABNORMALITIES

The diagnosis of a significant psychiatric disorder which could explain their symptoms in whole or in part excludes patients from the idiopathic fatigue group as defined by the CDC Committee. Most of the patients presenting *de novo* with chronic fatigue, however, have not had a detailed psychiatric work-up. Manu *et al.* studied 100 consecutive patients seen in a Fatigue Clinic. Of these patients 66 had one or more psychiatric disorders that contributed significantly to the fatigue (mood disorder - 47; somatisation disorder - 15; anxiety disorder - 9), and 5 patients had a definable medical illness. This left only 31 patients with an idiopathic fatigue syndrome[36]. Similar results were found in a study by Kruesi *et al.*, who found a high incidence of psychiatric illness in a chronic fatigue group; a historical review suggested this psychiatric illness often preceded the onset of the fatigue[37]. Both studies used a structured interview technique. Their findings suggest that the incidence of occult psychiatric illness in chronic fatigue patients may be quite high.

CONCLUSION

Research in many different disciplines has revealed abnormalities in the chronic fatigue syndrome. However, in most cases the abnormalities reported are not sufficient to explain the fatigue state in the majority of patients. Partly as a result of this, a fruitless dichotomy of viewpoint has arisen between those who regard the syndrome as purely physically based and those who see it as a form of neurotic reaction.

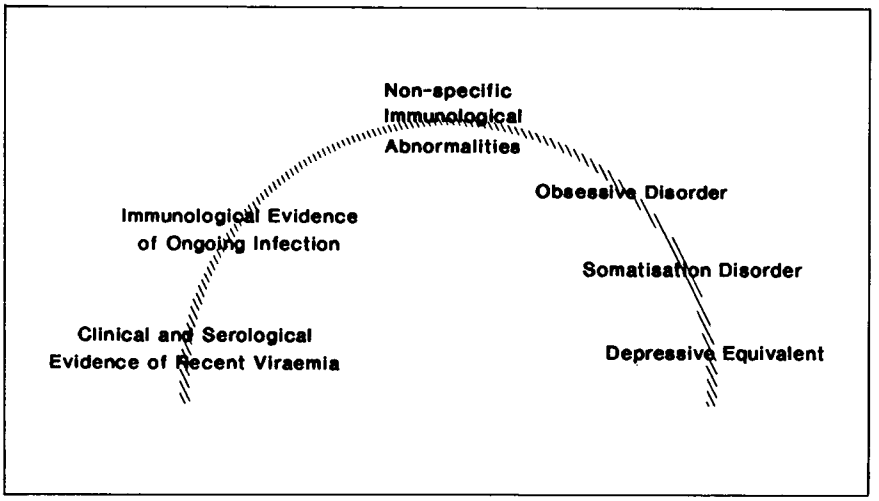

Fig 1 The chronic fatigue spectrum

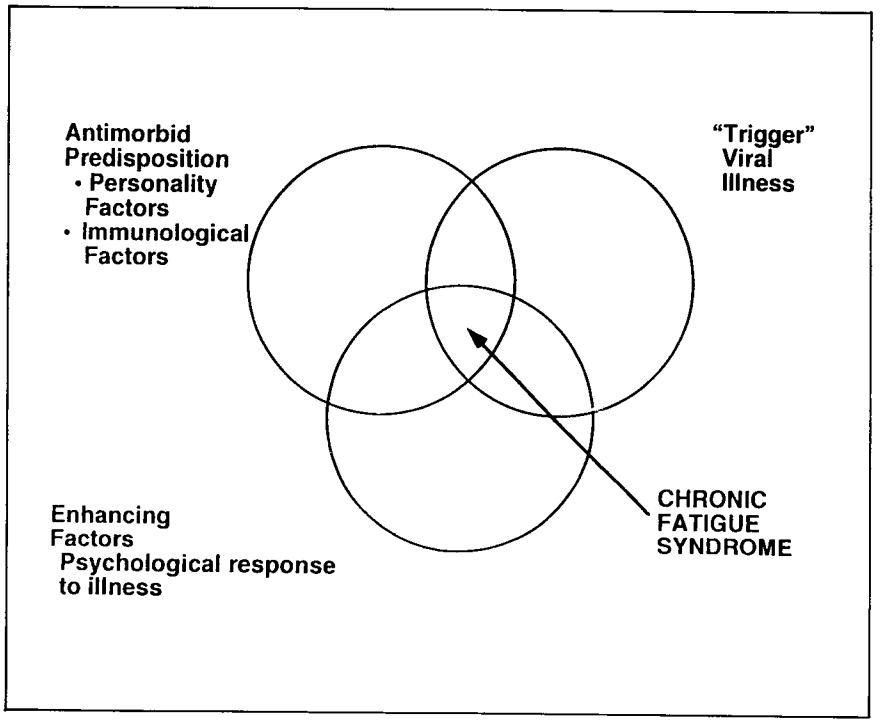

Fig 2 Overlapping factors resulting in the chronic fatigue syndrome

Examination of the available evidence indicates hat some patients can be identified who have histories compatible with their having had an acute viraemia and/or who have serological evidence of recent infection with one of several viruses. It is equally clear that this group represents a minority of all chronic fatigue sufferers. While one can postulate unidentified viral infections in the remainder, that remains conjectural. At the other end of the spectrum, it is clear that a significant number of patients suffering from chronic fatigue have a major psychiatric problem sufficient to explain their symptoms in whole or in part. Removal of these 2 groups leaves the majority of chronic fatigue patients in whom evidence of a purely infective or of a purely psychiatric aetiology is not convincing. These patients can be considered to comprise a fatigue spectrum with physical and psychiatric factors contributing to different extents in each case (Fig 1). Use of a Venn diagram model represents a convenient way to explore the aetiological factors in this multi-aetiology group. Pre-morbid factors which may predispose to chronic fatigue include psychological factors (depressive tendency) or, more speculatively, heredo-immunological factors (selective immunodeficiency for common viruses). Trigger factors may include acute viral infection or environmental stress with activation of a latent virus. Enhancing factors include the psychological response to illness. The coming together of all 3 factors (predisposition, trigger, enhancing factors) then results in the chronic fatigue syndrome (Fig 2). This model therefore involves a means of integrating the results of the available experimental studies from a number of disciplines and of avoiding a non-productive polarisation of views. Assessment of patients with the chronic fatigue requires a careful general medical and psychiatric assessment. In patients where a diagnosis of the chronic fatigue syndrome is established by exclusion, both physical and psychological factors must be evaluated and a comprehensive treatment programme evolved.

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LACK OF NEUROLOGICAL ABNORMALITIES IN LEWIS RATS WITH EXPERIMENTAL CHRONIC SERUM SICKNESS

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SUMMARY

Serum sickness in man may occur after treatment with foreign proteins such as tetanus or diphtheria antisera, and in some patients leads to neurological complications such as neuropathy or encephalomyelitis. Many of the effects of serum sickness are associated with the deposition of antigen-antibody complexes in the tissues. Chronic serum sickness in the rabbit has previously been shown to cause perivascular inflammation and demyelination in the nervous system. We induced chronic serum sickness in the Lewis rat by daily intraperitoneal injections of bovine serum albumin (BSA) in male rats that had previously received footpad inoculations of BSA. Two animals died of anaphylaxis and 15 were observed for periods of 39 to 142 days. Three animals injected with 3 mg or 4 mg/day of BSA, and 6 animals injected with up to 16 mg/day of BSA had no clinical abnormalities when sacrificed. Six animals were injected with 36 to 40 mg BSA/day and, at the time of sacrifice, were lethargic and had ruffled fur, but no neurological signs. In these animals, the production of chronic serum sickness was confirmed by the presence of immune complex deposits in the kidneys. In the nervous system, there was no evidence of inflammatory cell infiltration either in the parenchyma or the vessel walls. Immunofluorescence studies identified deposits of immunoglobulin in the choroid plexus of chronic serum sickness rats but not in controls. Staining with antibodies to immunoglobulin, complement and BSA showed marked staining of blood vessels of the nerve roots of the animals with chronic serum sickness. There was also some minor immunofluorescent staining with these markers in the blood vessels of the nerve roots of control animals, but this was always less than in chronic serum sickness animals.

Serum sickness due to the injection of foreign proteins is an immune-complex-mediated disease[1] and affects the nervous system in a small percentage of patients[2,3,4]. Serum sickness is no longer a common disease, but there is evidence implicating immune complexes in other diseases affecting the nervous system, including systemic lupus erythematosus[5] and post-infectious and post-vaccination syndromes[3,6,7], particularly the neuro-pathy associated with hepatitis-B infection[8]. Furthermore, immune complexes have been implicated in the pathogenesis of inflammatory demyelinating diseases including multiple sclerosis[9,10,11], the Guillain-Barré syndrome[9] and chronic inflammatory demyelinating polyradiculoneuropathy[12].

We were therefore interested to know whether circulating immune complexes can deposit in the nervous system and cause neuropathological changes. Experimental chronic serum sickness is a well established model of immune complex disease and has been used to study glomerulonephritis[13]. Previous studies in rats have shown that, in experimental serum sickness, immune complexes are deposited in the choroid plexus[14]. In rabbits, chronic serum sickness has been shown to cause vasculitis in the coronary arteries[1] and vasculitis and perivascular demyelination and axonal damage in the central and peripheral nervous systems[15,16]. To determine the effects of circulating immune complexes on the nervous system of the Lewis rat, we produced chronic serum sickness and studied the clinical, pathological and immunopathological consequences.

MATERIALS AND METHODS

ANIMALS

Male Lewis rats (JC strain) aged 3 to 4 months were obtained from the animal breeding facility of the University of Queensland.

INDUCTION OF CHRONIC SERUM SICKNESS

Chronic serum sickness was induced using the technique of Arisz et al.[13] which requires pre-inoculation with BSA followed by the gradual introduction of daily BSA injections. We used intraperitoneal inoculation which results in a higher incidence of immune complex deposition in extrarenal sites than does intravenous injection[17].

CLINICAL ASSESSMENT

Animals were weighed daily. They were assessed for general well-being including activity level, fur texture and cleanliness, and for neurological impairment using the scale devised by Pender[18].

HISTOLOGICAL STUDIES

At appropriate times animals were perfused with glutaraldehyde/formaldehyde[18] or with 4% formaldehyde in 0.1M phosphate buffer. Tissues were processed for routine histological examination in HistoResin (LKB Bromma) and stained with haematoxylin and eosin or cresyl fast violet[19]. Frozen sections were stained with haematoxylin and eosin or prepared for immunofluorescence. For immunofluorescent staining, 5 μm frozen sections were prepared, air dried, fixed in acetone, and then incubated with fluorescein-conjugated rabbit antibodies to rat immunoglobulin, complement and bovine serum albumin or fluorescein-conjugated $F(ab')_2$ fragments of goat antibodies to rat immunoglobulin (all antibodies from Cappel). The sections were examined with a Zeiss Axiophot microscope.

RESULTS

CLINICAL OBSERVATIONS

A total of 17 animals were injected with BSA as described above. Eight animals of the same age were untreated and were observed as controls. In the group injected with BSA, 2 animals died of anaphylaxis and 15 were observed for periods of 39 to 142 days. Three animals were given low doses (3 mg or 4 mg/day) of BSA. These animals had no clinical abnormalities when sacrificed at 46 to 67 days. Six animals were given increasing daily doses of albumin until day 39, when the daily dose was 16 mg/day. These animals had no abnormalities when sacrificed at 39 days. Six animals were injected with 36 to 40 mg/day of BSA and, when sacrificed at days 79 to 142, were lethargic and had ruffled fur, but had no neurological signs. One chronic serum sickness animal given 3 mg/day of BSA and one control animal were perfused with glutaraldehyde/ formaldehyde. Two chronic serum sickness animals given 36 to 40 mg/day of BSA and 2 control animals were perfused with formaldehyde for preparation of frozen sections.

HISTOLOGICAL FINDINGS

Kidney and heart

Kidneys and hearts from a control and a chronic serum sickness animal were

examined histologically. The kidneys of the chronic serum sickness animal showed mild cellular infiltration when compared to the control. The hearts of chronic serum sickness and control animals were histologically normal.

Nervous System

No abnormalities were found in the spinal cord, dorsal roots or sciatic nerves of the control or the chronic serum sickness animal.

IMMUNOFLUORESCENT STUDIES

Kidney

The kidneys of one chronic serum sickness and one control animal were studied. There was deposition of immunoglobulin, complement, and BSA in the glomeruli of the kidneys of the chronic serum sickness animal but not of the control.

Nervous System

In the choroid plexus of 2 chronic serum sickness animals but not of 2 controls there was deposition of immunoglobulin. There was deposition of immunoglobulin, complement and BSA in the blood vessel walls in the nerve roots of 2 chronic serum sickness animals. There was also some occasional immunofluorescent staining in the blood vessel walls in the nerve roots of control animals but this was always less than in chronic serum sickness animals. Haematoxylin and eosin staining of the sections was normal.

DISCUSSION

Lewis rats have previously been found susceptible to the development of chronic serum sickness[17]. In the present study, Lewis rats injected with high doses of BSA for 79 to 142 days became lethargic and had ruffled fur and evidence of immunoglobulin and complement deposition in the kidneys, confirming the production of chronic serum sickness.

However, in the present study no rats with chronic serum sickness developed clinical signs of neurological disturbance. One chronic serum sickness rat was examined histologically and had no abnormalities in the spinal cord or nerve roots. Two chronic serum sickness rats had evidence of immunoglobulin deposition in the choroid plexus and of immunoglobulin, complement and BSA deposition in the vessels of the nerve roots. Although immunoglobulin,

complement and BSA deposition was also present to some extent in the nerve roots of controls, it was always more prominent in chronic serum sickness animals. In previous studies Peress *et al.*[14] found immune complex deposits in the choroid plexus but not in the brain capillaries of Wistar rats with passive serum sickness. Peress and Tompkins[20] found no pathology or immune complex deposits in the brains of Wistar rats given weekly tail vein injections of albumin. However, these studies used low doses of antigen, and did not examine the nerve roots, and so would not have noted any immunoglobulin or complement deposition in the nerve roots as detected in the present study. It might be expected that immune complexes would deposit in the nerve roots because the blood-nerve barrier is relatively permeable in these regions[21,22].

Despite the evidence of immune complex deposition in the nerve roots we found no clinical or pathological evidence of damage to the nervous system such as observed in some cases of serum sickness in humans[1,2] or rabbits[15,16]. This may be because the dose of antigen was not comparable. Another possible explanation for this difference is that there are species differences in susceptibility to damage to the nervous system by immune complexes, and that the rat is relatively resistant to immune complex damage of the nervous system. Several possible mechanisms for such resistance can be suggested. Firstly, *in situ* formation of immune complexes may be pathogenic whereas deposition of pre-formed complexes, as presumably occured in the present study, may not be. *In situ* immune complex formation in the choroid plexus of rats has been demonstrated by Huang *et al.*[23] but there is no information about *in situ* complex formation in other parts of the nervous system. Secondly, it is possible that the immune complexes of only certain relevant antigens will deposit in the nervous system and cause damage. There is evidence that immune complexes deposit in the peripheral nerves in the neuropathy associated with hepatitis B[8] and that complexes of galactocerebroside and anti-galactocerebroside can cause neuropathy[24]. Thirdly, it may be that immune complexes *per se* are insufficient to cause damage but have a role in enhancing other immunological mechanisms, perhaps by damaging the blood-brain barrier thus facilitating access to the nervous system of lymphocytes and/or antibodies specific for neural antigens. The work of Colover[25], which demonstrated that experimental allergic encephalomyelitis was more severe if animals were pre-immunized with ovalbumin, may be explained by these postulated mechanisms.

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SENSORIMOTOR PERIPHERAL NEUROPATHY IN RHEUMATOID ARTHRITIS

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SUMMARY

We describe 3 patients with severe sensorimotor neuropathy complicating rheumatoid arthritis. Two patients had evidence of vasculitis and an axonal neuropathy. These patients were unusual in that the neuropathy occurred early in the course of rheumatoid arthritis. The third patient had a demyelinating neuropathy with a high cerebrospinal fluid protein level, and is a probable example of a chronic inflammatory neuropathy occurring in rheumatoid arthritis. All patients improved or were stabilized with corticosteroid therapy.

Rheumatoid arthritis may be complicated by compression neuropathy, symmetrical sensory neuropathy or mononeuritis multiplex[1,2,3,4,5,6,7]. Severe neuropathy affecting sensory and motor function is uncommon[3,7], is usually associated with rheumatoid vasculitis, commonly has the characteristics of axonal degeneration[6] and occurs late in the course of rheumatoid arthritis[4,7]. We report the histories of 3 patients with rheumatoid arthritis and severe sensorimotor neuropathy who differed from the usual clinical pattern.

CASE REPORTS

Case 1

This 73 year old male developed a left foot drop followed by numbness, pain and increasing weakness of the left lower limb. Three weeks later he developed pain in the right anterior thigh and calf and weakness of the right lower limb and was unable to stand

or walk. Two years previously he had developed pain and swelling in the wrists and in the metacarpophalangeal and proximal and distal interphalangeal joints of both hands. A diagnosis of rheumatoid arthritis was made by his local medical officer and he was treated with oral prednisone and ketoprofen, with relief of symptoms. Seven months before the onset of the foot drop he experienced further pain and swelling of the hands, and then symptoms were again successfully treated with corticosteroids. He had continued to take oral prednisone 10 mg/day until the onset of the weakness.

He had ulnar deviation of the fingers, symmetrical thickening of the metacarpophalangeal joints and wasting of the small muscles of both hands. Several splinter haemorrhages were present under the fingernails, and there were vasculitic skin lesions on the lower limbs and rheumatoid nodules on the flexor aspects of both wrists. There was wasting of both quadriceps and bilateral weakness of hip flexion. There was weakness of dorsiflexion and eversion of both feet. The deep tendon reflexes were normal in the upper limbs, but the knee jerks were reduced and the ankle jerks absent. The plantar responses were flexor. There was loss of pain and light touch sensation in a stocking distribution over both lower limbs up to the mid-calf, and bilateral impairment of joint position and vibration sense in the toes.

The erythrocyte sedimentation rate was 82 mm/hour, the platelet count was 498 x 10^9/l, the C-reactive protein level was 130 mg/l (normal <5) and testing for rheumatoid factor was positive with a level of 419 IU (nephelometry; normal <40). The antinuclear factor titre was 1:2560. Serum IgG immune complexes were 153 μg/ml (normal less than 118). Serum immunoglobulin and complement levels were normal. Syphilis serology, human immunodeficiency virus screen and hepatitis B screen were negative. The cerebrospinal fluid protein level was 360 mg/l (normal <400 mg/l). X-rays showed subluxation of the first metacarpophalangeal joints and of the interphalangeal joint of the left thumb and a large erosion of the left ulna. Results of peripheral nerve conduction studies (Table 1) were consistent with axonal degeneration. A lumbar myelogram plus computerized tomographic examination was normal. In the muscle biopsy there was a prominent segmental vasculitis seen as a lymphohistiocytic inflammatory infiltrate involving the walls of a small artery, with thrombosis of the lumen of the artery. There was lymphocytic cuffing of a venule in the adjacent adipose tissue. There was fibre grouping, and atrophic fibres were present. In the sural nerve, light microscopy revealed a severe loss of myelinated fibres. There was evidence of vasculitis affecting perineurial arteries, with lymphoid infiltration of the walls of some and eccentric fibrous scarring and thrombosis of others. Teased fibre examination showed evidence of severe axonal degeneration but no evidence of segmental demyelination. Electron microscopy showed loss of small unmyelinated fibres and evidence of axonal degeneration, but no evidence of primary demyelination.

A diagnosis of peripheral sensorimotor neuropathy secondary to rheumatoid vasculitis was made, and he was treated with prednisone 75 mg/day for 2 weeks. Azathioprine 150 mg/day was then added and the steroid dose was gradually reduced. This treatment produced improvement in his pain but no improvement in his weakness or wasting. The

C-reactive protein level fell to 6 mg/l and the ESR fell to 50 mm/hour. After 2 months, when the prednisone dose had been reduced to 50 mg/day, he developed increased weakness. The C-reactive protein level had risen to 165 mg/l. He was treated with methotrexate 10 mg twice weekly for 3 weeks. His course was then complicated by secondary infections which cleared after treatment with antibiotics and withdrawal of methotrexate. His condition is stable at the time of writing but he continues to have weakness of the lower limbs and is maintained on prednisone and azathioprine.

Table 1 Nerve conduction studies

	Controls	Case 1	Case 2	Case 3
Motor Conduction				
Median Nerve				
Terminal latency (msec)	2.6-4.0	4.5	3.2	7.3
Compound muscle action potential (mV)	5.0-20.0	10.0	6.0	1.0
Conduction velocity (m/sec)	50.0-65.0	47.9	-	45.0
Ulnar Nerve				
Terminal latency (msec)	2.0-3.1	4.3	3.0	5.9
Compound muscle action potential (mV)	7.0-16.0	5.0	5.0	2.0
Conduction velocity (m/sec)	50.0-66.0	59.7	48.0	35.5
Lateral Popliteal Nerve				
Terminal latency (msec)	2.9-5.6			10.2
Compound muscle action potential (mV)	2.5-14.0	No Response	No Response	<0.2
Conduction velocity (m/sec)	41.0-56.0			22.5
Sensory Conduction				
Median Nerve				
Sensory action potential (μV)	10.0-50.0	Absent	10.0	Absent
Ulnar Nerve				
Sensory action potential (μV)	5.0-44.0	Absent	8.0	Absent

Case 2

This 63 year old woman presented in December 1980 with 7 days of difficulty in walking. She noticed inability to dorsiflex the right foot and 6 days later inability to

dorsiflex the left foot. For one month she had also had numbness of both feet, particularly on the lateral aspects, and of the fingers. For 4 months she had experienced pain and stiffness of the fingers, wrists, elbows, shoulders, knees, ankles, feet and temporomandibular joints which responded poorly to treatment with non-steroidal anti-inflammatory drugs. In December 1985 she had experienced an episode of pancreatitis secondary to gallstone obstruction, and had undergone cholecystectomy in January 1986. One month before the onset of the presenting neuropathic symptoms she had been found to be diabetic.

There was swelling and tenderness of the shoulder, wrist, proximal and distal interphalangeal, knee and ankle joints bilaterally. There was wasting of the quadriceps and the intrinsic muscles of the hands. Both hands also had features of flexor tenosynovitis. There were no rheumatoid nodules. There was weakness of all muscle groups, but the weakness was worse distally and there was bilateral absence of ankle dorsiflexion. The deep tendon reflexes were normal in the upper limbs, but the knee jerks were reduced and the ankle jerks absent. There was reduction in perception of all modalities of sensation over the fingers of the right upper limb in the distribution of the ulnar nerve and over the feet up to the ankles, with additional sensory loss over the lateral aspects of the legs.

Serum urea, creatinine, electrolytes and thyroid function tests were normal. The blood glucose level was 13.6 mmol/l, and the glycosylated haemoglobin level was 12.4 (normal <6.5). Serum B_{12} and folate levels were normal. The creatine kinase level was 240 u/l (normal range 20-140 u/l). The ESR was 80 mm/hour at the onset of the neuropathy and the platelet count was 636 x 10^9/l. The C-reactive protein level was 216 mg/l (normal <5 mg/l), rheumatoid factor was present with a titre of 1:256 (Rose-Waaler) and the antinuclear factor titre was 1:160. Serum immunoglobulin and complement levels were normal. Hepatitis B surface antigen was not present. The CSF protein level was 260 mg/l (normal <400 mg/l). X-rays of the hands showed generalized osteoporosis and early juxta-articular erosions of the proximal phalanges of the left 5th and the right 2nd digits. Nerve conduction studies were consistent with axonal degeneration (Table 1). In the muscle biopsy there was evidence of type II muscle fibre atrophy, but no evidence of acute or chronic denervation or of polymyositis. One artery showed perivascular cuffing with a sparse mononuclear cell infiltrate that also focally invaded the arterial wall, which was thickened. A sural nerve biopsy showed extensive loss of myelinated fibres. There was a focal sparse lymphocytic vasculitis involving the small vessels of the perineurium. Skin biopsy showed a focal sparse lymphocytic vasculitis involving a small vessel near the sweat glands and several vessels of the superficial dermal plexus.

The patient was treated with insulin. However, her neurological problems became worse and she developed a vasculitic rash over the lower limbs, with the sudden onset of pain and numbness of the right thumb and weakness in the upper limbs. She also developed pain in the posterior thighs. Because of the progression of the neuropathy at the time of the development of vasculitic lesions, a diagnosis of rheumatoid vasculitis causing neuropathy was made. She was treated with 4 pulses of 1 or 2 g intravenous

methylprednisolone over 2 weeks and oral cyclosphosphamide 100 mg/day for one week and then cyclophosphamide 150 mg/day for 2 weeks. The neurological signs stabilized and the pain settled dramatically. After this initial therapy, oral prednisone 75 mg/day was commenced and the cyclosphosphamide dose was reduced. The ESR fell to 40 mm/hr. She has since been taking low dose (5 - 10 mg) prednisone daily and has become mobile and independent, although she continues to have symptoms and signs of neuropathy.

Case 3

This 72 year old female developed paraesthesiae in the feet and legs, pains in the legs and feet, lower limb weakness, loss of balance and difficulty in walking. She was admitted to hospital 2 weeks after the onset of symptoms and continued to deteriorate for another 4 to 6 weeks. She had a past history of rheumatoid arthritis which commenced at the age of 35 years and affected her hands, wrists, elbows, shoulders, neck, ankles, feet and hips. She had been treated at different times with non-steroidal anti-inflammatory drugs, gold injections and corticosteroids. She was not being treated with corticosteroids at the onset of the neuropathy, but was taking phenylbutazone and naproxen.

She had ulnar deviation of the fingers and swelling of the metacarpophalangeal joints. There was pain on movement of the neck, hands, wrists, knees and feet. There was deformity of the toes, and synovial thickening of the knees. There was no evidence of cutaneous vasculitis. Cranial nerve examination was normal. There was weakness of the lower limbs but in the upper limbs power was normal except for difficulties associated with the rheumatoid hand deformities. The upper limb reflexes were normal but the knee and ankle jerks were absent. There was impairment of all modalities of sensation in a stocking distribution up to the knees. In the upper limbs, sensation was normal. Romberg's sign was positive. She continued to deteriorate after admission to hospital, the weakness and sensory disturbance spreading to the upper limbs.

Serum urea, electrolytes, liver function tests and thyroid function tests were normal. Serum complement and immunoglobulin levels were normal. Serum electro-phoresis suggested an acute phase reaction. The ESR was 64 mm/h at the onset of the neuropathy. The platelet count was 321 x 10^9/l. Rheumatoid factor was present with a titre of 1:40 (Rose-Waaler). Testing for anti-nuclear factor was negative. The results of nerve conduction studies are shown in Table 1 and were consistent with primary demyelination. The CSF protein was 990 mg/l.

She was given oral prednisone 80 mg on alternate days and had a gradual reduction in pain and improvement in strength. The steroid dose was gradually tapered. About 6 months after the onset of neuropathy, when she was receiving prednisone 10 mg on alternate days, there was clinical and biochemical evidence of an increase in the activity of the rheumatoid arthritis. This responded to increasing the dose of steroids, and later to treatment with penicillamine. Six years after the onset of the first episode of neuropathy she became weaker and had increased pain in the lower limbs. The CSF

protein was 2,400 mg/l. She improved with an increased dose of prednisone and since then has been steroid dependent, with continuing evidence of peripheral neuropathy.

DISCUSSION

All 3 patients fulfilled the criteria for the diagnosis of rheumatoid arthritis[8] and had evidence of disease activity at the onset of their neuropathy, which in all cases was of a severe sensorimotor type. The first 2 patients had cutaneous vasculitis and mononeuritis multiplex with additional symmetrical neuropathy. In these patients the duration of rheumatoid arthritis before the onset of neuropathy was brief (4 months to 2 years). This contrasts with the observations of Chamberlain and Bruckner[4] that patients had a mean duration of rheumatoid arthritis of 9.9 years before the onset of severe sensorimotor neuropathy and with the view of Conn[7] that sensori-motor neuropathy develops in patients with longstanding rheumatoid arth-ritis. Patient 2 also had a history of diabetes mellitus which had developed after pancreatitis 12 months previously. However, the simultaneous occurrence of new neuropathic lesions and vasculitic skin lesions, the muscle, nerve and skin biopsy evidence of vasculitis, the biochemical evidence of active rheumatoid arthritis and the beneficial response to immunosuppression strongly suggest that rheumatoid arthritis was the cause of the neuropathy. These 2 patients are similar to those described by Vollertsen *et al.*[9] in a survey of rheumatoid vasculitis. In our patients the biopsies showed evidence of vasculitis and axonal degeneration such as described by Conn *et al.*[6] in rheumatoid neuropathy. Beckett and Dinn[10] also found axonal degeneration and arterial occlusion in their 2 patients with clinical rheumatoid neuropathy. Van Lis and Jennekens[11] and Conn *et al.*[6] have found immunoglobulin and complement deposition in the nerves of patients with rheumatoid neuropathy. In our patients the neuropathy was progressive until treated with aggressive immunosuppression. Beneficial effects of azathioprine in rheumatoid neuropathy have also been reported by Chamberlain and Bruckner[4] and Conn[7] recommended aggressive treatment of rheumatoid sensorimotor neuropathy. We confirm that early aggressive treatment of vasculitic neuropathy associated with rheumatoid arthritis is beneficial and may prevent involvement of other areas of the peripheral nervous system.

In Case 3, rheumatoid arthritis had been present for 35 years before the onset of neuropathy. There was no evidence of cutaneous vasculitis but laboratory tests indicated that the rheumatoid arthritis was active, although less so than in Cases 1 & 2. The CSF protein was increased, and the electro-physiological abnormalities were consistent with primary demyelination. These features, and

the clinical history of response to steroids and relapse with steroid withdrawal, are typical of an inflammatory demyelinating polyneuropathy such as chronic inflammatory demyelinating polyradiculo-neuropathy (CIDP). It is difficult to decide whether this was a chance relationship or whether the rheumatoid arthritis had influenced the development of neuropathy. There is a report of a patient with rheumatoid arthritis developing an acute inflammatory demyelinating polyradiculo-neuropathy[12], and studies of chronic inflammatory demyelinating polyradiculo-neuropathy have found that some patients have associated autoimmune diseases[12,13]. There are also reports of chronic demyelinating neuropathy developing in patients with other rheumatological diseases such as systemic lupus erythematosus or Sjögren's syndrome[14,15]. In the sural nerves taken from rheumatoid arthritis patients without clinical or electrophysiological evidence of neuropathy there was segmental demyelination[9]. Conn and Dyck[16] argued that, in rheumatoid arthritis, arterial occlusion causes ischaemic axonal degeneration and secondary demyelination. However, in our patient there was evidence of a primary demyelinating neuropathy. In the presence of active rheumatoid arthritis, it seems possible that the development of the neuropathy may have been directly or indirectly related to the rheumatoid arthritis. One mechanism by which rheumatoid arthritis could cause demyelinating neuropathy is that of 'vasculomyelinopathy' [17] where it is proposed that immune complex deposition in blood vessels may lead to the entry of inflammatory cells into the neural parenchyma, with resultant primary demyelination. Another explanation is that rheumatoid arthritis may be associated with a disturbance in immunoregulation which predisposes to the development of an inflammatory neuropathy. Thus, while it is not certain that the neuropathy in this patient was related to the rheumatoid arthritis, similar associations may be found with other autoimmune diseases, and there are possible mechanisms by which this can occur.

We have described subacute sensorimotor neuropathy with mononeuritis multiplex in 2 patients with active rheumatoid arthritis and vasculitis. These patients developed neuropathy within a short period of the onset of rheumatoid arthritis and obtained benefit from immunosuppressive treat-ment. In the third patient there was a relapsing sensorimotor neuropathy with primary demyelination but no clinical evidence of vasculitis. This patient also responded well to corticosteroids.

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PALMAR COLD THRESHOLD TEST AND MEDIAN NERVE ELECTROPHYSIOLOGY IN CARPAL TUNNEL COMPRESSION NEUROPATHY

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SUMMARY

The diagnosis of median nerve compression neuropathy at the carpal tunnel is usually confirmed by clinical electrophysiology. The classical findings of a significantly slowed median nerve conduction velocity for both sensory and motor fibres, with a prolonged distal motor latency and a reduced amplitude compared to age-related norms are unambiguous, but these criteria are often present only in part. In such cases another quantitative indicator of compression neuropathy would be extremely helpful. The present study aimed to test whether measurement of warm and cold sensory acuity in cases of putative median nerve carpal tunnel compression would aid diagnostic certainty. Warm sensation is mediated by unmyelinated C-afferents, while cold sensation is conveyed by thinly myelinated Aδ afferents. Because compression usually blocks larger diameter fibres first, cold perception on the skin of the palm distal to the compression should be more impaired than is warm perception. Standard electrophysiological measurements (median and ulnar motor and sensory nerve conduction velocities) were made, then perceptual thresholds for both warm and cold stimuli were measured on the skin of the wrist above the carpal tunnel and on the palm of the affected hand in 59 subjects. There was a significantly reduced median motor nerve conduction velocity and prolonged distal motor latency compared to normals. Further, although both thermal thresholds at the wrist were normal, those on the palm were elevated, cold being significantly raised ($P<0.02$) compared both to warm and to age-matched controls. Correlation of the nerve conduction velocity findings and thermal sensory acuity did not yield significant covariance of the positive and negative findings. Overall the results suggest that detection of preferentially elevated cold perceptual threshold (ie reduced cold sensory acuity) on the skin of the palm may aid in the diagnosis of putative carpal tunnel compression in patients with minimal or ambiguous

electrophysiological data and provide a functional index of recovery after decompression.

Historical landmarks relating to the effects of nerve compression and the diagnosis of compression neuropathy[1,2,3] have been reviewed felicitously by McComas[4] and Sunderland[5]. Observations on the effects of experimental ischaemia and compression by pneumatic tourniquet[6,7,8] are relevant to the pathophysiology of the carpal tunnel syndrome, as is the dissociation of cold and warm sensation during compression[8]. Previously, electrophysiological tests have been considered unnecessary when the history and physical examination provide clear-cut evidence of carpal tunnel compression neuropathy[5]. However, since Simpson's early description of electrical signs in carpal tunnel and related syndromes[9], the value of routine electrophysiological confirmation has been universally accepted.

The classical electrodiagnostic features of median nerve carpal tunnel compression[5] include a prolonged median sensory conduction latency from digit to wrist; a reduced amplitude or absence of the evoked sensory action potential at the wrist: a prolonged distal motor latency, a slowed motor nerve conduction velocity and EMG abnormalities. However, there are some patients with indisputable clinical evidence of a carpal tunnel syndrome who also have median nerve conduction times that are within generally accepted normal limits[5]. Recognising this, measurements of various other additional electrophysiological features have been proposed[10,11,12,13,14,15] in attempts to enhance electrodiagnostic certainty.

The aim of the present study was to evaluate a new quantitative test of thermal sensory function[16,17,18] as an adjunct to conventional electrophysio-logical measures in the diagnosis of carpal tunnel compression neuropathy. The strategy of the study relies on the fact that warm and cold sensations are differentially conveyed from their respective receptors by unmyelinated C-thermal and C-nociceptive afferents in the case of warm, while cold sensations utilise thin myelinated Aδ afferent fibres. Because compression usually blocks larger fibres first[5], cold perception on the palm distal to the carpal tunnel should be impaired earlier and more severely than warm perception[19,20]. The present study tests this hypothesis.

MATERIALS AND METHODS

Seventy patients who presented at the International Diabetes Institute, Caulfield General Medical Centre with putative carpal tunnel syndromes were screened for the study. Of these, 11 patients had diabetes mellitus according to WHO criteria, and were excluded

from this study. All the remaining 59 patients had warm and cold perception thresholds measured on the anterior aspect of the wrist and on the palmar skin of the most symptomatic hand by a Medelec TTT apparatus. In this automated thermal threshold test[16,17,18], warm or cold stimuli are delivered to the skin surface though a metal Peltier thermode. The magnitude and duration of the applied current regulate the thermal stimulus and a constant rate of change of temperature (1^0C per sec) is provided for each stimulus. Thermal stimuli are presented during only one of 2 time windows shown to the subject by a pair of illuminated light-emitting diodes and the subject must indicate using a switch in which time period each stimulus occurred. The subject's success rate is analysed by the microprocessor using the "up-down transform rule" to compute the temperature which the subject can detect reliably.

A Cadwell 5200A portable EMG machine was used to record the median and ulnar sensory and motor nerve conduction velocity and distal motor latency to the abductor pollicis brevis (APB) or abductor digiti minimi (ADM) respectively. Electrode placements and techniques were those of De Lisa and McKenzie[21].

Statistical analyses of the data were performed using the SPSS-X student package on an IBM PC 286-compatible microcomputer, and the Sigmaplot 4.0 statistical routines.

RESULTS

NERVE CONDUCTION STUDIES

Fig 1a displays in diagrammatic section the structures and pressure relationships within the carpal tunnel. In Fig 1b median sensory median sensory nerve conduction velocity is plotted for 43 study subjects: 21 of these (49%) showed nerve conduction velocity slowing below the lower 99% confidence limit of the normal range at the age of 40 years. This figure was reduced to 12 of 43, if age-corrected for all subjects (Fig 1b). The mean median sensory nerve conduction velocity for the carpal tunnel syndrome group was 46.4 ± S.D. 6.57 m/s.

Using surface EMG recording on the abductor digiti minimi (ADM), the ulnar motor nerve conduction velocities for 57 of the study patients are shown in Fig 2a and are seen to lie within the 99% confidence limits of the normal range for age. By contrast, in Fig 2b the median motor nerve con-duction velocity recorded at the abductor pollicis brevis (APB) is seen to lie below the normal age-corrected lower limit in 30 of the 59 patients with a carpal tunnel syndrome. The mean median motor nerve conduction velocity to the APB was 43.2 ± 6.90 m/s for the carpal tunnel syndrome group.

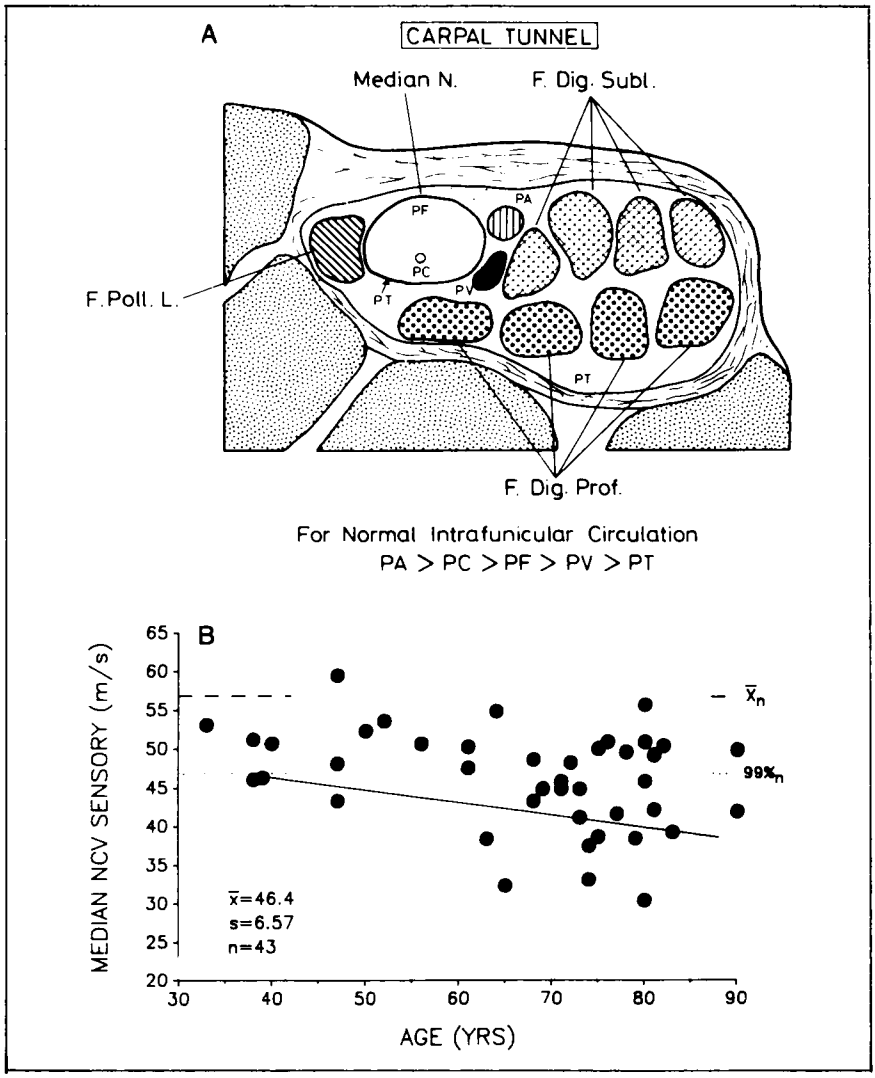

Fig 1a Diagrammatic section across the carpal tunnel showing the relationship between bony, ligamentous, vascular, tendinous and neural structures. The normal ranking of pressure relations are arterial (PA)> capillary (PC)> funicular (PF)> venous (PV)> intratunnel pressure (PT) for a normal median nerve intra-funicular circulation. [Based upon Sunderland[5]].

Fig 1b Shows median sensory nerve conduction velocity (m/s) plotted against age for 43 putative carpal tunnel syndrome subjects. The mean normal sensory median nerve conduction velocity (57.2 m/s) dashed line is for the decade 30-40 years. The lower 99% confidence limit of the normal range at age 40 is indicated by a dotted line. Only 12 of 43 subjects lie below the lower limit of the age-corrected range (solid line).

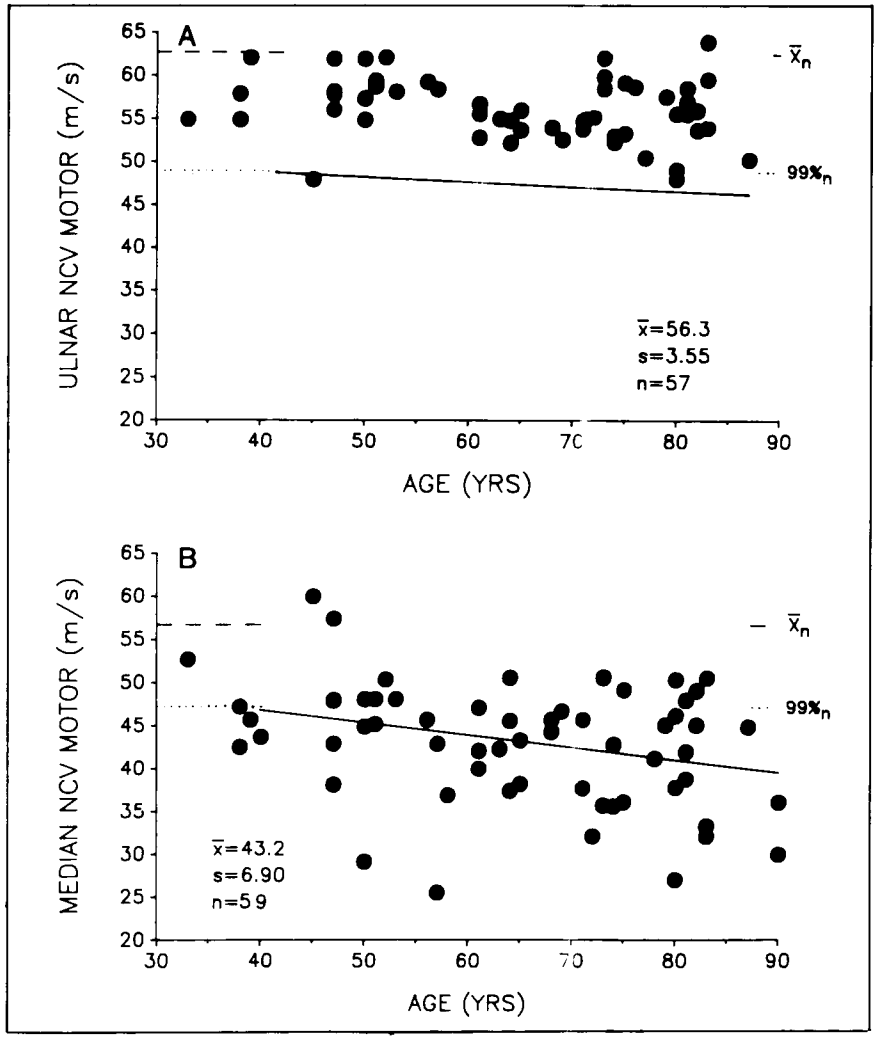

Fig 2a Ulnar motor nerve conduction velocity, recorded from the ADM, plotted against age for 57 subjects in the carpal tunnel syndrome group. The mean normal ulnar motor nerve conduction velocity $\bar{x}n$ 62.8 m/s dashed line is for the decade 30-40 years. Ulnar motor nerve conduction velocity for all carpal tunnel syndrome subjects is above the age-corrected normal lower limit (solid line) and the mean is 56.3 m/s.

Fig 2b Median motor nerve conduction velocity, recorded from the APB, plotted against age for 59 subjects in the carpal tunnel syndrome group. The mean normal median motor nerve conduction velocity $\bar{x}n$ 56.91 m/s (dashed line) is for the decade 30-40 years. The median motor nerve conduction velocity for 30 of 59 carpal tunnel syndrome subjects lies below the age corrected lower limit (solid line).

Fig 3a shows the differences in m/s for the ulnar motor nerve conduction velocity minus the median motor nerve conduction velocity for each study patient. Of the 55 study patients' data plotted, 31 showed differences in nerve conduction velocities greater than 12 m/s (upper 99% confidence limit for normal subjects). In Fig 3b median nerve distal motor latency to the APB is plotted for 58 study patients. Twenty of these were prolonged beyond the upper 99% confidence limit for normal subjects. The mean median distal motor latency to the APB was 4.54 ± S.D. 1.77 ms for the carpal tunnel syndrome group.

THERMAL PERCEPTION THRESHOLDS

Using the Medelec TTT device, warm and cold perception thresholds were measured for a site on the anterior aspect of the wrist and on the palm of the more symptomatic hand. These data from normal control subjects and patients with putative carpal tunnel syndromes are shown in Fig 4 and Table 1. In Fig 4a the forearm warm and cold perception thresholds for the carpal tunnel syndrome group both tended to be slightly higher, but not significantly different (Table 1) from those of control subjects for the same sites. In Fig 4b warm perception thresholds on the skin of the palm in the carpal tunnel syndrome group were significantly elevated (mean 0.61^0C) compared to those of the control group (mean 0.23^0C) - see Table 1. A more marked elevation of cold perception threshold was found on the palmar skin of the carpal tunnel syndrome group (mean 0.94^0C), significantly different from the control group (mean 0.21^0C) ($P<0.002$). The elevated cold thresholds in the carpal tunnel syndrome group were significantly different from the elevated warm thresholds ($P<0.05$). The detailed means and standard deviations for each group are given in Table 1.

Table 1 Warm and cold perception thresholds in ^{0}C for control subjects and patients in the putative carpal tunnel syndrome (CTS) group.

	Anterior forearm		Palm of hand	
	Warm(^{0}C)	Cold(^{0}C)	Warm(^{0}C)	Cold(^{0}C)
Control x	0.18	0.17	0.23	0.21
CTS x	0.30	0.27	0.61*	0.94**
Control s	0.22	0.11	0.17	0.15
CTS s	0.25	0.17	0.60	0.87
Control n	124	113	33	34
CTS n	44	46	53	59

* = $P<0.05$ ** = $P<0.002$

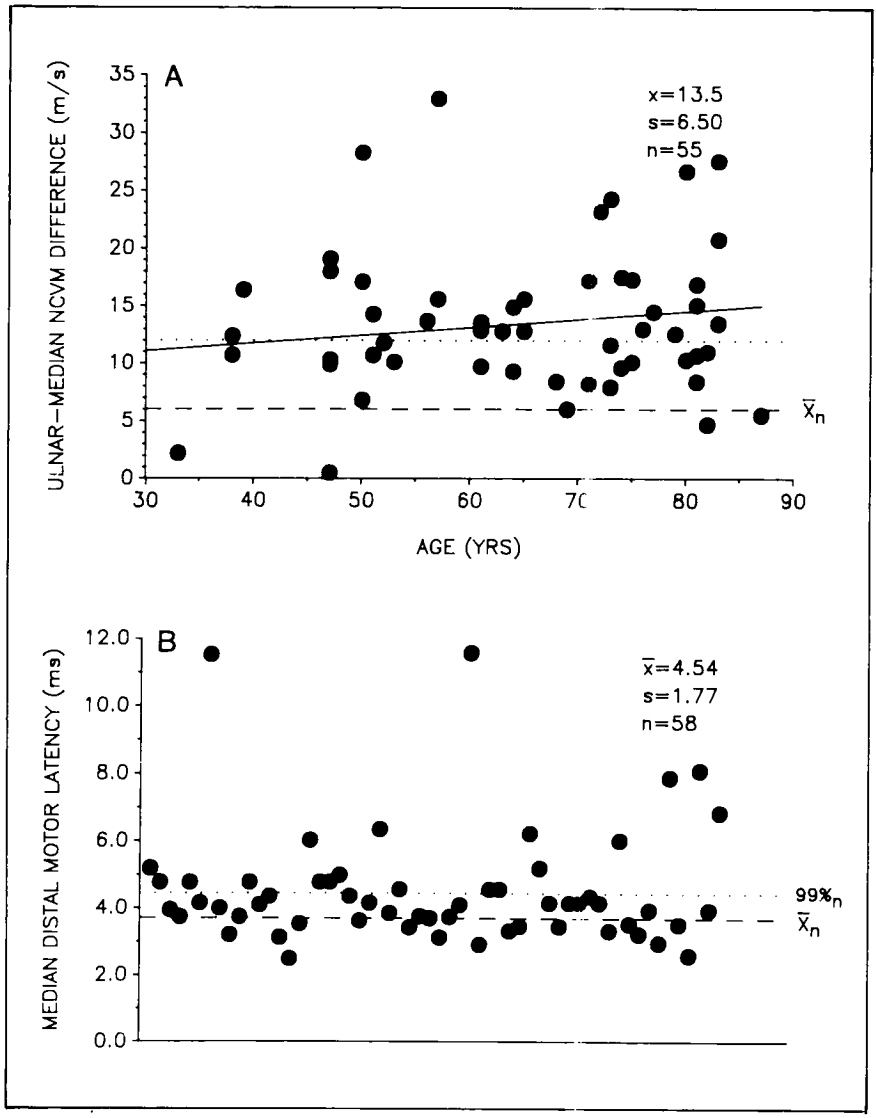

Fig 3a Showing the motor nerve conduction velocity difference in m/s for ulnar minus median nerve for each study subject. Of the 55 patients in the carpal tunnel syndrome group, 31 showed motor nerve conduction velocity differences greater than 12 m/s (upper 99% confidence limit for normal subjects).

Fig 3b Median nerve distal motor latency (ms) from the wrist to the APB shown for 58 subjects in the carpal tunnel syndrome group. Of these, 20 were prolonged beyond the upper 99% confidence limit for normal subjects (4.25 ms - dotted line).

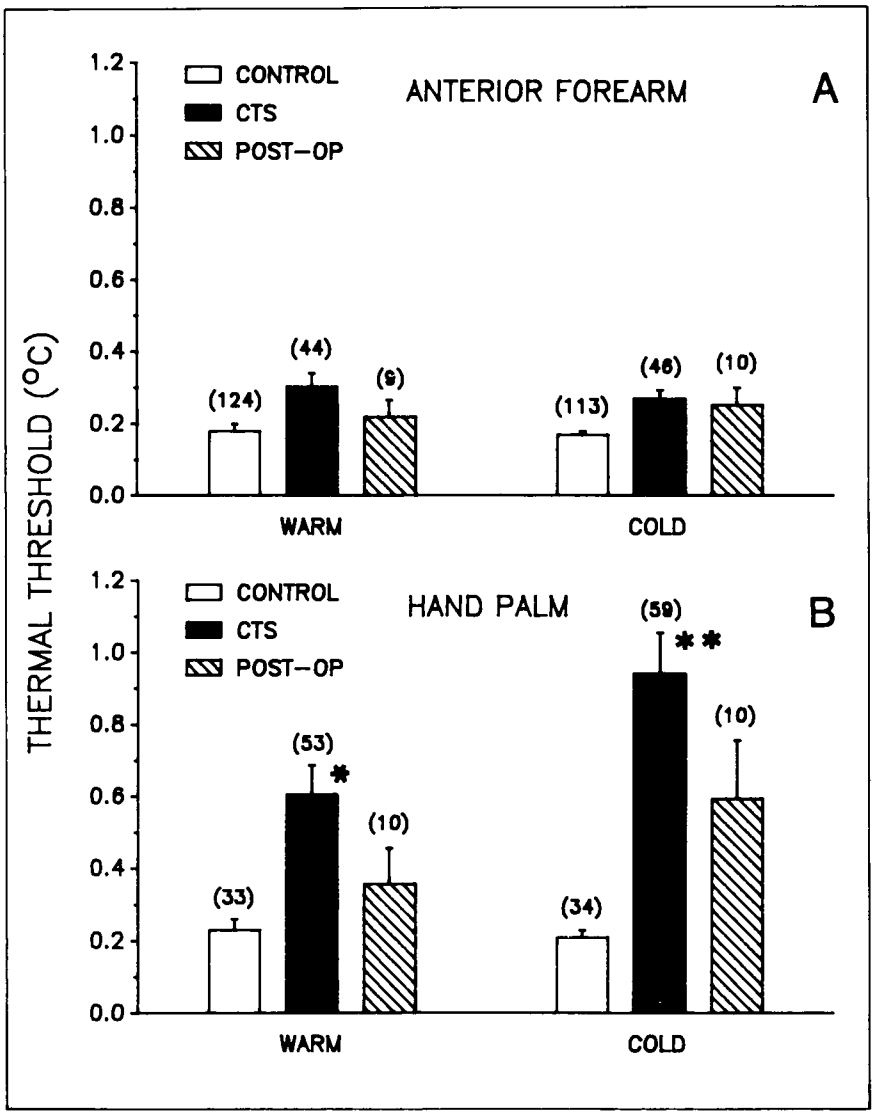

Fig 4 Histograms showing mean thermal perception thresholds for warm and cold stimuli on a: forearm and b: palm of hand. Means and standard error bars are shown for the control group (open rectangles) carpal tunnel syndrome group (solid rectangles) and 3-4 months post-decompression surgery (hatched). The number of subjects is given in parentheses above each histogram column.

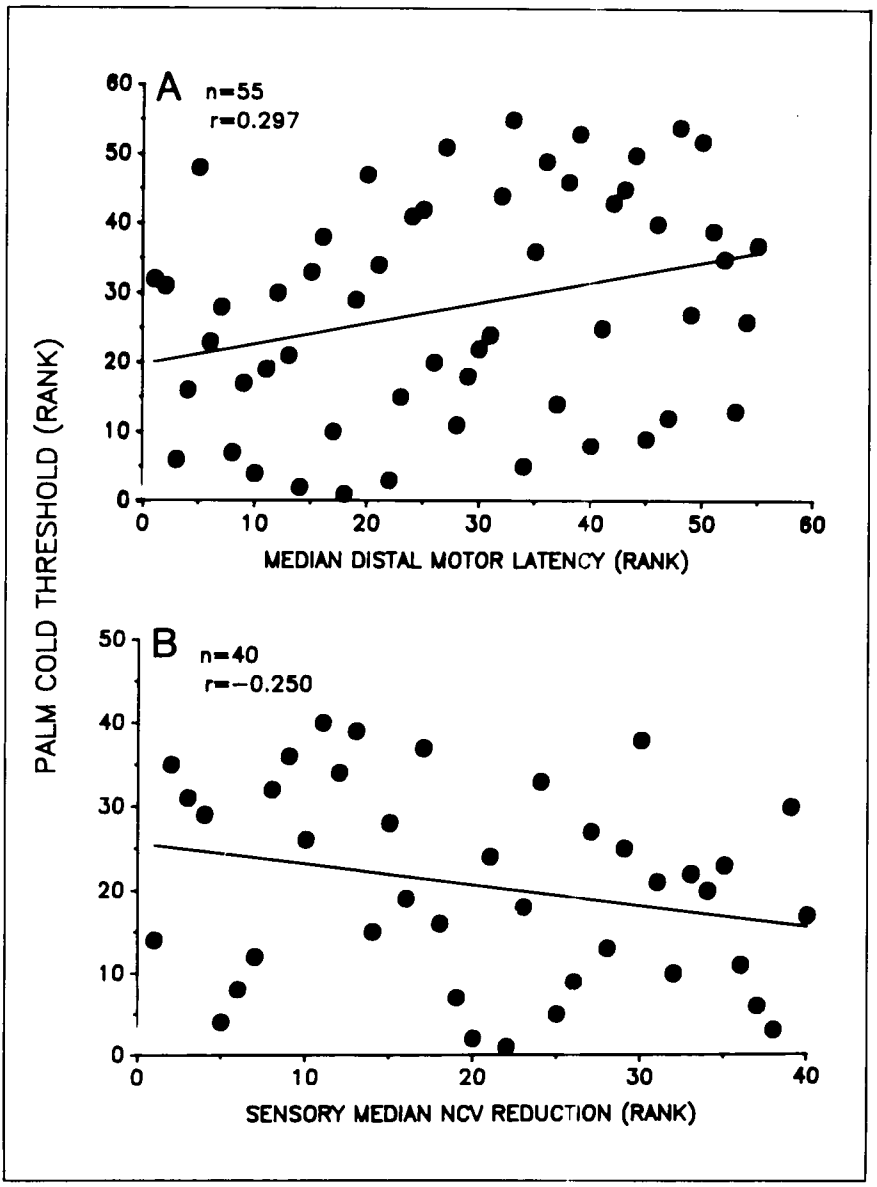

Fig 5 Graphical ranking for carpal tunnel syndrome subjects of cold threshold (y axis) against a: median nerve distal motor latency (n=55), and b: ranking of sensory median nerve conduction velocity reduction below the age-related normal limit (n=40). The 'r' values are given at the top left, but neither of the covariance regressions (solid line) showed statistical significance.

COVARIANCE OF ELECTROPHYSIOLOGY AND COLD THRESHOLD

Fig 5 displays the dependent variable cold threshold plotted against two main independent variables: Fig 5a - median distal motor latency; Fig 5b - median sensory nerve conduction velocity; these relationships showed a trend to some degree of covariance in the carpal tunnel syndrome group, but neither of the slopes in a or b was significant. The relationships between the ulnar-median motor nerve conduction velocity and the median motor nerve conduction velocity and the cold threshold also failed to show significant covariance, and are not illustrated.

DISCUSSION

In Fig 1a it can be seen that the anatomical boundaries of the carpal tunnel are bones and strong ligament, both unyielding. Pressure on the median nerve in the carpal tunnel increases if the capacity of the carpal tunnel canal is reduced, if the contents of the canal are increased or if movements of the wrist and structures passing though the carpal tunnel lead to dynamic compression of the nerve or its endoneurial vessels[5,22]. Indeed any alteration of the normal pressure relationships (Fig 1) may impair the intrafunicular circulation[5]. Irrespective of the cause of the carpal tunnel syndrome, in 11 out of 70 patients studied diabetes mellitus was a possible complicating factor and these patients were excluded from the study. In the 59 carpal tunnel syndrome patients analysed, there was a significant difference between the electrodiagnostic findings and the elevated cold threshold compared with the same parameters in a normal control group of subjects. In spite of this finding, there is not a significant covariance between the positive electrodiagnostic features and an elevated cold threshold. How may this be explained?

Firstly, while these carpal tunnel syndrome patients have been considered as a homogeneous group, it must be conceded that the patho-physiological disturbances may vary, or may be composite in any given patient. Such causal factors so far identified include (i) mechanical pressure leading to axonal structural changes[23] (ii) ischaemia or intraneural circulatory changes[7] (iii) impaired axonal transport[24] (iv) axonal membrane/myelin disturbance[25]. This means that in individual patients, even where the aetiology of the carpal tunnel syndrome appears idiopathic, the neural symptoms and functional disturbances may result from one or more different pathophysiological mechanisms, either alone or in combination. This could lead to different effects on the function of

different classes of nerve fibres. For example, damaged motor fibres in the median nerve in the carpal tunnel syndrome are abnormally susceptible to ischaemia[26].

Another possible explanation lies in the fact that different authors have no general agreement about the sequence of functional disturbances resulting from even a single factor causing conduction block, such as pressure[5]. Possible causal disturbances such as compression (whether acute[22], chronic or mixed), ischaemia and possibly traction are all relevant to the pathogenesis of the carpal tunnel syndrome[5]. In essence, all of these factors are capable of producing interruption of conduction with preservation of axon continuity. There is considerable experimental evidence that larger myelinated fibres are most susceptible to compression[6,27,28]. By contrast, ischaemia and hypoxia tend to block small fibres first[27,29,30,31]. These varied results reported in relation to fibre size, fibre function and survival time provide confirmation that the initial hypothesis in the present study was too simplistic.

Thus we have demonstrated in the presently studied carpal tunnel syndrome patients a significant functional impairment of thermal acuity, cold being more affected than warm. Although there was a clear tendency towards functional recovery of thermal sensation in the 11 patients retested 3 to 4 months post operatively, there is the paradoxical lack of any strong covariance between sensory and motor median nerve conduction slowing, increased distal motor latency and the elevated palmar cold threshold.

It is recognised that some patients with clinical features of the carpal tunnel syndrome have median nerve conduction times within normal limits. Because of this, additional electrodiagnostic features have been proposed to enhance the sensitivity of confirmatory tests[5]. These include: (i) the examination of the difference in distal motor latencies between median and ulnar nerve (normally < 1.2 ms and > 1.5 ms should be regarded as abnormal[10]); (ii) if the sensory nerve conduction velocity (digit to wrist) is equivocal, it should be measured separately from digit to palm and from palm to wrist (the latter is often abnormally slow[11,12]); (iii) in mild carpal tunnel compression, submaximal stimuli reveal an abnormally prolonged latency in $> 80\%$ (cf $< 50\%$ if supramaximal stimuli are used[13]); (iv) use of the superficial radial nerve for normal comparison rather than the ulnar nerve[14], cf[32]; (v) the ratio of the sensory action potential at the wrist recorded from the median (digit II) and ulnar (digit V) nerves being $>$ 1 in normal nerves and < 1 in the carpal tunnel syndrome[15].

Given the significant elevation of cold perception threshold on the median-innervated palmar skin demonstrated in the group of putative carpal tunnel syndrome patients, it would seem reasonable to add this cold thermal threshold test to the available battery of additional diagnostic criteria proposed above. Continued examination of the concordance and covariance of thermal function with other more conventional electrodiagnostic tests may clarify the value and place of quantitative sensory testing of cold in the diagnosis of the carpal tunnel syndrome.

ACKNOWLEDGEMENTS

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INTRAVENOUS IMMUNOGLOBULIN THERAPY IN THE INFLAMMATORY NEUROPATHIES

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SUMMARY

The inflammatory demyelinating polyneuropathies are presumed to be autoimmune diseases[1] and as such have been treated in the past with corticosteroids, plasmapheresis and immunosuppressants. Immunoglobulin infusions represent a fourth treatment with the potential to modify the activity of the immune system in disease states. Limited past experience suggests that both acute inflammatory polyneuropathy and chronic inflammatory demyelinating polyneuropathy may respond to immunoglobulin infusions with minimal morbidity. We here outline our successful experience of this treatment in 5 of 6 patients with inflammatory demyelinating polyneuropathies and review the literature describing its use.

Plasmapheresis has been shown to be of benefit in early acute inflammatory polyneuropathy[2,3], but is expensive and fraught with complications, including hypotension, in a patient group in which overt or subclinical dysautonomia is common. An anecdotal report[4] found immunoglobulin infusions to be effective in inducing remission acutely in 3 children. All showed significant improvement in muscle strength and walking within 48 hours of commencing treatment. A randomized trial[5] comparing immunoglobulin infusions and plasmapheresis has demonstrated that immunoglobulin infusions were superior in inducing a functional improvement 4 weeks from the instigation of treatment. However, at the time of writing, only preliminary findings have been published.

Chronic inflammatory demyelinating polyneuropathy may respond to plasmapheresis[6], steroids or immunosuppressive drugs[7,8,9], but is often associated with significant continuing morbidity either from treatment failure or from side-effects of the treatment. Experience of immunoglobulin infusions in chronic

inflammatory demyelinating polyneuropathy is still limited. Immunoglobulin infusions can induce longstanding remissions[10,11,12,13,14,15,16,17], but remissions are often incomplete[10,11,12,17] and relapses may be controlled only with repeated courses of immunoglobulin infusions[10,11,12], though immunoglobulin infusions have been shown to delay the onset of relapses when they occur[17]. Immunoglobulin infusions induce remissions in paraproteinaemia - related demyelinating polyneuropathies[18].

We describe 3 consecutive cases of acute inflammatory polyneuropathy and 3 of chronic inflammatory demyelinating polyneuropathy treated with immunoglobulin infusions. Remission was induced in 5 of 6 patients.

CASE HISTORIES

Patient 1

This 49 year old school teacher developed diarrhoea, nausea and fever 10 days prior to admission. Three days before presentation he noticed mild weakness of the fingers and hands whilst weight lifting and 1 day later was unable to hold cutlery or lift his hands above his head. On the day of admission he developed dysphagia and difficulty in walking. He was normotensive and without clinical features of dysautonomia, but was dyspnoeic at rest. Moderately severe, bilateral facial palsies were present in the absence of other cranial neuropathies. Neck flexion and extension were weak and there was a flaccid, hyporeflexic tetraparesis (upper limbs 4^{-}-3^{-}/5; lower limbs 4^{+}-3^{-}/5). He could walk with difficulty, but could not rise from the squatting position. Subjective hypoaesthesia of the tips of all the digits was the only sensory abnormality. The vital capacity was 2 l (predicted 4.3 l) and the forced expiratory volume at 1 second was 1.5 l (predicted 3.4 l). CSF analysis was normal. Over 12 hours he worsened symptomatically, but the only objective deterioration was a further diminution of the vital capacity to 1.7 l. He received immunoglobulin infusions at 0.4 g/kg/day for 5 days. Thirty-six hours after treatment was commenced the vital capacity was 2.5 l, several tendon reflexes had returned and limb power had increased (4^{+}-4/5 generally). At 96 hours the vital capacity was 2.4 l, the facial diplegia had partially resolved and limb power was almost normal (upper limbs 4^{+}/5; lower limbs 5/5). At 6 days motor function had returned to normal. There was no relapse after 3 months of follow up.

Patient 2

This 53 year old airline pilot had had an upper respiratory tract infection for 7 days when he awoke with mild visual blurring. Within 3 hours he had horizontal diplopia, an unsteady gait and tingling of the finger tips. Examination 5 hours after the onset of symptoms revealed a left abducens nerve palsy, mild weakness of neck flexion and extension, generalised hypotonia and areflexia with power at 4-4^{+}/5 in the upper limbs and

5/5 in the lower limbs, but no objective sensory loss. His gait was markedly ataxic. Vital capacity and forced expiratory volume at 1 second were 3.5 l (predicted 4.5 l) and 1.5 l (predicted 3.4 l) respectively. Twenty-four hours after the onset his pupillary reflexes were sluggish, the right upper eyelid was ptosed, the left medial and lateral recti were weak, there was a palsy of palatal elevation on the left. He was dyspnoeic and tachypnoeic at rest and generally weaker (at 4-4$^+$/5).

At 48 hours he was hypophonic and unable to walk independently with his power now being 4/5. There was no variation of heart rate on Valsalva, but the vital capacity and forced expiratory volume at 1 sec were stable at 3.5 l and 2 l respectively. CSF was normal other than for 10 mononuclear white cells/ml. He underwent plasmapheresis with a 3 l exchange, becoming precipitously hypotensive with loss of consciousness while supine and with recovery only after hours of aggressive fluid replacement. A similar bout of hypotension was precipitated by a second exchange. His neurological status continued to decline and he was commenced on 'Intragam' (0.4 g/kg/day for 5 days). Twenty-four hours after the first course of immunoglobulin infusions he was stronger (power 4$^+$-4/5), the ptosis was reduced and the normal variation of heart rate during the Valsalva manoeuvre had returned, but he remained areflexic. Ninety-six hours after starting immunoglobulin infusions, neurological examination was normal other than for areflexia and mild residual ptosis.

Patient 3

This otherwise well 14 year old schoolgirl presented with 2 weeks of progressively worsening lower limb weakness and difficulty walking, with calf myalgias. She was areflexic, hypotonic and generally weak with involvement of all the limbs (power 4$^-$-4$^+$/5) and more profound weakness of the truncal musculature and the neck extensors and flexors, but with sparing of the cranial nerves. Vital capacity and forced expiratory volume at 1 second were reduced at 2.1 l (predicted 3.1) and 1.9 l (predicted 2.8) respectively. She walked independently, but could not stand unassisted from the seated position. She steadily deteriorated over the next 48 hours, becoming generally weaker (3$^+$-4$^-$/5) and mildly dyspnoeic. Right median and ulnar distal sensory latencies over 9 cm at the wrist (3.2 and 3.8 ms) and median motor conduction (42.7 m/s) were slowed, the median compound muscle action potential was dispersed (amplitude 1.17 mV, duration 14 ms) and the upper limb F waves were abnormal (latency 46.4 ms, 10% persistence). Right common peroneal motor conduction was normal peripherally, but the F waves were absent. CSF analysis was normal. In view of her continued deterioration, immunoglobulin infusions were commenced (0.4g/kg/day for 5 days). Forty-eight hours after commencing immunoglobulin infusions her power had subjectively increased and at 96 hours she had clearly improved (4$^+$-5/5) with return of some tendon reflexes. Complete clinical recovery was achieved 1 week after immunoglobulin infusions was commenced.

Patient 4

This previously well 34 year old man developed mild weakness of both hands with an

upper respiratory tract infection. He progressively worsened over the next 3 months with increasing weakness of all 4 limbs before making a spontaneous, partial remission 6 months after the onset of his symptoms. A relapse was induced by the 'flu' 9 months later. He was generally but mildly wasted and unable to walk on his heels or toes or to rise from the squatting position. The limbs were areflexic and weak (4^{-}-4^{+}/5, most marked distally). Sensory and cranial nerve examination was normal. Chronic inflammatory demyelinating polyneuropathy was confirmed by a sural nerve biopsy and other causes of a chronic demyelinating polyneuropathy were excluded.

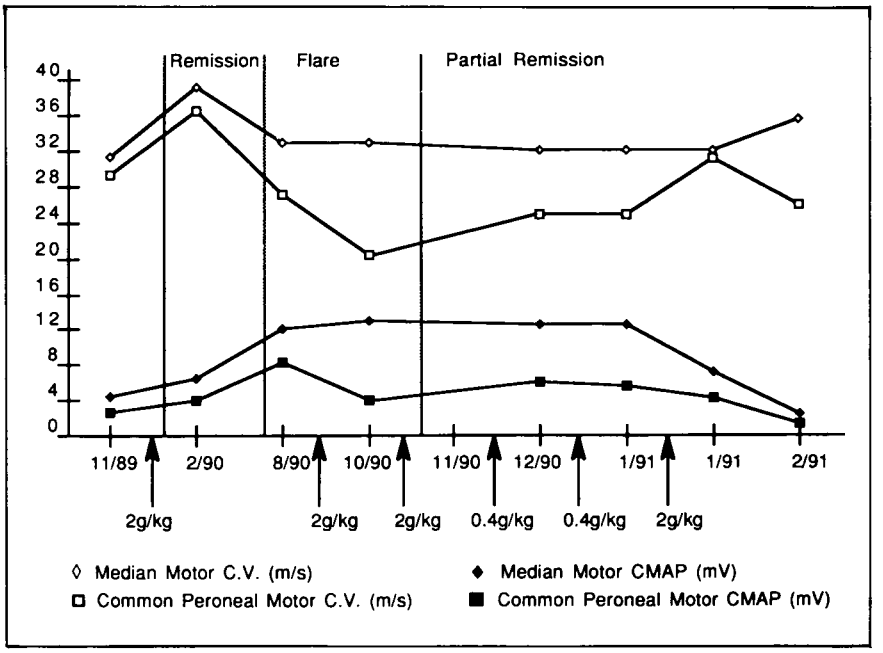

Fig 1 Patient 4. Motor nerve conduction velocity (m/s) and CMAP amplitude (mV) increased and decreased with clinical remissions and relapses. Remission was associated with stabilisation of peripheral nerve conduction. Parallel changes were observed in F wave latencies and persistence (not shown).

Immunoglobulin infusions were begun (0.4g/kg/day for 5 days) and a complete clinical remission was induced. Eight months later a further viral illness induced a relapse and in 3 weeks power in the limbs decreased from 5 to 3-4/5 generally in association with areflexia and mild distal sensory loss. Immunoglobulin infusions (0.4g/kg/day for 5 days) induced a partial remission, maximal by 3 weeks (power 4-4^{+}/5), although he remained areflexic. Another relapse occurred 2 months later and again a good partial remission was achieved 1 week after a course of immunoglobulin infusions. In an attempt to prevent further relapses he was commenced on maintenance immunoglobulin infusions of 0.4g/kg/month for 3 months. He continued to improve gradually. Limb power was 4-5/5

and the previous quadriceps wasting had resolved, although the areflexia persisted. He received a full course of immunoglobulin infusions (2g/kg) in an attempt to induce a complete remission and has continued to improve clinically (power 4^+-5/5).

At his initial assessment, sensory nerve action potentials were abolished in all the limbs tested, motor conduction velocities ranged from 14 to 31 m/s, F waves were absent or grossly delayed (latency >100 ms), multiple sites of conduction block were found and the compound motor action potentials were generally desynchronised and attenuated (0.5-5.5 mV). Thereafter nerve conduction, as assessed electrophysiologically, has waxed and waned with his clinical state (Fig 1). Remissions have been accompanied by increased motor conduction velocities, relief of conduction block and by return of F waves and generally reduced F wave latencies. Similarly, relapses have been accompanied by deterioration in these parameters.

Patient 5

This previously well 67 year old housewife presented with 6 weeks of increasing painful numbness of the hands and feet and some difficulty in walking, but no other motor symptoms of note. She was hypoaesthetic over the ophthalmic division of the left trigeminal nerve and there was mild, subjective hypoaesthesia for all modalities of sensation affecting the 4 extremities distally, mild wasting of the interossei and generalized hyporeflexia, but no muscle weakness. A sural nerve biopsy confirmed the diagnosis of chronic inflammatory demyelinating polyneuropathy and all other causes of subacute polyneuropathy were excluded. Her CSF protein was 1.35 g/l without oligoclonal banding. She was treated first with carbamazepine and subsequently with dothiepin, but suffered from continuing pain and progressively increasing unsteadiness of gait and limb weakness such that, after a further month, power was reduced to 4^+/5 distally in all limbs. At 15 months, persisting neurogenic pain and rapidly increasing weakness precipitated by a viral illness prompted immunoglobulin infusions (0.4g/kg/day for 5 days). Prior to treatment she was housebound and generally wasted, hypotonic, hyporeflexic and weak (power 3^+-4^+/5) and a postural tremor of the left upper limb was present. Distal hypoaesthesia involving all sensory modalities extended to both elbows and knees. Within 1 week of treatment the only objective change was abolition of the tremor, but 1 month later there had been an increase in power (4^--4^+) and in the upper limb tendon reflexes and an improvement in the pain, but no change in the sensory examination. She received 2g/kg immunoglobulin infusions on a monthly basis for 4 months and continued to improve (power 4^+-5/5) and was able to garden without rest for up to 6 hours. Another respiratory tract infection precipitated worsening peripheral dysaesthesia, but there were no objective changes to motor function or nerve conduction.

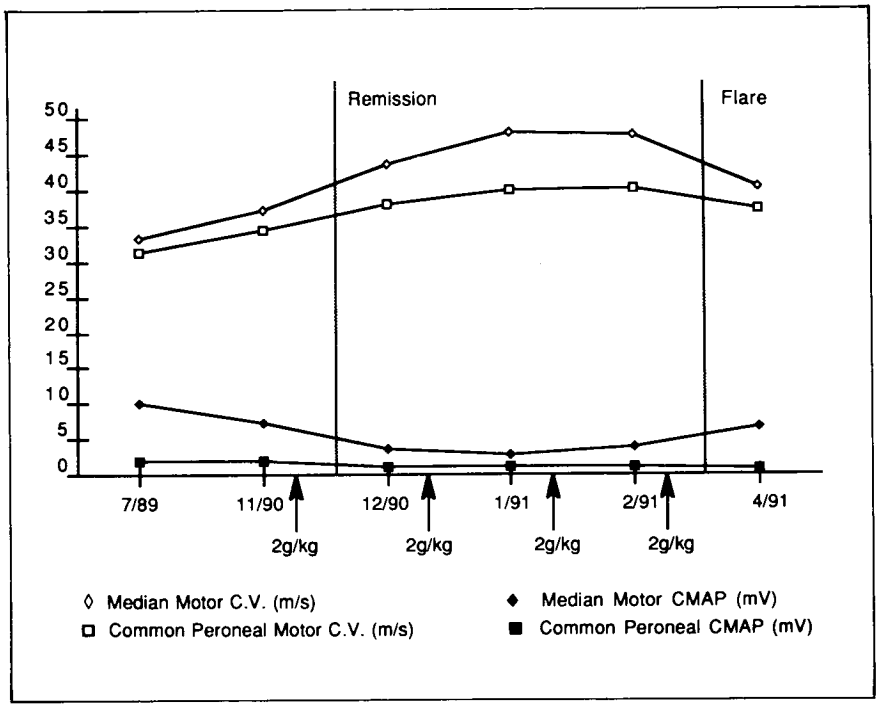

Fig 2 Patient 5. Motor nerve conduction velocity (m/s) and CMAP amplitude (mV) increased with clinical remissions. Remission was associated with stabilisation of peripheral nerve conduction. Parallel changes were observed in F wave latencies and persistence (not shown).

Initial electrophysiological studies revealed slowed peripheral sensory conduction (median and ulnar latencies over 9 cm at the wrist were 2.88 and 2.84 ms. respectively), slowed motor conduction (35-48 m/s), absent or delayed F waves (upper limb latencies 39 - 43 ms) and an attenuated and delayed H reflex (60 ms). Improvements in her clinical state were paralleled by increasing motor conduction velocities and by normalisation of F wave latencies (Fig 2).

Patient 6

This 67 year old veteran had a history of 2 strokes, hyperlipidaemia and hypertension. He presented with 3 years of tingling and numbness, at first involving the left hand, but subsequently spreading to the other extremities and associated with clumsiness and weakness of the digits. A mild residual left hemiparesis was the only sign of his previous stroke. He was generally hyporeflexic, the left-sided interossei were wasted, ankle dorsiflexion and the intrinsic muscles of the left hand were mildly weak ($4^+/5$) and there was hypoaesthesia to pinprick of the left C_6 dermatome in addition to a symmetrical, distal pattern of sensory loss affecting all modalities. His CSF was normal other than for

a protein of 0.56 g/l without oligoclonal banding. Immunoglobulin infusions (2g/kg over 3 days) were given in preference to corticosteroids or plasmapheresis in view of his frailty and induced a mild serum sickness-like reaction. One month after treatment his sensory symptoms had markedly decreased in severity, but there was no objective improvement on examination. Three weeks after immunoglobulin infusions he suffered a small midbrain stroke that was unrelated to the immunoglobulin infusions and which led to no longterm sequelae. He remained symptomatically stable over the subsequent 3 months. In view of his poor health and previous mild reaction to immunoglobulin infusions his management continues to be expectant.

Initial nerve conduction studies found F waves to be either absent or grossly delayed (upper and lower limb latencies 35 - 41 and 94 - 98 ms respectively), motor conduction to be generally slowed (25 - 52 m/s), the soleus H reflex to be absent and multiple blocks to motor conduction to be present. There was no change to nerve conduction after treatment in this man, who failed to respond clinically to immunoglobulin infusions.

DISCUSSION

The inflammatory demyelinating radiculopolyneuropathies (i.e. acute inflammatory polyneuropathy and chronic inflammatory demyelinating polyneuropathy) have in the past been treated with plasmapheresis, corticosteroids and immunosuppressants on the assumption that, as autoimmune diseases, they should respond to immunomodulation[1,7]. Immunoglobulin infusion is a fourth and more recent immunotherapy which acts at many points of the immune system. Non-specific actions include reticulo-endothelial blockade[19], increased T suppressor activity[20] and reduced natural killer cell activity[21]. Antibody synthesis is also reduced, possibly by the action of antiidiotypic antibodies within the infusion[22].

The immunopathogenesis of both polyneuropathies remains poorly understood[1]. In the case of acute inflammatory polyneuropathy, the importance of humoral immune mechanisms is suggested by the clinical response to plasmapheresis seen in many early cases[2,3], the presence of complement-fixing, antimyelin antibodies in titers roughly parallel to the disease activity[23,24], the induction of demyelination in experimental models by the passive transfer of the serum of patients with acute inflammatory polyneuropathy[25,26] and the presence of complement activation products in the CSF of those with acute inflammatory polyneuropathy[1]. Evidence of T cell activation is provided by elevated serum levels of interleukin 2 receptors (IL2-R)[27], increased T cell expression of the HLA DR antigen and IL2-

R[28]. Macrophage activation[28,29] and breakdown of the blood-brain barrier[30] also occur. Thus in acute inflammatory polyneuropathy it appears that all arms of the immune and reticuloendothelial systems contribute to nerve damage.

Humoral and cell mediated immune mechanisms also appear to be involved in the pathogenesis of chronic inflammatory demyelinating polyneuropathy although the evidence is less consistent. Plasmapheresis is of benefit in some patients[6], complement-fixing antimyelin antibodies have been identified in the sera of most patients with chronic inflammatory demyelinating polyneuropathy[23] and sera from chronic inflammatory demyelinating polyneuropathy patients have induced demyelination in some in vitro experiments[1,31]. Activated macrophages have been shown to infiltrate nerves in chronic inflammatory demyelinating polyneuropathy[29] and T cell activation has been demonstrated in a minority of those with chronic inflammatory demyelinating polyneuropathy[27].

Of 3 consecutive patients here reported with acute inflammatory polyneuropathy, all were progressing, 2 fulminantly, when immunoglobulin infusions was commenced and all showed a rapid clinical response. Substantial clinical improvement was seen in each within 48 hours of starting immunoglobulin infusions and all had made a full recovery less than 1 week after commencing the infusions. One patient with fulminant acute inflammatory polyneuropathy and dysautonomia was unable to tolerate the fluid shifts inherent in plasmapheresis and appeared not to have responded to that treatment after 2 courses, but tolerated immunoglobulin infusions and made a rapid improvement when this therapy was commenced.

Our experience is similar to that of other groups. One study of 3 children with apparently severe acute inflammatory polyneuropathy treated with immunoglobulin infusions alone found that all had significantly improved within 48 hours of starting treatment[4]. A single randomised, prospective trial has compared immunoglobulin infusions and plasmapheresis in 150 patients and found that, using functional improvement 4 weeks after randomisation as an index of efficacy, immunoglobulin infusions were significantly superior[5]. As yet the results of this study have been published in abstract form only. Plasmapheresis is maximally efficacious in acute inflammatory polyneuropathy when commenced within 7 days of the onset of symptoms[2] and in patients requiring respiratory support[2]. The optimal timing of immunoglobulin infusions is unknown, but it is not unreasonable to suppose that, analogous to plasma exchange, immunoglobulin infusions will be most effective when given early. It was striking that in our hands the 2 patients with early and fulminant disease resulting in respiratory distress had a more dramatic and rapid response to

immunoglobulin infusions than the patient with more indolent disease.

Three personal patients with chronic inflammatory demyelinating polyneuropathy received immunoglobulin infusions, and a partial clinical remission was induced in 2. Patient 6, a frail, elderly man with clinically mild chronic inflammatory demyelinating polyneuropathy, suffered a serum sickness-like illness during immunoglobulin infusions and subsequently sustained a mild, unrelated brainstem stroke. Immunoglobulin infusions induced symptomatic improvement in this patient, but after one course there was no objective clinical or electrophysiological improvement so that this must be counted as a treatment failure. Of the 2 patients with chronic inflammatory demyelinating polyneuropathy who responded clinically and electrophysiologically to immunoglobulin infusions, both required multiple courses to maintain remission and both have suffered relapses responsive to further immunoglobulin infusions. Immunoglobulin infusions therapy has allowed both patients to lead normal lives; one remains in full-time employment as an accountant and the other as a housewife, whereas prior to immunoglobulin infusions neither was able to continue with his or her normal work duties. We found that clinical remissions and relapses were paralleled by changes in F wave latency and persistence, peripheral motor conduction velocities and compound motor action potential amplitudes and the severity of conduction block. Similar findings have been obtained by other groups[10,11,12].

Our experience with immunoglobulin infusions in chronic inflammatory demyelinating polyneuropathy is similar to that of other groups[10,11,12,13,14,15,16,17]. Overall in these studies, immunoglobulin infusions induced remission in 77% of patients, but when the information was provided, relapses occurred in 60% and remissions were often partial even when substantial and multiple courses were required to maintain the remissions[10,11,12,13,14,15,16,17]. Most studies were retrospective, uncontrolled and unblinded and none directly compared immunoglobulin infusions to other forms of treatment. A single randomised, prospective, double blind, placebo-controlled study has found that immunoglobulin infusions delayed the onset of relapses[17], although all patients subsequently relapsed. Established treatments of chronic inflammatory demyelinating polyneuropathy include corticosteroids, plasmapheresis and immunosuppressive drugs[7]. All are associated with substantial side effects, many patients are refractory and relapses are common. Prednisolone[8] and plasma exchange[6] offer at least a modest, but significant benefit to many. The immunosuppressive agent azathioprine has been reported anecdotally to be efficacious[9], but the only randomised prospective trial[2] comparing prednisolone alone and in combination with azathioprine found that the latter drug conferred

no additional benefit. The rate of relapses with immunoglobulin infusions has not been directly compared to that seen with other treatments, although retrospective studies that have indirectly compared immunoglobulin infusions to corticosteroids, plasmapheresis and immunosuppressants have concluded that immunoglobulin infusion is as efficacious[13] or less efficacious[14] than these other therapies.

In our opinion immunoglobulin infusion is a safe and effective treatment for the inflammatory polyneuropathies. Immunoglobulin infusions reliably induce remission in acute inflammatory polyneuropathy and may be superior to plasmapheresis in this respect. Immunoglobulin infusions are likely to be better tolerated than plasmapheresis in patients with dysautonomia. In chronic inflammatory demyelinating polyneuropathy a substantial clinical remission with improvement in electrophysiological parameters of nerve function can be reliably induced by immunoglobulin infusions in many, but not in all patients. Chronic maintenance immunoglobulin infusion therapy is likely to be necessary to maintain remission in many patients. There has been no adequate study comparing immunoglobulin infusions to other treatments for chronic inflammatory demyelinating polyneuropathy. A controlled, prospective trial is required to determine the place of immunoglobulin infusions in this often refractory condition.

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A PROSPECTIVE STUDY OF ACUTE RADICULOPATHY AFTER SCOLIOSIS SURGERY

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SUMMARY

We have prospectively studied 45 patients undergoing scoliosis surgery (48 procedures) for evidence of postoperative acute radiculopathy. Posterior spinal fusion was performed in 42 patients (Cotrel Dubousset 28, Harrington rod with wires 9, Hartshill rectangles 5); anterior spinal fusion in 5 (Webb Morley) and an anterior release procedure in 5. Fourteen patients (29%) had sensory and/or motor signs of radiculopathy post-operatively, with moderate to severe symptoms in 10 and mild symptoms in 4. The radiculopathies were considered traumatic in 7 patients, in whom radiculopathy correlated with placement of a hook or passage of a sublaminal wire. In the remaining 7 patients, traction was considered the likely mechanism of injury; in these there was a significant association with the degree of postoperative correction of the scoliosis where it was substantially beyond the preoperatively demonstrated flexible range (p=0.008). A system of intraoperative electromyographic monitoring for possible prevention of this complication is described. Radiculopathy is a common complication of scoliosis surgery.

Spinal cord injury is a devastating and well known complication of corrective scoliosis surgery. Radicular injury is less well recognised, and is considered to be a rare complication of scoliosis surgery. However, the reported incidence, from less than one percent to 15%, is based on retrospective analyses[1,2,3]. Symptoms or signs of radiculopathy may be obscured by a number of factors. Patients are usually young, sedated and distracted by pain from the surgical site. Detailed neurological assessment of patients immediately following scoliosis surgery can be difficult, and is often not attempted

We have prospectively evaluated patients undergoing corrective scoliosis surgery, to determine the incidence, mechanism and aetiology of post-operative radiculopathy.

METHODS

Scoliosis surgery was performed by two specialist scoliosis surgeons at Royal Perth Rehabilitation Hospital. All patients were assessed in a scoliosis clinic with decisions on management being made on orthopaedic criteria. Radiological assessment of these patients included magnitude of the scoliosis curve (Cobb angle), flexibility of the scoliosis curve (percentage correction of curve when placed in traction), post-operative correction of scoliosis curve (correction of scoliosis curve post-operatively expressed as a percentage of the pre-operative curve), and percentage correction of scoliosis in terms of the flexible range (post-operative correction in degrees, divided by the correction of the scoliosis with traction in degrees, and expressed as a percentage).

All patients were examined by a neurologist prior to surgery and within the first few days post-operatively and were evaluated pre- and intraoperatively with somatosensory evoked potentials (SEP's)[4].

Patients were considered to have sensory radiculopathies if new sensory symptoms and signs were found in a dermatomal distribution. Motor involvement was considered to be present when post-operative examination revealed weakness in myotomes consistent with the sensory symptoms, confirmed when possible by electromyography (EMG).

RESULTS

Forty five patients (33 female and 12 male) with a mean age of 16 years (10 - 40 years) underwent a total of 48 separate operative procedures. The scoliosis was idiopathic in 30 patients, congenital in 3 patients, and secondary to neuromuscular disorders in 11 patients. One patient had an isolated kyphosis. The curves were single in 36 patients (26 thoracic, 7 thoracolumbar and 3 lumbar), and double in 8 patients. Right thoracic curves predominated. The operative procedures performed are presented in Table 1, with illustrations of the procedures presented in Figs 1-3, demonstrating the pedicle and laminar hooks and sublaminal wires used as fixators.

Fig 1 Antero-posterior and lateral radiographic views of Cotrel Dubousset apparatus

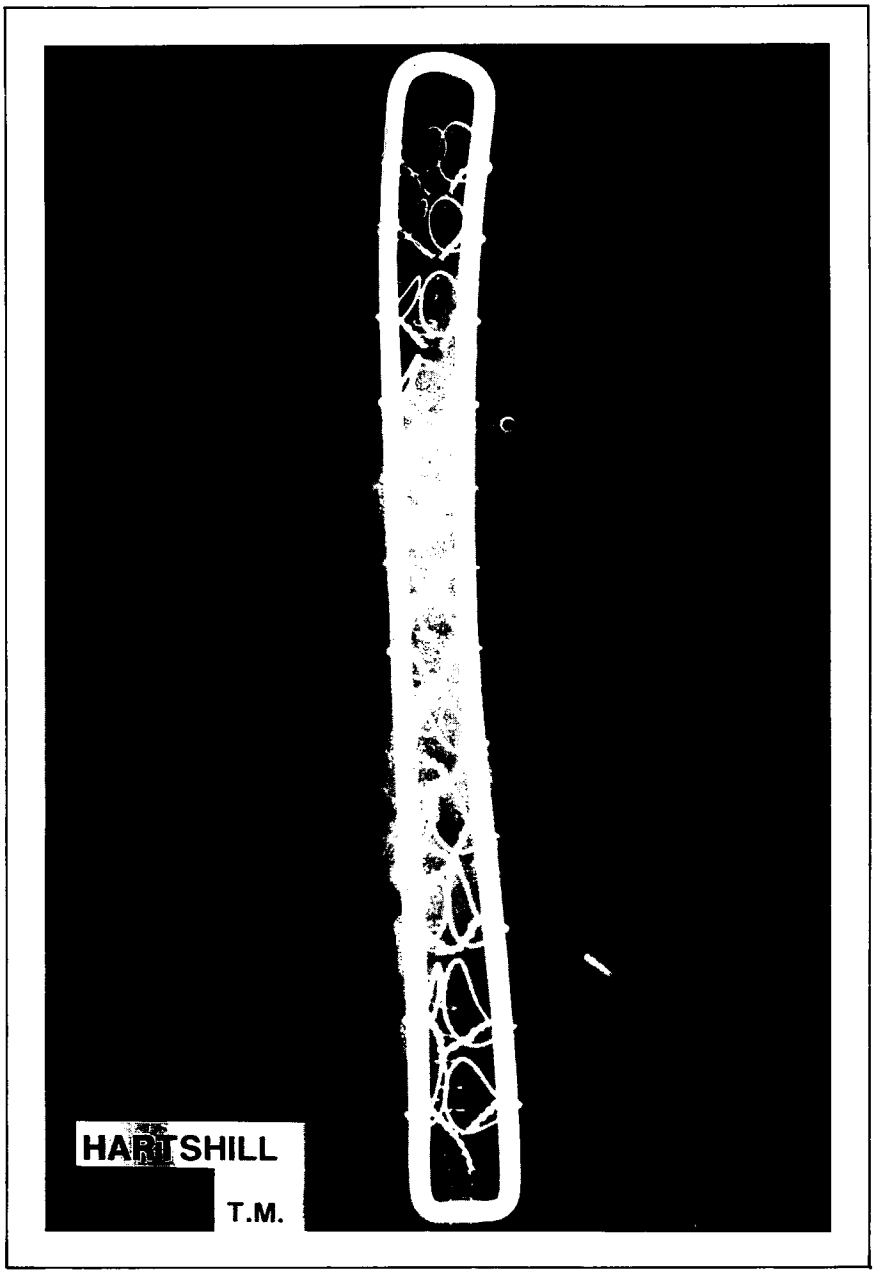

Fig 2 Antero-posterior radiograph of Hartshill rectangle

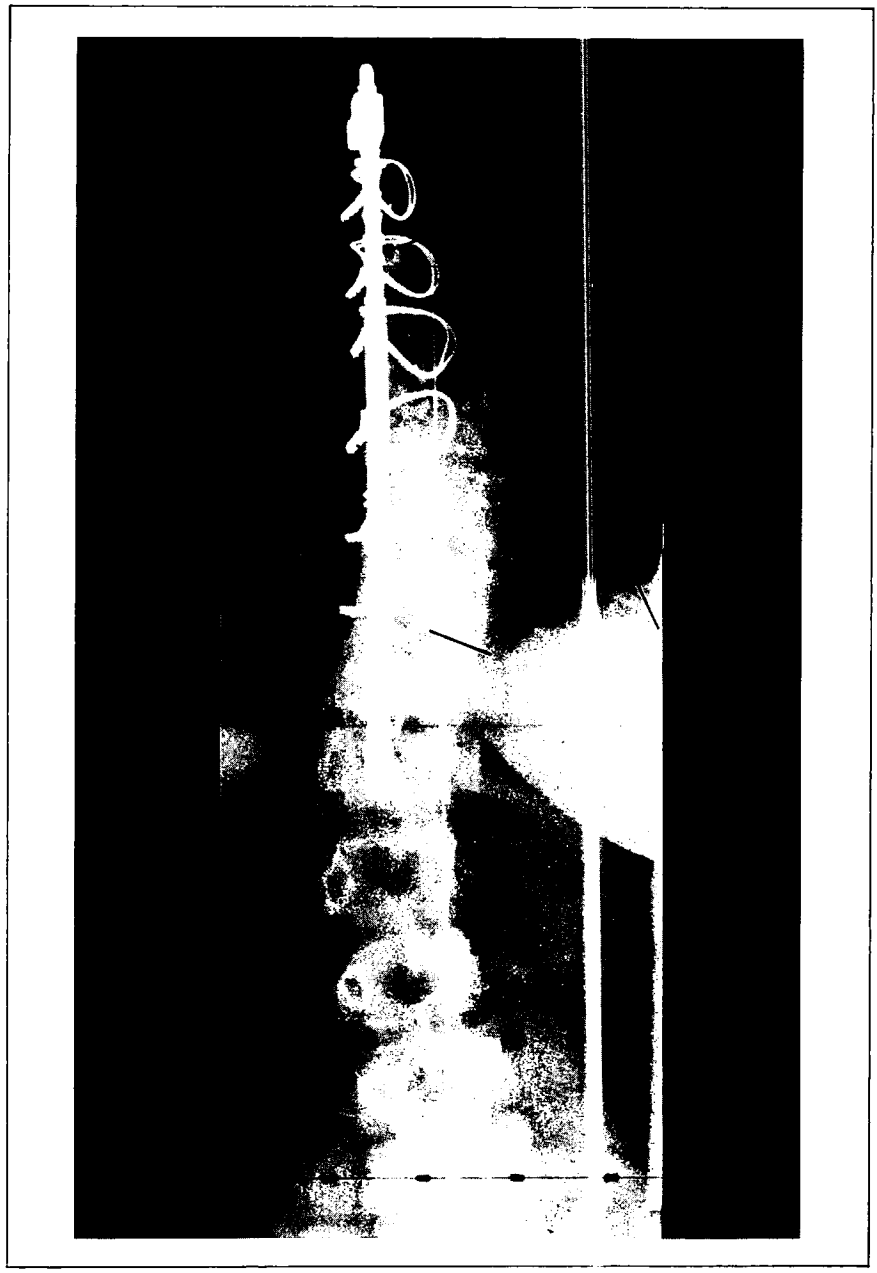

Fig 3 Antero-posterior radiograph of Harrington wires

Table 1 Operative procedures carried out

Procedure	Number	
Posterior spinal fusion	42	
Cotrel Dubousset		28
Harrington rod ± wires		9
Hartshill rectangles		5
Anterior spinal fusion/release	10	
Webb Morley		5
Release		5

(A total of 48 procedures were monitored. Some patients had anterior and posterior approaches performed sequentially.)

Radiculopathy patients

Fourteen patients developed symptoms of radiculopathy post-operatively. Sensory radicular symptoms were mild in 4 patients and moderate to severe or associated with weakness in 10 patients. The sensory symptoms most commonly included hyperaesthesia or dysaesthesia (9 patients), hypoaesthesia or anaesthesia (6 patients), and paraesthesia (3 patients). In several patients the radiculopathies were very distressing. Four patients had myotomal weakness, confirmed by EMG abnormalities.

The duration of symptoms was variable from days to months. Prognosis for recovery was good.

These 14 patients can be divided into two distinctive groups.

1) *Traumatic radiculopathy* (7 patients)

Most of these radiculopathies were not suspected intraoperatively, and were diagnosed as traumatic post-operatively since the location of the radiculopathy was congruent with the site of surgery, position of hooks, sublaminal wires and hardware (Table 2). Two patients were included in this group (cases 6 and 7) because of the passage of sublaminal wires at the level of radiculopathy, although their pattern of radiculopathy was more suggestive of the nontraumatic radiculopathy patients. The patients with traumatic radiculopathy were more often those who had underlying causes for their

Table 2 Traumatic radiculopathy patients showing diagnosis (cause of scoliosis), scoliosis (type of curve), operation (see Table 1), cause (of radiculopathy, with Cases 6 and 7 being possible traumatic radiculopathies as per text), and level of radiculopathy.

Case	Diagnosis	Scoliosis	Operation	Cause	Radiculopathy
1	secondary	single (L) lumbar	Harrington	Pedicle hook	(R) L_3
2	idiopathic	double (R) thoracic	CD	Pedicle hook	(L) T_{7-8}
3	idiopathic	double (L) thoracic	CD	Laminar hook	(L) L_3
4	secondary	double (R) thoracic	CD	Laminar hook	(L) L_3
5	secondary	single (R) th/lumbar	CD	Pedicle hook	(R) T_4
6	secondary	single (R) th/lumbar	Hartshill	? subliminal wires	(L) L_5-S_2
7	secondary	double (L) thoracic	Hartshill	? sublaminal wires	(L) L_3-L_5

CD = Cotrel Dubousset

Table 3 Non-traumatic radiculopathy patients showing diagnosis (cause of radiculopathy), scoliosis (type of scoliosis), operation (see Table 1), and level of radiculopathy (with side of lesser involvement in parentheses).

Case	Diagnosis	Scoliosis	Operation	Radiculopathy	
				Left	Right
8	idiopathic	single (L) th/lumbar	Webb Morley	L5-S1	
9	kyphosis	kyphosis	CD	L4-S1	(L4-S1)
10	idiopathic	single (R) thoracic	CD	S1	
11	congenital	double (R) thoracic	(L) Harrington with wires	L5-S1	(L5-S1)
12	idiopathic	single (R) thoracic	CD	L3-L4	(L3)
13	secondary	single (R) thoracic	CD		L5
14	idiopathic	single (R) thoracic	(L) Harrington with wires	L4-S1	(S1)

CD = Cotrel Dubousset

scoliosis and who had more complex (double) curves but they were not statistically different in terms of the magnitude of the resting or postoperative curve.

2) *Non traumatic radiculopathy* (7 patients)

This group was defined by the presence of radiculopathy not attributable to direct trauma from the instrumentation. These were most commonly lumbosacral radiculopathies (Table 3) and were bilateral in 4 of the 7 cases, although usually one side was of greater severity. Whilst patients with nontraumatic radiculopathy had scoliosis curves and postoperative corrections similar to those of all other patients, they tended to have reduced flexibility with a significantly greater correction of the scoliosis beyond the flexible range (248% compared with 152%, p=0.008: Table 4). This suggests traction injury as the basis for these radiculopathies.

Table 4 Comparison of non-traumatic radiculopathy patients and all others, for pre- and post-operative scoliosis measurements

Thoracic	Non traumatic radiculopathy patients Mean	All other patients Mean	Significance
Curve	66°	57°	p = 0.23
Flexibility#	27%	37%	p = 0.08
Post-op correction	48%	55%	p = 0.22
% Correction* flexible range	245%	152%	p = 0.008

$$\#\text{Flexibility} = \frac{\text{correction with traction x 100}}{\text{resting curve}}$$

$$*\%\ \text{correction flexible range} = \frac{\text{post-op correction (degrees) x 100}}{\text{correction with traction}}$$

DISCUSSION

We have found a 29% incidence of radiculopathy following scoliosis surgery, with at least half due to traction injury, and the remainder due to direct trauma. Whilst the incidence of radiculopathy is significantly higher than has been reported previously, this paper presents the first prospective study specifically focussing on this complication. In the large retrospective study of 7885 patients by MacEwen *et al*[1] in 1975, there was a reported incidence of 0.72% of patients with neurological problems. However only two patients were reported as having 'patchy anaesthesia over the trunk' consistent with a thoracic radiculopathy. Harper *et al*[2] reported 4 patients from a series of 184 patients with motor and sensory radiculopathy following corrective scoliosis surgery but the aetiology was uncertain. Other authors have found transitory sensory changes in 13-15% of patients and have been impressed by the nondermatomal nature of the sensory changes and have postulated posterior column injury during passage of sublaminal wires as the likely mechanism[3].

Our findings suggest 2 major mechanisms for radiculopathy after scoliosis surgery. Traumatic radiculopathies may be related to direct trauma, secondary to root compression (by haemorrhage, swelling) or due to vascular injury. We believe the nontraumatic radiculopathies are caused by traction on the lumbosacral nerve roots with correction of the scoliosis.

In the identification of nerve root irritation during scoliosis surgery, SEP's and motor evoked responses are poor indicators. There are however characteristic EMG patterns that can identify irritation of lower motor neurones, thus providing a warning to the surgeon. Neurotonic discharges are distinctive discharges which occur in response to mechanical irritation of a nerve. EMG techniques have been developed primarily for monitoring cranial nerves during posterior fossa and parotid surgery, but are readily adapted to scoliosis surgery using almost identical methodology[2].

Intraoperative EMG monitoring is currently being evaluated at Royal Perth Rehabilitation Hospital. It may be a useful technique for the prevention of radiculopathies in association with scoliosis surgery. We are assessing a technique developed at the Mayo Clinic utilising special nylon coated nichrome wire electrodes which are inserted through a standard 26 gauge needle into the muscle. The advantage of the thin wire is the flexibility that allows secure placement and stabilisation before commencement of the operative procedure. Real time, unprocessed and continuous EMG display and audio are monitored. EMG settings utilise gains of 200 to 500 μV sweep speeds of 10 ms/cm, and a

bandpass of 50Hz-15kHz. In view of the frequency of lower lumbar/sacral nerve root involvement, we monitor the tibialis anterior referenced to lateral gastrocnemius through a single channel which provides information on the L4-S2 nerve roots. With multiple channels available, additional selected myotomes can be monitored.

CONCLUSION

Radiculopathy after scoliosis surgery is common with an overall incidence of 29%. Dysaesthesia and hyperaesthesia are the most common symptoms. Two major mechanisms are responsible for the radiculopathy, direct trauma at the sites of instrumentation and stretch or traction injury which mainly involves lumbosacral nerve roots.

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BICYCLING INDUCED PUDENDAL NERVE PRESSURE NEUROPATHY

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SUMMARY

Pudendal neuropathies are well recognised as part of more generalised peripheral neuropathies; however, focal abnormalities of the pudendal nerve due to cycling-related injuries have been infrequently reported. We describe two patients who developed pudendal neuropathies secondary to pressure effects on the perineum from racing-bicycle saddles. Both were male competitive athletes, one of whom developed recurrent numbness of the penis and scrotum after prolonged cycling; the other developed numbness of the penis, an altered sensation of ejaculation, with disturbance of micturition and reduced awareness of defecation. Both patients improved with alterations in saddle position and riding techniques. We conclude that pudendal nerve pressure neuropathy can result from prolonged cycling, particularly when using a poor riding technique.

The pudendal nerve supplies sensation to the penis, urethra, anus and pelvic floor, and innervates the bulbocavernosus, external urethral and anal sphincters, and the pelvic floor musculature[1]. The nerve may be involved in generalised neuropathies or, in rare cases, compressed within the pudendal canal.

Prolonged cycling can produce ulnar neuropathy, as reported by several institutions, including our own[2]. More recently we have seen 2 patients with pudendal nerve pressure neuropathy secondary to poor riding technique, in one case following the use of triathlete handle bars. Clinical and electrophysiological findings are described, with discussion of the mechanism of injury.

CASE HISTORIES

Case 1

A 47 year old triathlete presented with loss of sensation over the distal ⅔ of the penis, altered sensation on orgasm and ejaculation, perianal numbness and reduced anal control. The symptoms began following the use of a new racing bicycle with triathlete handle bars (Fig 1), and an increase in his training schedule to riding an average of 100 km per week. The combination of the firm narrow seat and leaning forward to use the triathlete handle bars produced a pressure sensation at the base of the scrotum after approximately 30 mins riding. After 3 months he became aware of persistent paraesthesiae and diminished sensation over his penis and perianal area, altered sensation of defecation and ejaculation, urinary urgency and terminal dribbling.

Examination revealed reduced light touch and pinprick sensation over the penis; however, perineal and perianal sensation was normal. The anal and bulbocavernosus reflexes were absent. Anal tone was normal. The remainder of the general and neurological examination was normal. MRI examination of the lumbar spine showed a normal cauda equina without any significant nerve root entrapment. Tibial and pudendal evoked potentials were normal. Electrical recording of the bulbocavernosus reflex (stimulating the dorsal nerve of the penis and recording from both the pelvic floor with surface electrodes and the bulbocavernosus with a bipolar needle electrode) showed early and late responses of normal latencies. Sural nerve sensory studies were also normal. Needle electromyography revealed large, sometimes polyphasic, motor unit potentials and reduced recruitment in the bulbocavernosus and the external urethral sphincter. The clinical and electrophysiological findings were those of a patchy sensorimotor pudendal neuropathy, without evidence of a more proximal or generalised lesion. Initial rest, and then alteration of his riding technique by returning to standard handle bars and choosing a softer saddle, produced resolution of his symptoms.

Case 2

A 31 year old man was involved in a motor vehicle accident in which he was knocked from his bicycle to the ground. He sustained soft tissue injuries including bruising to his buttocks and perineum. These resolved, but following this he noted that prolonged bicycle riding in which he adopted a racing position would result in a feeling of coldness and numbness in his penis and scrotum. There was no disturbance of bladder, bowel or sexual function. The general examination was normal. Neurological examination including perineal, scrotal and perianal sensation was normal. The pressure effects on the pudendal nerve from the bicycle seat which occurred when he lent forward when riding long distances, were perhaps predisposed to by the previous trauma. Following a period of abstinence from cycling his symptoms resolved.

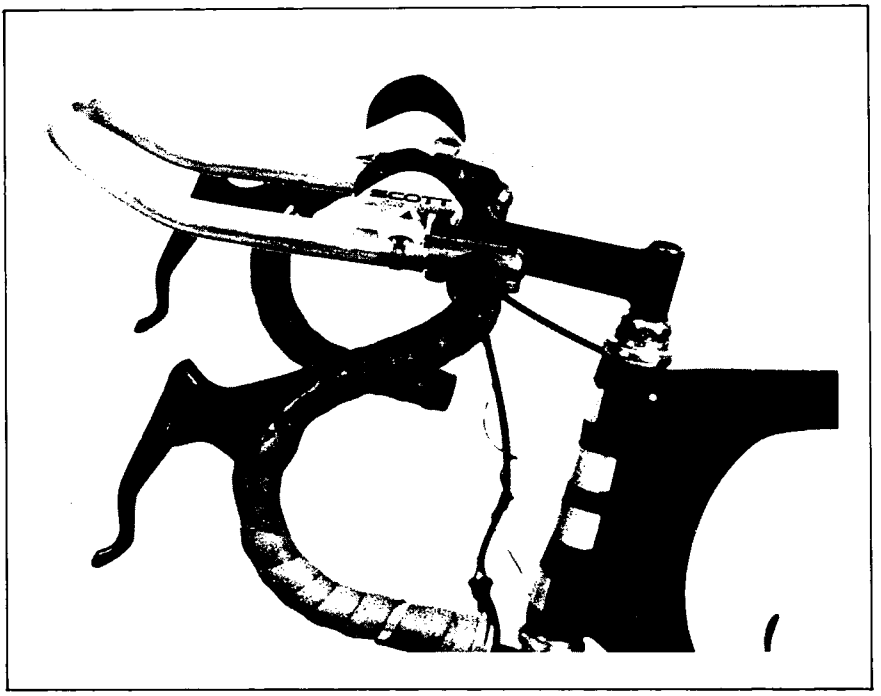

Fig 1 Triathlete handle bars

DISCUSSION

The pudendal nerve is the direct continuation of the lower cord of the sacral plexus. Its branches include the inferior rectal nerve within the pudendal canal (on the lateral wall of the ischiorectal fossa), before it divides to become the perineal nerve and the dorsal nerve of the penis (or clitoris) (Fig 2). The inferior rectal nerve supplies the lower anal canal and perianal skin and innervates the external anal sphincter. When involved in a neuropathy, perianal paraesthesiae and a feeling of loss of anal sphincter control (as in Case 1) may occur. The perineal nerve is the larger of the 2 terminal branches. Its cutaneous fibres supply the posterior part of the scrotum and perineum, and motor fibres innervate the bulbocavernosus, external urethral sphincter and other muscles of the pelvic floor. The dorsal nerve of the penis (or clitoris) supplies sensation to the penis (or clitoris and distal vagina). Abnormalities of the pudendal nerve may therefore affect bladder, sexual and bowel function.

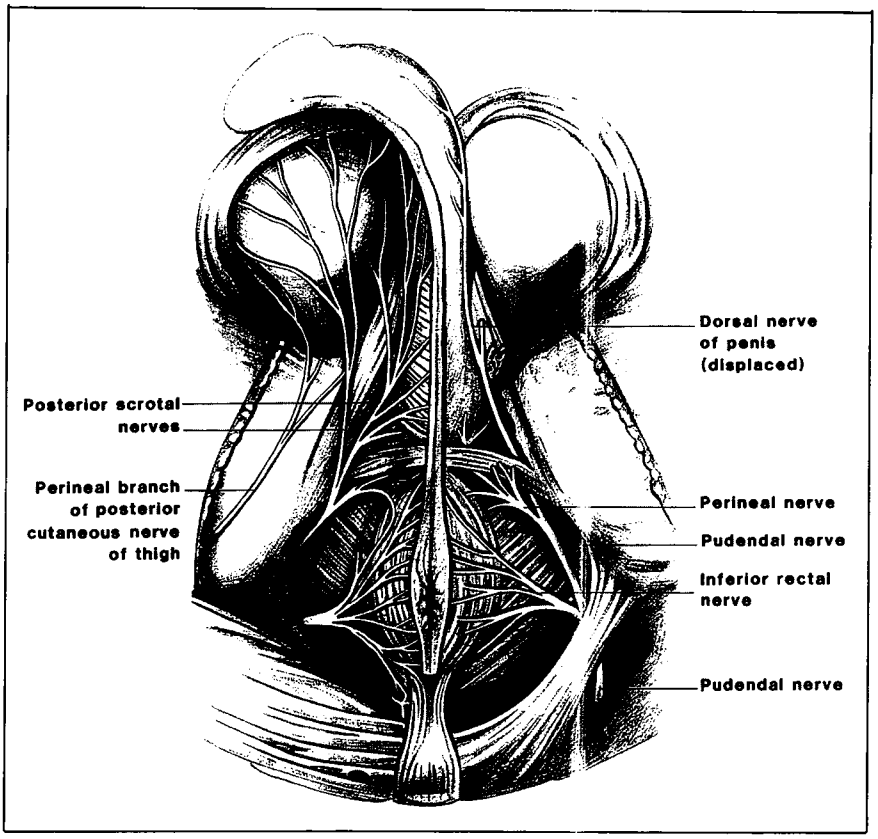

Fig 2 Anatomy of the pudendal nerve and its branches. Modified from Cunningham's textbook of anatomy: Romanes GJ. (Ed) 11th edition. Oxford University Press, Ely House, London 1972. page 763. Used by permission of Oxford University Press.

Although well known in the sporting literature[3,4,5,6,7], reports of focal abnormalities of the pudendal nerve due to cycling-related injuries are infrequent in the medical literature[8,9,10,11]. In the single cases reported, the most common symptoms have been penile numbness, urinary symptoms and impotence. One of the patients developed the neuropathy following use of triathlete handle bars. These handle bars became popular in the early 1980s with the increasing popularity of triathlons and long distance cycling. The forward-leaning posture required to use these handle bars, in combination with the hard-racing bicycle saddles, places pressure on the perineum anteriorly and adjacent to the ischial spines, with the resultant compression of the pudendal nerve (Fig 3). Incorrect

seat and pedal positions are also major contributors to these symptoms. Both of our patients improved with alterations in riding technique and avoidance of prolonged cycling.

Many of the current day exercise enthusiasts who participate in recreational and amateur cycling may be unaware of the mechanism of their symptoms. Consideration of pudendal neuropathy due to cycling with triathlete handle bars and/or poor bicycle preparation is important in the assessment of any patient with symptoms of bladder or sexual dysfunction.

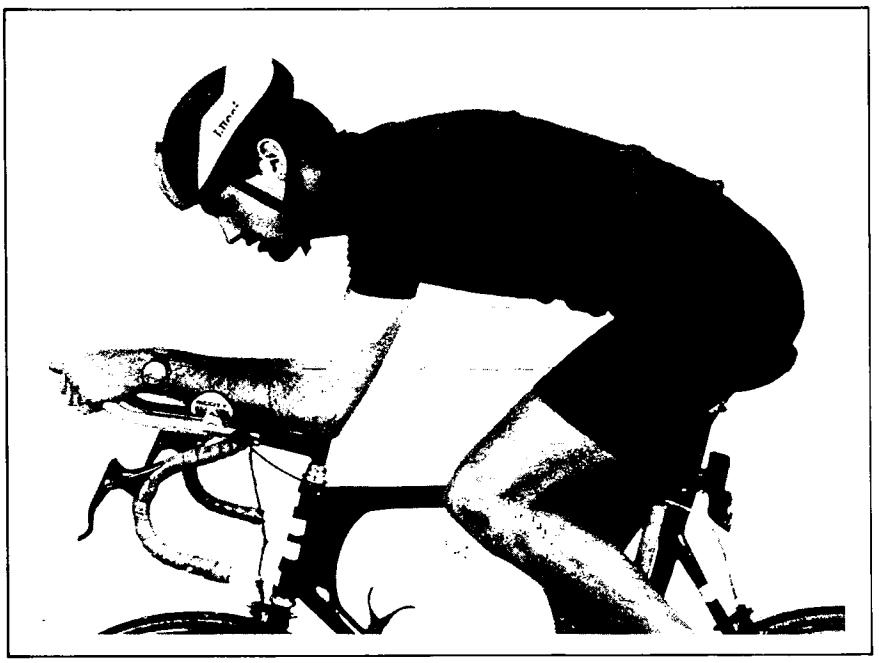

Fig 3 Racing cyclist using triathlete handle bars demonstrating forward leaning posture

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BOTULINUM TOXIN TREATMENT OF SPASMODIC TORTICOLLIS

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Botulinum toxin is the most potent microbial toxin known. Intramuscular injection of minute amounts of botulinum toxin is a very effective and safe way of treating a number of movement disorders, such as blepharospasm, hemifacial spasm, Meige syndrome, spasmodic dysphonia, focal hand dystonias, and spasmodic torticollis[1].

MATERIALS AND METHODS

We have treated 90 spasmodic torticollis patients with botulinum toxin. There were 55 females and 35 males (F:M ratio 1.6:1). Their mean age on onset was 41 years and the mean duration of their disease was 8.4 years. None of the patients had responded to standard therapy. Precipitating events included neck trauma in 10, emotional crises in 6 and major tranquilliser intake in 5 individuals. A significant family history was obtained in only 5 patients. In 15 individuals the spasmodic torticollis occurred in the setting of segmental or generalised dystonia. Patients were assessed using the rating system devised by Tsui[1] and by using self assessment. There was a high correlation between the two arms of the assessment. Patients were given intramuscular botulinum toxin injections, at a mean quantity of 160 mouse units, in divided doses, into 2 or 3 of the most severely affected muscles. The injections were repeated at a mean interval of 14 weeks. The mean follow up was 12 months, over which time 3 to 4 injection sessions took place.

RESULTS

There was a highly significant improvement on both the objective rating scale (mean improvement of 8 on a 25 point scale) and on the self assessment scale (mean improvement of 3 on a 5 point scale). The improvement increased during the course of several treatments. All but 4 patients improved and none was made

worse by the treatment. Significant side effects were very infrequent (dysphagia or dysphonia in 4 patients only). In no case were the adverse effects severe enough to require hospitalisation or suspension of treatment.

CONCLUSION

Botulinum toxin in doses of less than 200 mouse units at approximately 3 monthly intervals is an effective and safe method of treatment for spasmodic torticollis.

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THE VALUE OF NON-INVASIVE SPINAL CORD MONITORING DURING SPINAL SURGERY AND INTERVENTIONAL ANGIOGRAPHY

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SUMMARY

The study describes 51 patients, aged 10 to 57 years, who underwent spinal surgery (47) or interventional angiography (4). Multi-channel somatosensory evoked potential (SEP) monitoring was used to measure the functional integrity of the spinal cord. Alternating unilateral tibial SEPs permitted the detection of lateralised and milder abnormality. A combination of recording sites enhanced the certainty of detecting spinal cord dysfunction. Monitoring the ascending peripheral nerve volley below the operative site ensured adequate stimulation. Above the level of surgery, recordings outside the operative field were the simplest to make and did not require the direct assistance of the surgeon. Rapid and reliable recording of spinal cord and subcortical responses was possible in all surgical cases. Even though cortical SEPs could not be relied on as the sole monitor, their reproduceability was improved with the use of different electrode derivations. It is concluded that non-invasive methods of spinal SEP monitoring are a safe, reliable and easily performed alternative to more invasive methods.

The main aim of intraoperative monitoring during spinal surgery and interventional angiography is to prevent spinal cord injury. Whilst uncommon[1,2], such injury is nonetheless devastating for those who awaken paraplegic. During spinal surgery, a traditional monitoring method has been the 'wake-up' test, in which the patient is awoken on the operating table after insertion of the instrumentation and asked to move his or her legs[3]. Whilst this test can be helpful, the information is usually limited to a single observation, results may be equivocal, or obtained too early to prevent or too late to reverse spinal cord damage[4,5,6]

Somatosensory evoked potential (SEP) monitoring has therefore been applied in the hope of replacing the 'wake-up' test[7,8,9,10,11,12]. A number of different monitoring techniques can be employed. Epidural recording electrodes are used by many centres; such near-field potentials have high amplitudes that require fewer averaged stimuli for adequate resolu-tion[7,8,11,12,13]. However, their proximity to the surgical field makes them vulnerable to mechanical artifacts, monitoring cannot be continued during wound closure when late changes may occur[4,5,6], and they are difficult to apply to some procedures where the epidural space is not exposed. We have therefore attempted to develop reliable and more practical methods of SEP monitoring from outside the operative field.

METHODS

A 5-channel Medelec MS20 Mystro evoked potential machine served as both the stimulating and recording apparatus. Left and right tibial SEPs were recorded. Each tibial nerve was electrically stimulated at the ankle, the rate of stimulation being varied. A lead-plate ground was applied to the mid-calf. Preoperative recordings were made within the week before operation in all patients. Intraoperative recordings of the ascending peripheral nerve volley were made by either surface bipolar popliteal electrodes or a sciatic near-nerve needle electrode (DANTEC No. 13162, Skovlunde, Denmark - Fig 1). Cervical potentials were recorded either by a monopolar needle inserted to rest directly on the C5-C7 vertebral laminae or inserted into the interspinous ligament to the level of the ligamentum flavum as guided by image intensification, referencing to various sites (Fig 2). Local infiltration with 0.25% bupivacaine hydrochloride enabled painless insertion of these electrodes in the conscious patients undergoing angiography. Oesophageal electrodes were inserted by the anaesthetist during spinal surgery, positioned at approximately the C6 spinal level. Subcortical potentials were measured using nasopharyngeal (No. 001510, Rochester Electro-Medical Inc., Florida) and surface gold disc ear electrodes referenced to various sites (Fig 2). For cortical recordings, scalp surface electrodes were applied according to the International 10-20 system. The bipolar scalp derivations most commonly employed were Cz-Fz and C2-C1.

Left and right tibial SEPs were performed in alternation from the induction of anaesthesia until awakening. Normalised averaged responses of 1,000 sweeps (preoperative) and 128-500 sweeps (operative) were obtained, using a bandpass of 20Hz-2kHz and acquisition time of 90 msec. Real-time unprocessed monitoring of all channel inputs ensured initial circuit continuity before draping, and allowed the recognition of other artifacts. Spinal motor evoked potentials (MEPs) were evoked by an insulated monopolar needle cathode inserted to rest directly on the C5 vertebral lamina and referenced to a surface anode[14]. MEP recordings were made with bipolar surface electrodes over the medial gastrocnemius and from near-nerve sciatic needle electrodes.

Methods during spinal diagnostic and interventional angiography were the same, except sciatic needle, oesophageal and nasopharyngeal electrodes were not used, nor MEPs attempted.

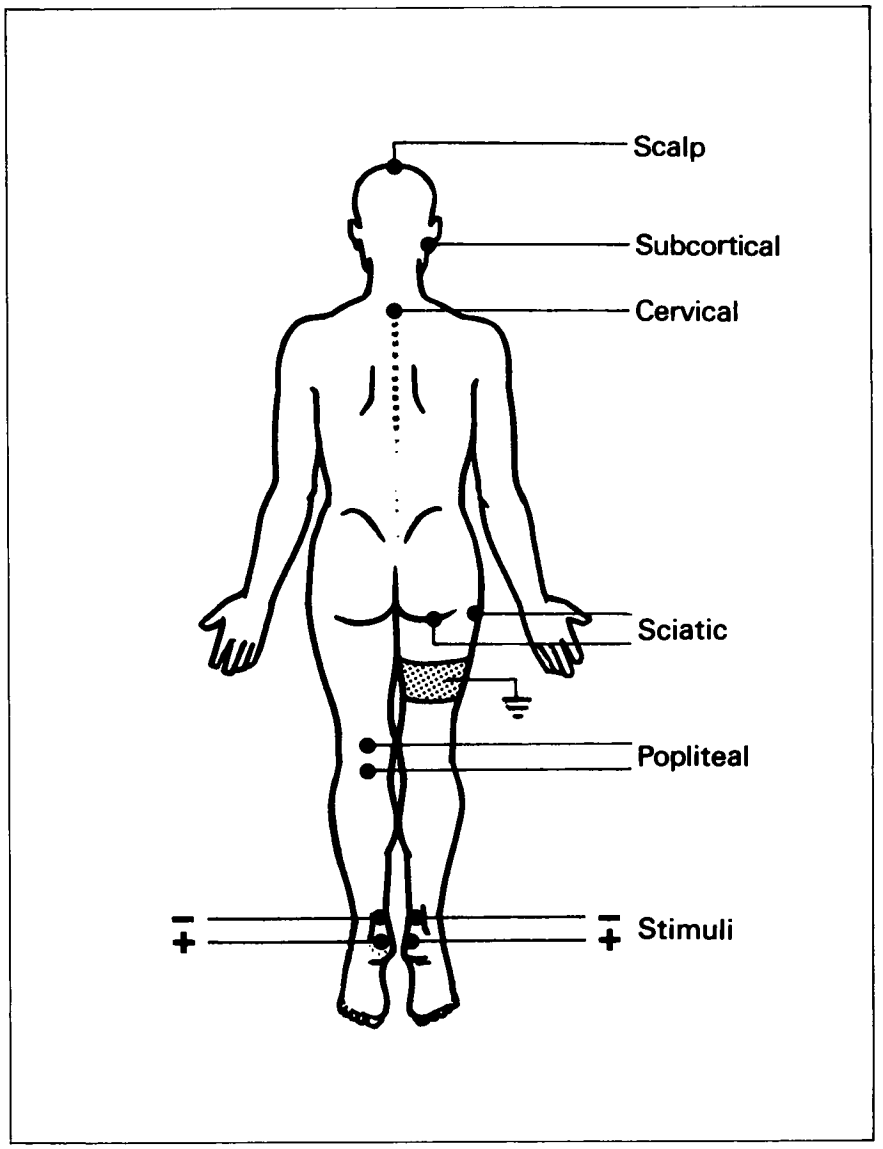

Fig 1 Schematic diagram of intraoperative monitoring technique. Each tibial nerve is stimulated at the ankle, recording from peripheral and central sites as shown.

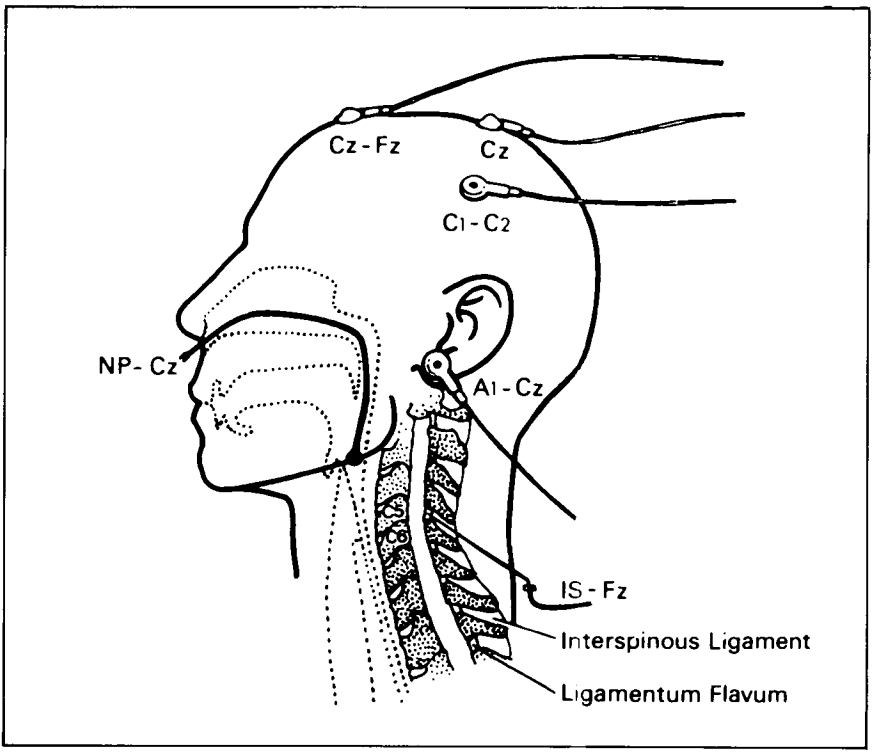

Fig 2 Schematic diagram of recording sites above the operative field: interspinous neck (IS-Fz), nasopharyngeal(NP-Cz), ear(A1-Cz) and scalp(Cz-Fz, C1-C2)

RESULTS

Surgical monitoring was used during 50 procedures on 47 patients (34 women, 13 men) of ages 10 to 57 years (mean 17 years). Posterior spinal fusion was performed in 41, and anterior spinal fusion in 9. The diagnosis was idiopathic scoliosis in 28 patients and congenital scoliosis in 6, none of whom had preoperative signs or symptoms except pain. Thirteen patients had secondary scoliosis, with a range of preoperative neurological deficits.

Four patients, 3 men and one woman of ages 32 to 56 years, with thoracic or thoracolumbar arteriovenous malformations underwent spinal angio-graphy with sodium amytal testing, one proceeding to therapeutic embolic occlusion with glue. All had spastic paraparesis and abnormal preoperative SEPs, 2 with bilateral radiculopathies. Monitoring/operative times varied from 2.0 to 7.7 hours (average 4.4 hours). No technical failures were encountered.

STIMULATION

For surgical monitoring, stimulation rates between 5.1 and 9.2 Hz permitted adequate recordings at all levels and one-minute trials. Although they increased cortical SEP amplitudes, slower rates lengthened the acquisition time and increased the vulnerability to intermittent artifacts and baseline variations. Faster rates of up to 20 Hz did not degrade peripheral, neck and subcortical responses significantly, and allowed rapid trial acquisition times of 10 to 50 sec. Such rapid rates attenuated cortical potentials, albeit of lesser importance when reliable cervical and subcortical potentials were obtained. In conscious patients undergoing angiography stimulation rates of 1.3-3.1 Hz were well tolerated.

RECORDING

Popliteal surface and sciatic needle electrodes were both reliable peripheral monitors in all procedures. The sciatic potentials were of higher amplitude and stability, and allowed recording of neurogenic MEPs. The ascending cervical cord potentials recorded from the neck proved to be the most reliable above the operative site, with only 2 technical failures in spinal surgery cases due to faulty connectors. High amplitude, stable responses were recorded from both interspinous (10 procedures) and laminar (44 procedures) needle electrodes with adjacent cervical or Fz references, although the interspinous electrodes were perhaps superior. However, in the 4 conscious patients the cervical responses could be measured only in 2 because of degradation by muscle artifact. During spinal surgery, additional neuromuscular blockade could be given when real-time display of unprocessed input signals determined a need for this. As with all SEP recording sites, considerable individual variations in amplitude and waveform were encountered, although in a single patient SEPs remained consistent in morphology. Although no recording derivation was immune, the oesophageal SEP was particularly vulnerable to 50Hz and other higher frequency electrical artifacts, being unreliable in 29 of 35 procedures so monitored.
The subcortical recording sites, nasopharyngeal (14 procedures) and ear (7 procedures), proved to be useful. These best displayed responses equivalent to the later component of the cervical potential (Fig 3).

Cortical SEPs recorded from the tangentially arrayed bipolar derivations of Cz-Fz (all procedures) and C_2-C_1 (17 procedures) proved to be complementary. In the anaesthetised patient, C_2-C_1 often showed well-defined scalp responses after their disappearance from Cz-Fz, although the reverse less commonly applied. The cortical potentials frequently attenuated shortly after induction, with higher concentrations of volatile anaesthetic, and with increasing duration of the

procedure. They were particularly vulnerable to these effects in younger patients and those with preoperative SEP abnormalities. Whilst unreliable as an exclusive monitor during anaesthesia, cortical responses were consistently recorded throughout in 39 of 50 spinal surgical and all 4 angiographic procedures, where they proved the best monitor. By excluding the 7 procedures with expired isoflurane concentrations of >1.1%, successful surgical monitoring was possible in 90%.

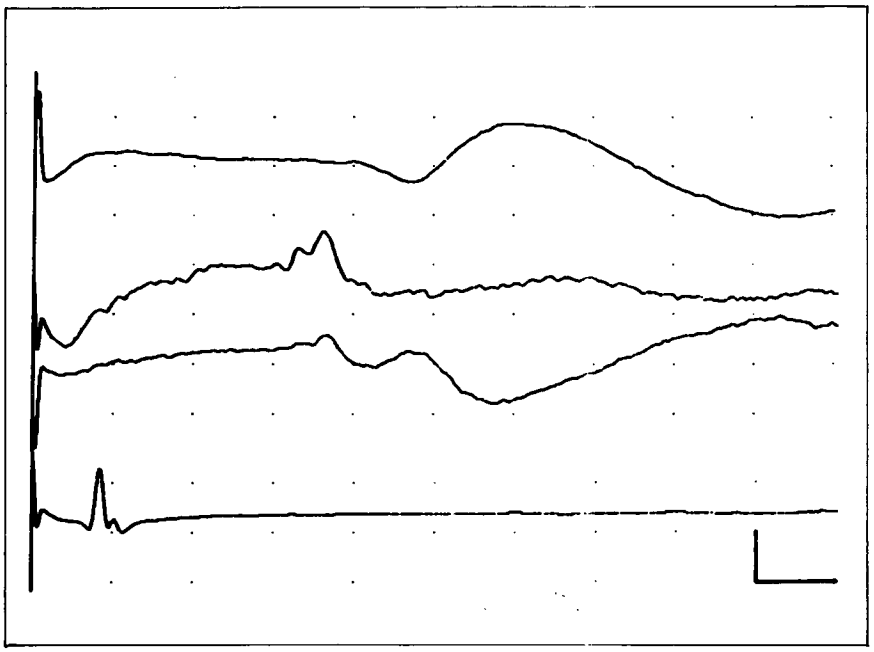

Fig 3 SEP monitoring during spinal surgery. Stimulation of left tibial nerve at 5.1 Hz. Recording from four sites (traces in descending order): scalp(C_Z-F_Z), neck needle(6th cervical lamina-F_Z), nasopharyngeal(NP-C_Z), popliteal electrodes. Calibration bar: 1μV popliteal 5μV) and 90 msec.

ABNORMALITIES

Two patients had a rapid and reproducible loss of SEPs above the level of the procedure. An 18 year old girl undergoing posterior spinal fusion for severe congenital scoliosis (Harrington instrumentation) had a sudden bilateral attenuation followed by a loss of cervical and cortical potentials immediately after distraction. Placement of an epidural electrode confirmed the loss of SEPs. The instrumentation was removed, and the return of SEPs shortly thereafter was supportive evidence for transient cord dysfunction. A lesser degree of scoliosis

correction did not influence the SEPs and she awoke with a moderate left L5 radiculopathy, but without spinal cord injury. In a patient with a thoracic cord arteriovenous malformation, sodium amytal injection into the main arterial pedicle produced a transient unilateral loss of cortical SEPs attended by moderately severe ipsilateral leg weakness, but without sensory symptoms.

DISCUSSION

Spinal cord damage during surgery may be related to cord compression, distraction or ischemia. Various models of spinal cord injury have been used to study the effects of these insults on recorded evoked potentials. Animal studies have shown that compressive and traction injuries to the spinal cord produce a progressive reduction in the amplitudes of the monitored spinal cord and cortical SEPs, and that the effects can be reversible[9]. Therefore, the SEP has been used as an indirect monitor of the motor pathways, since any event sufficient to cause motor pathway damage is likely to disturb the spinal somatosensory pathways. Observations in human subjects have paralleled the animal research, with post-operative neurological deficits or the results of 'wake-up' tests being accurately predicted by SEP abnormalities[6,7,15]. To be helpful, monitoring needs to be safe, to provide rapid and reliable feedback to the surgeon, and to not interfere with surgery. There is probably no single best way of achieving this; rather, optimum results are obtained by attention to many details[12,18]. We have found that alternating unilateral tibial SEPs are practical to perform and can detect more localised and milder abnormalities. In surgical monitoring, a stimulation rate of 5.1-9.2 Hz permits one-minute trials without major loss of cortical response amplitudes.

Multiple-channel recordings are essential. If recording from a single site and the responses change or disappear, it is difficult, if not impossible, to determine whether this is due to technical problems or to an alteration in spinal cord function. Monitoring responses both above and below the level of surgery is recommended. For SEPs, the peripheral nerve or spinal cord responses are measured below to ensure that peripheral nerve stimulation is adequate and that the afferent volley is travelling up the dorsal columns. Above the level of surgery, multiple recording sites serve as a cross check. We have found that rapid and reliable recordings of peripheral, spinal cord and subcortical responses are possible from outside the operative field. Neck needle[4,7,9,19], nasopharyngeal and ear electrodes give reliable recordings that, when compared to epidural electrodes, are less prone to mechanical artifacts, allow continuous monitoring from the time of induction until the patient awakens and are widely applicable.

Cortical SEPs are very sensitive to the effects of anaesthesia, and cannot be relied upon as the sole monitor. However, anaesthesia has differential effects on the components of the cortical SEP[20,21], and using tangentially oriented scalp derivations (Cz-Fz and C1-C2) whilst maintaining the concentration of expired isoflurane <1.1% permitted reliable recordings in 90% of our patients.

Technical problems are common in the operating room, and correct identification of the many causes of loss of potentials require much caution and ingenuity. Wherever possible several electrodes should be placed so that intra-operative malfunctions can be corrected without disrupting the surgery. Although some of the early series reported a relatively high incidence of technical failures, the 51 consecutive patients in this study were monitored without a single technical failure. The type and level of anaesthesia, blood pressure, body temperature and other physiological variables will all affect intraoperative recording of EPs. Collaboration between the anaesthetist and neurophysiologist is particularly important.

COMBINED MONITORING

Whilst posterior column and lateral corticospinal tract injuries most often occur concurrently, this is not invariably the case. There are now reported cases of post-operative paraplegia with preserved SEPs[4,7,9,16,7]. This has provoked a search for methods to test the motor pathways directly in order to provide for more sensitive and comprehensive monitoring of spinal cord function[22,23,24,25,26]. We are using electrical cervical cord stimulation and recording MEPs as a descending peripheral nerve potential or as a muscle twitch in the limbs, since no additional set-up or equipment is needed[14,27,28,29,30]. The sciatic nerve recordings have the advantages of less variability, allowing free use of muscle relaxants and perhaps greater specificity for limb motor function[30].

CONCLUSION

Spinal SEP monitoring can safely and practically be performed from outside the operative field during spinal surgery and interventional angiography. The techniques are reliable, allow continuous monitoring, are widely applicable and do not interfere with the operative procedure. This allows the surgeon or radiologist to devote his full attention to the technical aspects of the procedure.

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LATE-ONSET ACID MALTASE DEFICIENCY IN A CHINESE GIRL

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SUMMARY

Late-onset acid maltase deficiency is a rare disorder. We describe a nineteen year old Chinese girl who presented with diarrhoea, limb-girdle weakness and respiratory failure requiring mechanical ventilation. Electromyography showed polyphasic potentials and myotonic discharges. Muscle biopsy revealed features characteristic of acid maltase deficiency. Assay of acid α-glucosidase in cultured skin fibroblasts confirmed the diagnosis. Supportive treatment with nocturnal intermittent positive pressure ventilation via a nasal mask and dietary supplementation with branched-chain aminoacids proved effective in this patient. The cause of diarrhoea remained uncertain. This is the first documented case of acid maltase deficiency in Chinese adult.

Acid maltase (acid α-glucosidase) is a lysosomal enzyme which hydrolyzes glycogen to glucose and is deficient in glycogen storage disease type 2. According to the clinical features and pathological findings, acid maltase deficiency can be divided into 2 types, infantile-onset and late-onset. The invariably fatal infantile-onset type is more common and results in more widespread organ involvement, including the myocardium, liver and tongue[1]. The inheritance of late-onset acid maltase deficiency is an autosomal recessive one. Recently at least 6 different mutations were found in 14 patients with acid maltase deficiency[2]. This may explain the observed clinical heterogenicity of late-onset acid maltase deficiency patients.

CASE HISTORY

An 18 year old girl was admitted to the Prince of Wales Hospital because of progressive weakness, dyspnoea and dysphagia. She was born of a normal gestation and delivery. Her developmental milestones were normal. She could not run as fast as her classmate in primary school and seldom participated in high school sports. She complained of diarrhoea for 3 years. Her stool was well formed but the frequency of her bowel motion was increased to about 3 times a day. Stool examination and cultures for bacteria and parasites were negative when she was investigated in a gastroenterology clinic. Barium enema of the colon was normal.

She developed progressive weakness over 12 months, and dyspnoea on exertion with difficulty in swallowing solid food for 6 months before her admission to hospital.

Her parents and 2 of her 3 siblings were healthy but her elder brother had died of a muscle disease in another hospital at the age of 10 years. He had also presented with diarrhoea one year before his death.

On examination, the patient was in respiratory distress with central cyanosis and right heart failure. There was no ptosis or ophthalmoplegia. There was grade 4 proximal weakness of all limbs. She was unable to sit up from the supine position. Her tendon reflexes were generally depressed and her anal tone was decreased.

Investigation confirmed type 2 respiratory failure (pO_2 = 7.1 KPa, normal 10.0-13.0; pCO_2 = 4.6, normal 4.7-6.0; pH = 7.23, normal 7.35-7.45), with polycythaemia (haemoglobulin = 18.4g/dl, normal 11.5-14.3) and a raised creatinine kinase level (249 U/l, normal 32-180). Needle electromyography showed increased numbers of polyphasic potentials and occasional myotonic discharges.

She developed a chest infection and required mechanical ventilation 4 days after admission. Muscle biopsy of the right quadriceps showed a severe vacuolar myopathy with large, confluent cytoplasmic vacuoles in the myofibres (Fig 1). PAS preparations revealed globular cytoplasmic glycogen deposits removable by diastase (Fig 2). Increased lysosomal acid phosphatase activity was also demonstrated. Electron microscopy confirmed the presence of pools of glycogen particles lying free in the sarcoplasm, though some were membrane-bound in lysosomal bodies (Figs 3 & 4). Review of the muscle biopsy performed on her deceased brother showed similar though less severe abnormalities. Acid maltase deficiency was diagnosed. Acid α-glucosidase and β-galactosidase activities were assayed in cultured skin fibroblasts. There was marked deficiency of acid α-glucosidase activity (0.85 nmol/h/mg, control fibroblasts 123 nmol/h/mg, normal 21-130). β-galactosidase activity was within normal limits (1173 nmol/h/mg, control fibroblasts 1631, normal 300-1600).

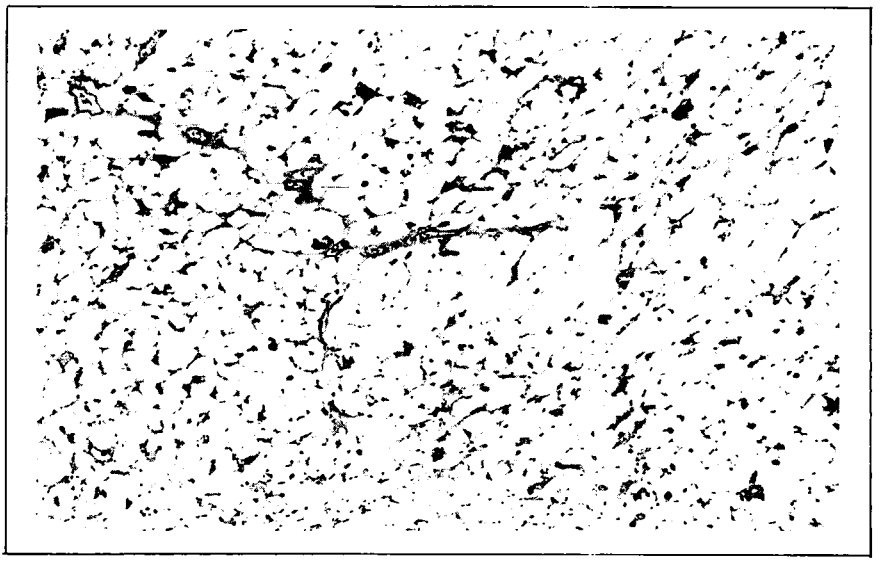

Fig 1 Muscle biopsy showing extensive vacuolation of myofibers (H & E paraffin section, x 60)

Fig 2 Many vacuoles are distended with glycogen deposits (frozen section, periodic acid-Schiff preparation, x 300)

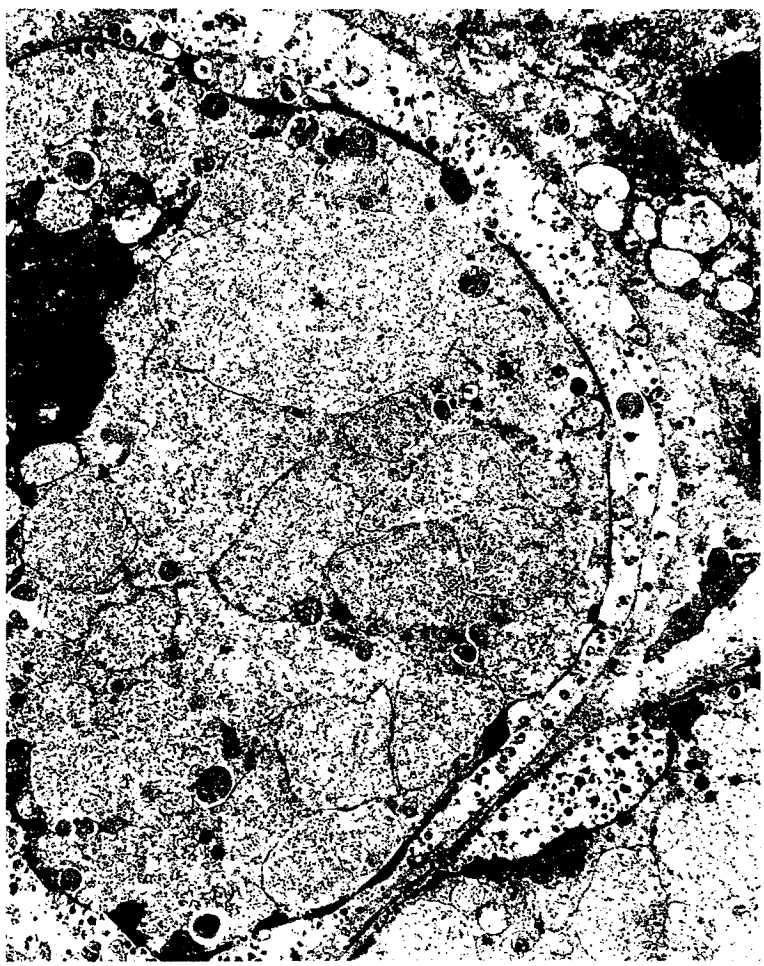

Fig. 3 Ultrastructure of muscle fibres with vacuoles distended with glycogen particles

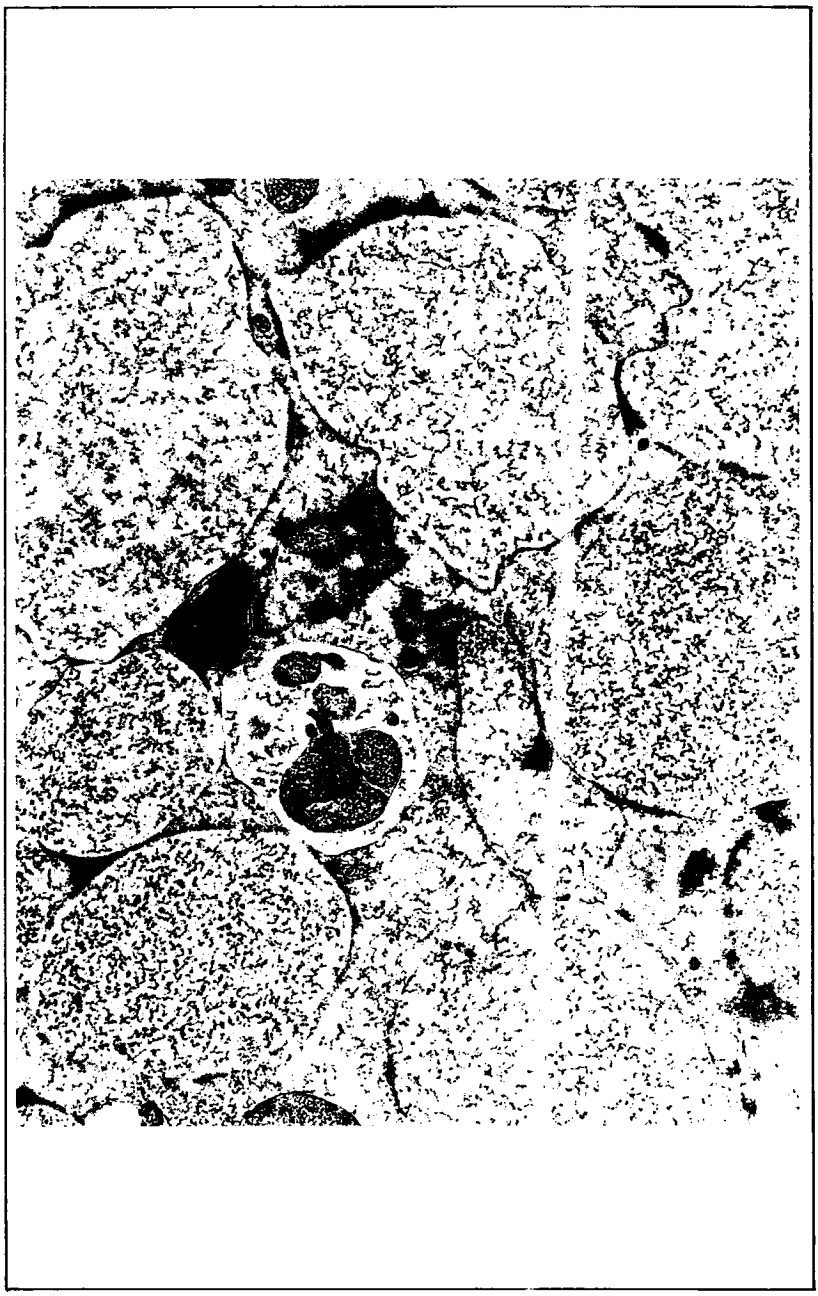

Fig 4 Electron microscopy of muscle fibres with membrane-bound glycogen particles as well as particles lying free in the sarcoplasm (x 8,200)

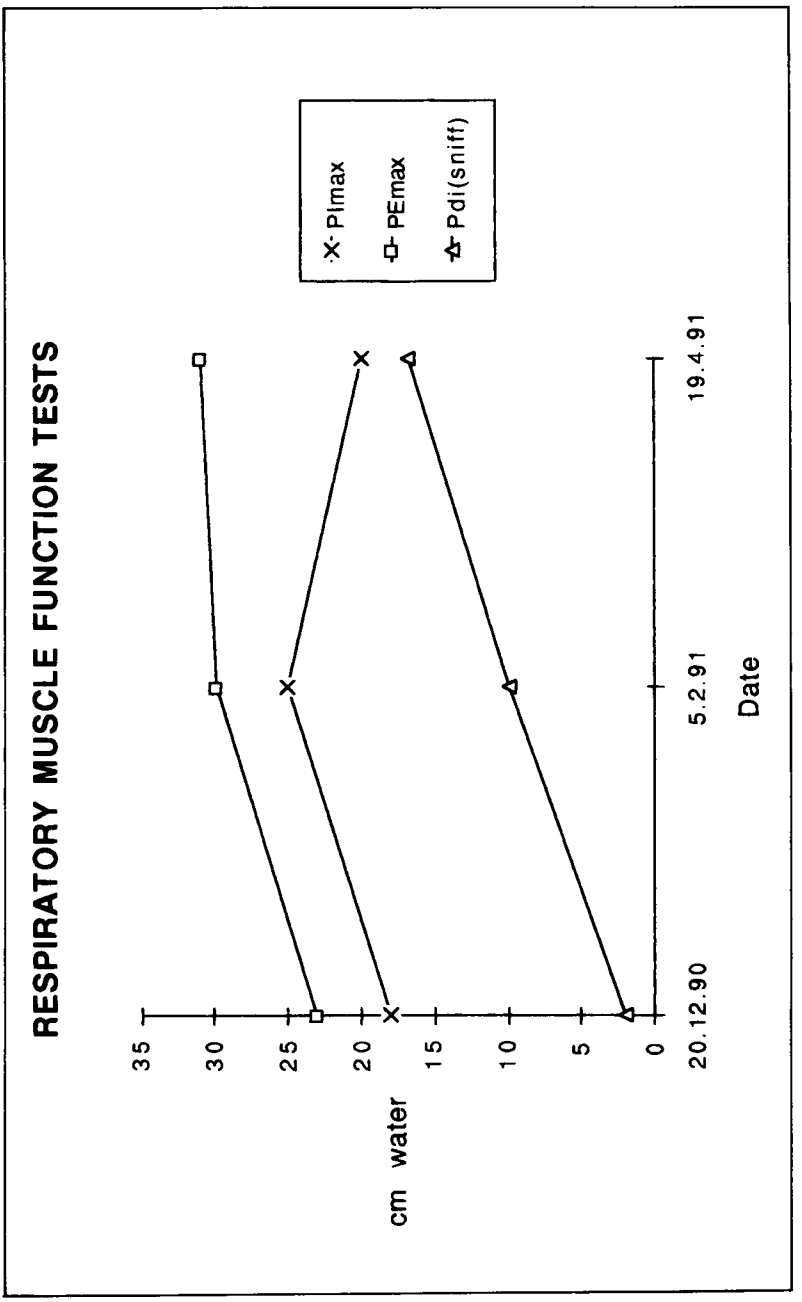

Fig 5 PImax = mouth pressure during maximal inspiration; PEmax = mouth pressure during maximal expiration; Pdi = transdiaphragmatic pressure during sniff

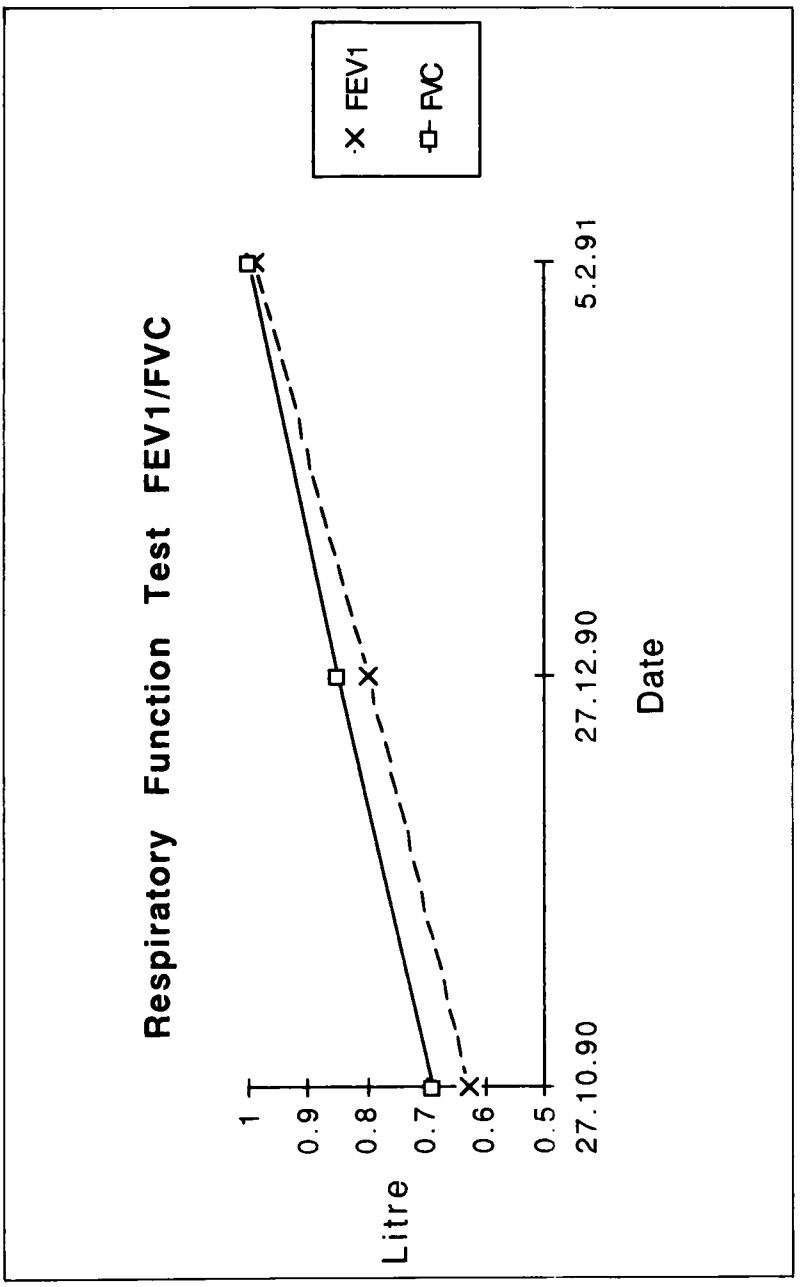

Fig 6 FEV_1 = Forced expiratory volume in 1 second; FVC - Forced vital capacity

Tracheostomy was required for 2 weeks, after which time she was maintained on intermittent positive pressure ventilation delivered via a nasal mask. She tolerated the treatment well and overnight oximetry demonstrated more than 90% oxygen saturation.

Branched-chain aminoacids 13.4g thrice daily were given as a supplement to a high protein diet. Nocturnal intermittent positive pressure ventilation via nasal mask was continued and she was discharged home 8 weeks after admission. Serial respiratory assessments showed gradual improvement in spirometry and respiratory muscle function (Figs 5, 6). She was able to live an independent life and work full-time as a ward clerk in a regional hospital.

DISCUSSION

Acid maltase deficiency is rare in adults. The disorder should be included in the differential diagnosis of patients presenting with limb-girdle type weakness and respiratory failure. Clinically, it is difficult to distinguish late-onset acid maltase deficiency from other myopathic disease without a muscle biopsy. The enzyme defect can be documented in muscle, lymphocytes, cultured skin fibroblasts or urine. The clinical features of the patient described above are typical of late-onset acid maltase deficiency. However, the cause of the diarrhoea remained uncertain although the weak anal tone may have contributed. A rectal biopsy a revealed normal mucosa with no evidence of vacuolation in the muscular layer.

There is no definitive treatment for late-onset acid maltase deficiency. However, supportive treatment with correction of the metabolic abnormality and ventilatory failure may improve the patient's condition markedly, as in the present patient. Recently, mechanical ventilation using intermittent positive pressure ventilation delivered non-invasively by nasal mask has been shown to control nocturnal hypoventilation and relieve chronic respiratory failure[3]. Another advance in the management of late-onset acid maltase deficiency patients is the availability of dietary therapy. Since it was postulated that muscle catabolism contributes to muscle weakness in late-onset acid maltase deficiency, a high protein diet was suggested as an alternative energy source for such patients[4]. More recently, branched-chain aminoacid supplements were introduced, as these compounds are the principal aminoacids involved in muscle protein synthesis and utilization[5]. Since there has been only one previous report of the use of branched-chain aminoacids in late-onset acid maltase deficiency, a larger series of cases will be required to confirm whether there is any real benefit.

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INTEROPERATOR VARIABILITY IN QUANTITATIVE ELECTROENCEPHALOGRAPHY

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SUMMARY

The purpose of the study was to determine whether quantitative or discriminant analysis of the electroencephalograph (EEG) would vary significantly when the same EEG was analysed by 3 different operators.

EEGs on 10 healthy volunteers were recorded on the Cadwell Spectrum AT 386, using the Electrocap (10-20 system). The EEGs were analysed independently, with each operator selecting the first 48 artifact-free epochs. The results were analysed using the non-parametric Friedman two-way analysis of variance (ANOVA) for the discrimination analysis and a one-way ANOVA for the monopolar and bipolar Absolute Power raw measures.

Statistical analysis of the discriminant data showed no significant differences between operators, with 7 of 10 studies yielding the same results. The remaining 3 studies were classified either as borderline or normal when analysed by different operators. Although a series of "t" tests comparing 2 operators showed most variability occuring in Absolute Power as compared with Relative Power, Power Asymmetry and Coherence, ANOVA of the raw mono- and bipolar Absolute Power measures showed no significant differences between the operators at the $P = 0.05$ level.

Thus the differences between the operators were non-significant when comparing quantitative EEG analyses with respect to both the raw measures and the discriminant analyses.

Acquisition of new brainmapping equipment, while requiring the establishment of a normative database for the authors' laboratory, also required assessment of the equipment, methods and operator variability. With respect to the latter, a

literature search did not reveal any inter-operator reproducibility studies on brainmapping, but only inter-test[1,2,3,4,5,6] reproducibility studies.

We therefore designed a study to determine whether quantitative or discriminant analysis of the electroencephalograph (EEG) would vary significantly when the same EEG was analysed by 3 different operators.

METHODS

The study was performed with The Queen Elizabeth Hospital Ethics Committee approval and all subjects gave written informed consent. Twenty-one channel EEGs on 10 healthy (medically screened) volunteers were recorded on the Cadwell Spectrum AT 386, using the Cadwell Electrocap (10-20 system). Three additional channels - 2 ocular and 1 ECG - were recorded to facilitate the selection of artifact-free epochs. The quantitative EEG was analysed independently in each case, with each operator selecting the first 48 artifact-free epochs from the resting section of the recording.

Initially the results were compared using a series of 2-tailed "t" tests (P = 0.05) to determine the variability between pairs of operators. The Neurometrics "t" test package allowed comparison of all 4 mono- and bipolar parameters - the Absolute Power (AP), as well as the derived parameters Relative Power (RP), Power Asymmetry (PA) and Coherence (Coh). Subsequently the data were analysed more appropriately by means of analysis of variance (ANOVA) using the Statistical Package for the Social Sciences (SPSS). The mono- and bipolar Absolute Power raw measures were analysed using a one-way ANOVA. The report results from the discriminant data were analysed using the non-parametric Friedman two-way ANOVA, the results of the Neurometrics Analysis (quantitative EEG) discriminants reports being coded as 1 - normal, 2 - abnormal, 3 - borderline and 4 - unable to classify.

RESULTS

The report results from the discriminant data (Table 1) were analysed using the Friedman two-way ANOVA and yielded mean ranks of 1.95 for operators 1 and 2 and of 2.10 for operator 3. There was no significant difference between the mean ranks for the operators ($\chi^2_r = 0.15$, P = 0.93).

Comparison of the data from pairs of operators using the "t" test package i.e. operators 1 and 2, 2 and 3, 1 and 3 (maximum number of differences shown in Tables 2 and 3) revealed considerable variation in mono- and bipolar AP scores, by comparison with RP, PA and Coh values.

Table 1 Results of Neurometrics (quantitative EEG) discriminants reports

Subject	Operators		
	1	2	3
1	N	N	B
2	A	A	A
3	N	N	N
4	A	A	A
5	U	U	U
6	B	N	N
7	N	N	N
8	N	B	B
9	N	N	N
10	B	B	B

N = Normal ("This patient's discriminant scores lie within the normal limits expected for an individual of this age.")
B = Borderline ("This patient's discriminant scores do not allow a confident determination of the presence of abnormalities.")
A = Abnormal ("This patient's discriminant scores lie outside of the normal limits expected for an individual of this age.")
U = Unable to classify ("At this time there is no appropriate discriminant function to evaluate this patient's data.")

Table 2 Maximum number of significant differences between the 3 operators in the monopolar raw measures "t" test

Measure	n	Frequencies			
		δ	θ	α	β
AP	21	13	18	21	13
RP	21	0	1	0	0
PA	8	0	0	0	0
Coh	8	0	0	0	1

Table 3 Maximum number of significant differences between the 3 operators in the bipolar raw measures "t" test.

Measure	n	Frequencies			
		δ	θ	α	β
AP	8	4	8	8	4
RP	8	0	0	0	0
PA	4	0	0	0	0
Coh	4	0	0	1	0

The AP raw measures were then analysed using oneway ANOVA on the mono- and bipolar scores. These measures have not been tabled as each operator generated 840 monopolar and 320 bipolar measures (21 electrodes, 4 frequencies, 10 subjects and 8 electrodes, 4 frequencies, 10 subjects, respectively). The multiple range test (Tukey procedure) gave a range difference of 3.50 and, at the P = 0.05 level, no two groups were found to be significantly different.

DISCUSSION

Visual comparison of quantitative EEGs is difficult since there are as many as 232 monopolar and 104 bipolar measures (AP, RP, PA and Coh measures in the δ, θ, α and β frequencies) to compare in the one subject, particularly when, as pointed out by Oken *et al*[7], some measures may be abnormal by virtue of chance. For example, monopolar absolute power has 84 measures (21 electrodes, 4 frequencies) and, purely by chance, using a P = 0.05 level of significance, 7 of these measures may fall outside the ± 1.96 standard deviation (SD) limit, using the formula and program as documented by Desbiens *et al*[8].

For our initial analysis the Neurometrics "t" test brainmapping software program supplied for the Spectrum equipment was used. This, however, only allowed comparison of 2 individual records at a time. When the maximum numbers of significant differences between any 2 operators were pooled, there were a considerable number of statistically significant differences in the values for Absolute Power. These could be a reflection of: (i) the increased number of abnormalities resulting from use of the "t" test to compare more than 2 variables[9], (ii) the use of this "t" test package on z-scores and for comparing 2 records each using 48 epochs, and (iii) the selection of different epochs by different operators.

Following this preliminary analysis, the statistically more appropriate oneway ANOVA was performed and showed no significant differences between the operators at the P = 0.05 level for both mono- and bipolar raw measures.

By comparison, albeit with inter-test reproducibility studies on children, John *et al*[1] have reported correlations varying from a minimum of 0.42 (6 to 8 months between tests) to a maximum 0.97 (1 week between tests) using Neurometrics. Gasser *et al*[2] showed similar correlations in children, varying from 0.44 to 0.89 for Absolute Power and 0.37 to 0.90 for Relative Power (approximately 10 months between tests), using their own software package. Sebban *et al*[5] reported Relative Power inter-test reproducibility to be fairly good, although they did find a significant increase in slow α frequencies, probably due to habituation. We did not compare Relative Power, Power Asymmetry or Coherence, as these measures are derived from the Absolute Power raw measures.

Statistical analysis of the discriminant analysis results showed no significant differences between operators, with 7 out of the 10 studies yielding exactly the same results, and the remaining 3 studies being classified as borderline or normal when analysed by the different operators. This compares well with previously reported inter-operator comparisons of visual EEG analysis where Williams[10] reported variation of 62% to 92% (normal/ abnormal) between 100 operators.

While we have detected differences between operators, these have been shown to be non-significant when comparing quantitative EEG analyses with respect to both the raw measures and the discriminant reports. Thus this method of analysis can be used interchangeably by the different operators in the authors' laboratory, although it is accepted that any additional variable could increase the number of differences detected when comparing records.

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THE USE OF MAGNETIC RESONANCE IMAGING IN NEUROLOGICAL PRACTICE - A LOCAL EXPERIENCE

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SUMMARY

From April 1990 to September 1990, 170 magnetic resonance imaging (MRI) examinations of the brain were made with the Siemens 1.5 Tesla machine (the "Magnetom") in the Hong Kong Baptist Hospital. The indications for the investigation on the referral forms and the results were analysed. The MRI was particularly useful in making the diagnosis in 2 cases of multiple sclerosis, one case of an Arnold Chiari malformation, 6 cases of cerebro-vascular accidents, and 2 cases of encephalitis. MRI has replaced computerised tomography as the study of choice for the majority of central nervous system disorders.

Magnetic resonance imaging (MRI) is one of the most significant advances in medical imaging in this century. It has been increasingly used in the diagnosis of neurological problems. The present paper reports the MRI studies of the brain carried out in the Hong Kong Baptist Hospital, which is the largest private hospital in Hong Kong with 740 beds serving a population of 4.5 million in the Kowloon Peninsula and New Territories. The MRI machine used was the Siemens 1.5 Tesla (Magnetom).

METHOD AND RESULTS

From April to September 1990, 170 examinations of the brain were made with the Siemens 1.5 Tesla machine (the "Magnetom"). The indications for the investigation on the referral forms and the results were analysed (Tables 1 and 2). The commonest indications for referral were seizure disorders, headache, vertigo and dizziness, and stroke. Doctors referring patients for the study were mainly general physicians, neurologists and neurosurgeons.

Table 1 Indications for MRI studies

Indication	Number
Seizure disorders	30
Headache	24
Vertigo or dizziness	24
Stroke	19
Visual disturbance	12
Head injuries	11
Facial numbness and pain	7
Gait ataxia	5
Meningoencephalitis	5
Nasopharyngeal carcinoma	4
Mental changes	4
Multiple sclerosis	3
Anoxia	2
Miscellaneous	20
Total	170

Table 2 Results of MRI studies

Findings	Number
Normal	86
Cerebrovascular disease	28
Brain tumour	21
Encephalitis	4
Arteriovenous malformation	3
Multiple sclerosis	2
Subarachnoid haemorrhage	2
Porencephalic cyst	2
Anoxia	2
Hydrocephalus	2
Colloid cyst of 3rd ventricle	1
Miscellaneous	17
Total	170

Since there is as yet no comprehensive medical insurance system in Hong Kong, the patient has to pay the cost of his or her investigations. Therefore the majority of patients would choose computerized tomography scanning (CT scanning) first, as this is cheaper than MRI. However, more wealthy people would choose MRI because there is no radiation hazard and also no need for contrast injection. The reason for the commonest indication for referral being seizure disorders is probably that Chinese patients with epilepsy or headache did not like contrast injection as they are worried that the contrast injection might bring on their presenting symptom. As the MRI was better in detecting small lesions in the posterior fossa, it was also commonly used for investigation of the symptoms of vertigo and dizziness.

The MRI was found to be particularly useful in a number of cases where the CT scan was negative (Table 3). In 5 instances of cerebrovascular accident, the MRI showed the corresponding lesions while the CT scan failed to do so. We managed to perform MRI angiograms on 4 stroke patients and were able to show the related vascular lesions in 2. In one case of subarachnoid haemorrhage with a left anterior communicating artery aneurysm and paraparesis due to anterior cerebral artery spasm, MRI was able to show the ischaemic areas in the frontal lobe while CT scanning was entirely normal. There were 3 cases of arteriovenous malformations. We managed to perform a MRI angiogram in one case in which the blood supply to the lesion was well displayed, the result being comparable to the digital subtraction angiogram that was also done. Multiple sclerosis is rare in Hong Kong but 2 instances were encountered. One presented with a bilateral internuclear ophthalmoplegia, and the other had recurrent optic neuritis. Although the CT scans were negative, the MRI studies showed paraventricular white matter demyelinating lesions.

Table 3 Details of cases with a negative CT study but a positive MRI scan

Disease	Number
Cerebrovascular disease	
Stroke	5
Subarachnoid haemorrhage	1
Multiple sclerosis	2
Encephalitis	2
Arnold Chiari malformation (Type 1)	1
Total	11

In cases with brain tumour, the oedematous area was more extensively shown in the MRI but the delineation of the tumour margin was less clear in the MRI than in the CT scan. This deficiency could well be improved by the use of gadolinium contrast injections which we have tried in one patient and which yielded improved visualization of the

tumour margin. In one patient with a tumour of the corpus callosum the CT scan showed the main extent of the tumour and the extensive neighbouring oedema. The MRI appearance was less definite and could have been considered consistent with multiple cerebral metastases if the sagittal cut had not shown the anatomical relationships fairly clearly, with a lesion in the corpus callosum indenting the roof of the third ventricle.

There were 2 patients with viral encephalitis followed with serial MRI studies showing changes in the white matter which completely resolved when the patients recovered. The corresponding changes were not shown on CT scanning.

One case of cerebellar tonsillar herniation (the Arnold Chiari malformation type 1) presented with spastic paraparesis and was initially misdiagnosed as having an idiopathic cervical myelopathy with a negative cervical myelogram and CT scan. However, the lesion was clearly shown in a MRI study, especially in the sagittal cut. This illustrates the usefulness of MRI in the detection of cervico-medullary junction lesions.

DISCUSSION

In the study here reported, the role of MRI in the diagnosis and management of brain disorders was compared with that of the CT scan. Eleven of the 170 patients studied had a negative CT scan but a positive MRI study. In these cases the MRI was very helpful in achieving the diagnosis of the underlying disease and was responsible for the management being altered. Because of its superior soft tissue contrast resolution, mutiplanar imaging capabilities, and lack of need for the use of ionizing radiation, MRI has replaced CT as the investigation of choice for the majority of abnormalities of the central nervous system. However acute cerebrovascular accidents, intracerebral haemorrhages, haemorrhagic infarctions and subarachnoid haemorrhages, may not be as well shown by MRI as by CT because, in the first 24 to 48 hours following the ictus, since the blood content (which would be mainly oxyhaemoglobin) would be isodense in the MRI[1,2]. With continuing hypoxia, there is formation of desoxyhaemoglobin and methaemoglobin, which would appear as a high signal intensity on T_1-weighted images and might also be seen as a high signal intensity on T_2-weighted images. Thus subacute and chronic haematomas are better defined by MRI than by CT scanning, because of the presence of paramagnetic methaemoglobin in the lesions[3].

Although vascular malformations and flow in vascular tumours are detected equally well by MRI and by CT, MRI gives better resolution of abnormal vessels, and shows areas of previous bleeding better. MRI angiographic studies, in which no injection of contrast media is required, have offered a useful advance

in the visualization of the vascular supply of arterio-venous malformations[4] and also in demonstrating the pathology of blood vessels in instances of cerebrovascular accident. With the recent development of MRI to show abnormalities of cerebrospinal fluid flow related to ventricular system obstruction, useful information can be obtained in patients with hydrocephalus[5].

There are disadvantages in using MRI in tumour detection. The tumour itself is frequently obscured by the high signal from the surrounding oedema. However, the use of the paramagnetic contrast media has resulted in clear demonstration of most neoplasms[6].

Thus, overall, MRI has the attributes of a superior imaging tool, with high resolution, high contrast, high sensitivity, and a wide range of selectable scanning parameters that allow one to study blood flow as well as tissue characteristics in central nervous system abnormalities. With the use of a blood-brain barrier contrast agent, many of the past limitations of MRI can now be eliminated. MRI has clearly become the main imaging tool for the detection of disease of the brain, with the exception of some acute haemorrhagic lesions.

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NEUROPSYCHOLOGICAL ASSESSMENT IN LAMOTRIGINE TREATED EPILEPTIC PATIENTS

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SUMMARY

A double-blind, placebo controlled cross over study assessed the efficacy of lamotrigine as adjunct therapy for patients with refractory partial seizures. In addition to the main study, a neuropsychological component evaluated three main areas of cognitive function. These included:

i) Concentration and attention;
ii) General Cerebral Efficiency, and
iii) Mnestic functions - immediate, short term and new learning ability.

Ten subjects (4 males, 6 females, age range 22 to 53, mean age 31.3 years) were involved in the study, each assessed 3 times - baseline, end of phase I and end of phase II. Whilst statistical analysis proved impracticable due to differing scores across cells, between the results of lamotrigine and placebo, clinically, there appeared to be a marginal reduction in General Cerebral Efficiency during the lamotrigine phase.

In the light of these tests, the conclusion is advanced that lamotrigine does not specifically impair cognitive function, and that it does not impair mnestic function. An alternate hypothesis of interaction effects is posited for the slight reduction in speed of information processing.

Lamotrigine is a novel antiepileptic drug, chemically unrelated to the antiepileptic drugs in current use. In pharmacologic tests lamotrigine has an antiepileptic profile resembling that of phenytoin and carbamazepine, being effective in maximal electroshock and maximal pentylenetetrazol tests and ineffective in threshold tests[1]. A controlled trial by Jawad et al[2], reported that the use of lamotrigine showed a statistically significant reduction in seizures as

compared with placebo for total seizures, partial seizures and secondarily generalized seizures. This study also reported a significant reduction in total seizure days. The most common adverse reactions to lamotrigine reported during the trial were diplopia, drowsiness, tiredness, ataxia, and headache, but although these were more frequent during lamotrigine treatment, the differences as compared with placebo were not statistically significant.

MATERIALS AND METHODS

This investigation was part of a multi-centre placebo controlled double-blind randomised cross-over study of lamotrigine as adjunct therapy for patients with refractory partial seizures receiving no more than two other standard antiepileptic drugs. The study design employed a 3 month baseline recording period requiring a minimum of 4 partial seizures per month to allow inclusion in the study. There needed to be an absence of concomitant medication and no confounding medical or psychiatric disturbances. There were two active treatment periods (lamotrigine or placebo) of 12 weeks duration punctuated by a one week reduction of medication and 3 weeks of placebo, with a similar washout phase at the end of the study.

SUBJECTS

Twelve patients were initially selected to participate in this aspect of the antiepileptic drug trial. Fully informed consent was obtained from all patients for participation in the trial and in the neuropsychological assessment component. Two patients did not complete all 3 assessments and their results were discarded. Details of the remaining 10 are presented in Table 1.

APPARATUS

A standardised neuropsychological assessment protocol was devised using the following tests:

Intellectual level

National Adult Reading Test (NART). The NART was specifically designed to provide a means of estimating the premorbid intelligence levels of adult patients suspected of suffering from intellectual deterioration. It has been demonstrated that word-reading ability and general intelligence are highly correlated and it was utilised in this test protocol as an efficient and reliable measure to test and re-test intelligence.

Table 1 Patient details, drug therapy and lamotrigine dosage

Patient No.	Sex	Age (years)	Drug Therapy	Daily Dose (mg)	LTG Daily Dose (mg)
1	M	22	CBZ	2000	150
			VPA	2500	
2	M	50	PHT	450	150
			VPA	500	
3	F	22	CBZ	1200	300
			Clob	20	
4	F	34	CBZ	3000	150
			VPA	1400	
5	F	35	CBZ	1400	300
			Clob	20	
6	F	20	CBZ	600	150
			VPA	2000	
7	M	24	CBZ	1200	300
8	M	28	VPA	3000	150
			PRM	1000	
9	F	20	CBZ	1600	300
			Clob	60	
10	F	37	CBZ	1000	300

LTG = lamotrigine; CBZ = carbamazepine; PHT = phenytoin; VPA = sodium valproate; PRM = primidone; Clob = Clobazam

Concentration and attention

Stroop Colour Word Test. A single colour plate is used on which colour names are printed in incongruous colours (e.g. 'red' is printed in green print, 'green' is printed in blue print, etc.) In the first part of this procedure, the person simply reads the words as quickly as possible and ignores the colours of the print. The neuropsychological indicator is the number of words read in 45 seconds. In the second part of the test, the person must name colours only and in the third part the person must read the colours of the print while ignoring what the words say. This section is very difficult and requires a great deal of concentration. The test appears to be a good index of distractibility.

General Cerebral Efficiency (GCE)

Trail Making Tests A and B. In part A, the patient connects (in order) circles numbered 1 to 25 on a piece of paper as quickly as possible. In part B, 25 circles are also connected as quickly as possible but with orderly alternation between numbers and letters (1-A-2-B-3-C etc.). As with the Stroop test, errors must be corrected before the test can

proceed. This test is used to measure overall cerebral efficiency, level of distractibility and ability to comprehend a novel task quickly. The neuropsychological indicator for this test is the time taken to complete part B.

Digit Symbol. Though speed and accuracy both influence success, this subtest of the Wechsler intelligence scales is generally considered more a straightforward test of pyschomotor speed than any other subtest within the Wechsler battery. The neuropsychological indicator is the number of items completed in 90 seconds, and clearly speed, not power, nor accuracy, receives greater credit[3].

Mnestic functions - immediate, short term and new learning ability

Digit Span. There is a difference of opinion as to whether this subtest measures memory, attention, anxiety or distractibility, or some combination of these[4]. An immediate memory factor is obviously involved. More specifically, this subtest of the Wechsler scales measures immediate auditory memory for digits. A series of digits is presented to the patient in an order of increasing quantity (i.e. 2 digits, 3 digits, 4 digits etc.). Two trials are presented at each level of difficulty. The process is then repeated with the patient being required to reverse the digits (i.e. '719', answer: '917'). The neuropsychological indicator is the number of forward and backwards digits the patient can recall.

Rey Complex Figure Test. A 'complex figure' was devised by Rey (1941) to investigate new learning, perceptual organisation and visual memory in brain damaged patients. Neuropsychological indicators include accuracy of copy and of delayed recall drawing (30 minutes delay with distracting material in between drawings); procedural method of drawing and omissions and embellishments to the drawing itself.

PROCEDURE

The assessment process took approximately one hour to complete and was carried out at the point of acceptance into the study, and at the conclusions of Phases I and II (after 12 weeks of either lamotrigine or placebo). Patients were tested by the same examiner at all 3 asessments and the investigator was blinded as to the use of lamotrigine or placebo in either Phase I or II. Tests were administered in the following sequence:

All patients were initially assessed with the NART, then the 'copy' stage of the Rey Complex Figure (RCF). The Digit Span and Digit Symbol were presented next, followed by the Trail Making Test parts A and B. Finally the Stroop colour and word test and the recall drawing of the Rey Complex figure were administered. Given the time delays between assessments (average 12 weeks) the alternate versions of the RCF were not used.

Before breaking 'code' and determining whether patients were being treated with placebo or lamotrigine therapy during the double-blind study an attempt was made to predict the active versus the placebo treatment based on the patient's neuropsychological assessment results.

RESULTS

Table 2 shows the total seizure frequencies during both phases and the resulting percentage change between the two phases. Of the subjects involved, only two patients reported more seizures occurring during the lamotrigine phase than occurred during placebo treatment period, and overall the median reduction of seizures was 27% on lamotrigine as compared to the placebo phase. The results from the neuropsychological assessments are presented in Table 3.

Table 2 Patient total seizure counts and percentage change between periods

Patient No.	Sex	Treatment Sequence	Total Seizures LTG	Total Seizures Placebo	% Change
1	M	LTG/PLO	26	45	42
3	F	LTG/PLO	195	153	*22
6	F	LTG/PLO	34	77	56
8	M	LTG/PLO	37	50	26
2	M	PLO/LTG	8	24	67
4	F	PLO/LTG	28	30	7
5	F	PLO/LTG	21	29	28
7	M	PLO/LTG	65	86	24
9	F	PLO/LTG	27	47	43
10	F	PLO/LTG	21	20	*5

* = percentage **increase** in seizures whilst on lamotrigine

When attempting to predict the phase in which lamotrigine therapy was in use, prior to decoding the patient/phase sequence. False predictions were obtained for patients 3, 5 and 10 based on the colour/word scores of the Stroop test. The prediction of lamotrigine therapy was appropriate in the remaining patients.

Table 3 Selected neuropsychological assessment results

Patient No.	Treatment	Trail making (Part B) (%'ile)			Digit Symbol (Scaled Score)			Stroop c/w (T score)			Complex Figure Test Recall (%'ile)		
Phase of Study*		B/L	I	II	B/L	I	II	B/L	I	II	B/L	I	II
1	LTG/PLO	75	75	90	6	4	9	54	48	52	30	20	30
3	LTG/PLO	10	10	10	6	7	9	32	36	36	10	40	90
6	LTG/PLO	10	10	25	5	4	5	26	24	26	10	10	10
8	LTG/PLO	10	10	10	5	4	5	44	40	42	10	10	20
2	PLO/LTG	10	10	25	4	4	3	24	22	24	50	25	50
4	PLO/LTG	10	10	10	4	4	3	36	36	34	10	20	10
5	PLO/LTG	10	10	10	5	5	4	24	30	20	10	10	10
7	PLO/LTG	25	25	10	9	8	6	32	32	26	60	70	50
9	PLO/LTG	50	25	10	5	5	4	30	32	22	20	20	10
10	PLO/LTG	90	90	90	11	12	11	54	48	50	10	10	10

*B/L = baseline; I = phase I; II = phase II

N.B. in all of the above tests, the higher the score, the better the performance

The Stroop Colour/Word measure of cognitive efficiency (and distractibility) together with the Digit Symbol subtest of the Wechsler scale were the most sensitive of the measures involved. Scores from these two measures appropriately reflected period changes on 7 of the 10 patients. The recall segment of the Complex Figure Test also provided additional support for the prediction of treatment sequence of 6 of the patients.

There were no discernible differences in many of the tests employed, for example the Trail Making Test Part A, and the Stroop word and colour segments of the test (only the 3rd segment involving the distractibility component returned any differences).

DISCUSSION

The differing format of scores across cells (i.e. scaled scores, percentiles, IQ scores and T-scores) and the presence of incomplete data sets for some individual tests, made it impossible for parametric statistical methods to be employed[5].

Whilst the neuropsychological data collection for lamotrigine is still in its infancy it was readily apparent from this investigation that this antiepileptic medication has few, if any, of the sedating properties previously associated with the older generation antiepileptic drugs, particularly phenobarbitone and phenytoin.

Predictions of the patient's treatment sequence (lamotrigine as compared with placebo) was determined solely on the basis of clinical interpretation of the raw scores in Table 3, acknowledging that higher scores reflect better performance. It was evident that the most reliable psychometric tests to determine active treatment as compared to placebo were the Digit Symbol, the Stroop colour/word segment, and to a lesser extent the Complex Figrue Test 'recall' item. These tests specifically focussed on speed of psychomotor efficiency, visuo-percuptual organisational skills and levels of distractibility (and concentration). Test information from the remaining measures provided no further insight into patient differences between the two phases of the investigation.

In reviewing the results overall, a number of issues need to be considered, not the least of which is polytherapy and reduced efficiency of concentration and mental manipulation. Shorvon and Reynolds[6] and Fishbacher[7] reported beneficial results in terms of improvements to psychomotor performance and behaviour as antiepileptic medication was reduced.

CONCLUSIONS

In addition to an evaluation of the anticonvulsive benefits of a novel drug lamotrigine, a study assessing the neuropsychological impact of the drug was performed.

Ten subjects, 4 males and 6 females (age range 22 to 53, mean age 31.3 years) were assessed 3 times (baseline, end of Phase I and end of Phase II) using measures of mnestic

function, cerebral efficiency, concentration, and immediate verbal and visual memory. Clinically the results suggested that lamotrigine did not affect mnestic function or specific cognitive abilities. From the data there were indications of reduced cerebral efficiency though it was unclear whether this was due to lamotrigine alone or due to presumed polypharmacy effects.

It is imperative that a double-blind single drug cross-over study be undertaken to better assess the effect of lamotrigine whilst removing the influence of multiple antiepileptic drugs. It suffices to indicate for the moment that lamotrigine continues in the path of the current generation of antiepileptic drugs by demonstrating effective seizure control with minimal cognitive impact.

ACKNOWLEDGEMENT

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ZETA WAVES: A DISTINCTIVE TYPE OF INTERMITTENT DELTA WAVE STUDIED PROSPECTIVELY

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SUMMARY

Zeta waves are a distinctive form of sharply contoured biphasic delta waves that have been associated with underlying structural lesions. We have prospectively interpreted the EEGs of 840 consecutive patients blinded for clinical details. Thirty three patients had zeta waves in at least one recording and 87% of these had an underlying structural lesion on neuroimaging. By excluding those with bifrontal intermittent rhythmic delta activity and bifrontal zeta waves, the positive predictive value of zeta waves for an underlying structural lesion increases to 96%. We conclude that zeta waves are distinctive and easily recognisable delta waves which are highly predictive of recent or residual cerebral damage from a variety of causes, including cerebral trauma and infarction.

Zeta waves were first reported in the Dutch EEG literature in the early 1970s, but have since fallen into oblivion[1]. They consist of broad, sharply contoured delta waves that have a saw-tooth configuration like an inclined letter "Z" and hence their name (Fig 1). They may occur singly, or in trains of 2 or 3 but tend to have a constant form throughout a given recording. Magnus and Van der Holst[2], in the only previously reported series of zeta waves, described 76 EEGs (20 patients) out of a total of 2500 EEGs with zeta waves[2]. An association with underlying (usually acute or subacute) severe brain lesions was found but no patient had cerebral infarction.

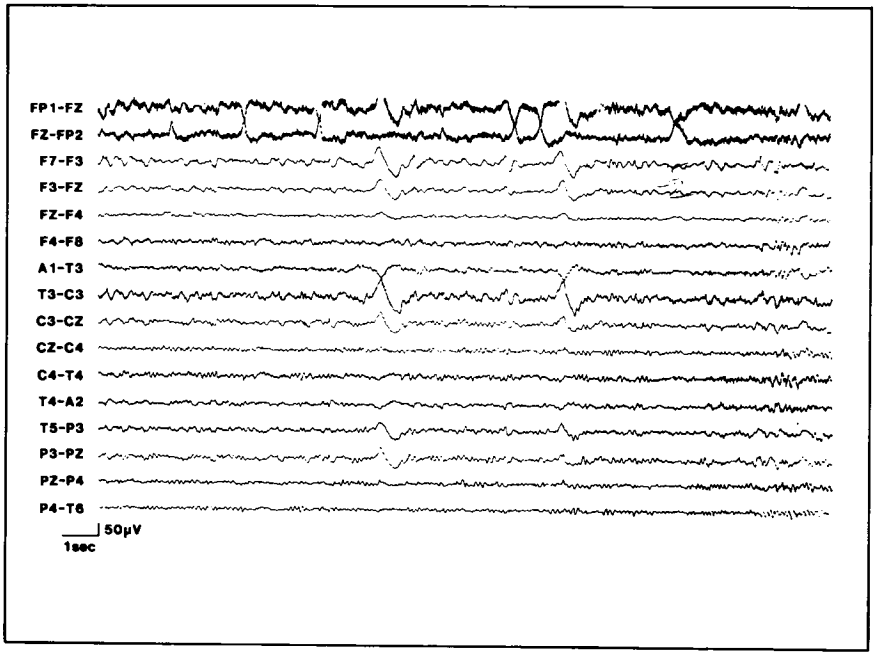

Fig 1 Transverse bipolar montage with left frontotemporal zeta waves

MATERIALS AND METHODS

One of us (JWD) has prospectively interpreted the EEGs of 840 consecutive unselected patients referred to the Royal Perth Hospital Department of Neurology for EEG. All EEGs were reported blinded for clinical details, and were performed using the International 10 - 20 system of electrode placement, with 16 or 21 channel recordings at paper speeds of 30 mm/sec, and 50 - 70 microvolts per cm amplification (for most recordings). A combination of bipolar and referential montages was used.

Zeta waves were defined as sharply contoured slow waves with an initial negative phase, followed by a relatively steep positive phase crossing the baseline, and then a slow return to the baseline. Their frequency and characteristics (including amplitude in the longitudinal bipolar montage) were studied in addition to other associated findings. Clinical and radiological details were then obtained on all patients.

RESULTS

PRIMARY DIAGNOSIS

Thirty-three patients had zeta waves in at least one recording. These patients had a variety of diagnoses (Table 1).

Table 1 Diagnoses

Category	Diagnosis	Number of Patients
Vascular		9
	Cerebral infarction	5
	Acute cerebral haemorrhage	2
	Acute subarachnoid haemorrhage	1
	Acute cerebral vasospasm	1
Head Injury		10
	Old head injury	5
	Acute head injury	5
Epilepsy		4
	No underlying structural lesion	2
	Cerebral palsy/postictal	1
	Cerebral infarct/postictal	1
Infective		4
	Herpes simplex encephalitis	3
	Syphilitic cerebritis	1
Metabolic		2
	Heat stroke/encephalopathy	1
	Hyperglycaemic hyperosmolar coma	1
Tumor		3
	Glioblastoma multiforme	1
	Cerebral secondaries (lung)	1
	Meningioma	1
Post Operative		1
	Post excision of AVM	1

EPILEPSY

Twenty-four of the 33 patients had epileptic seizures: 23 had partial seizures (with or without secondary generalisation) and 1 had myoclonic seizures as part of a metabolic encephalopathy. Eleven of the 33 patients' EEGs showed epileptiform abnormalities.

IMAGING

Of the 31 patients who underwent neuroimaging (cranial CT, MRI or both), 27 had an underlying structural lesion congruent with the zeta waves on EEG (Fig 2). The positive predictive value of zeta waves for the presence of an underlying structural lesion on imaging was 87%. Single patients with negative neuroimaging studies had a history of significant head injury, vasospasm after balloon occlusion of a caroticocavernous fistula, a metabolic encephalopathy, or poorly controlled epilepsy.

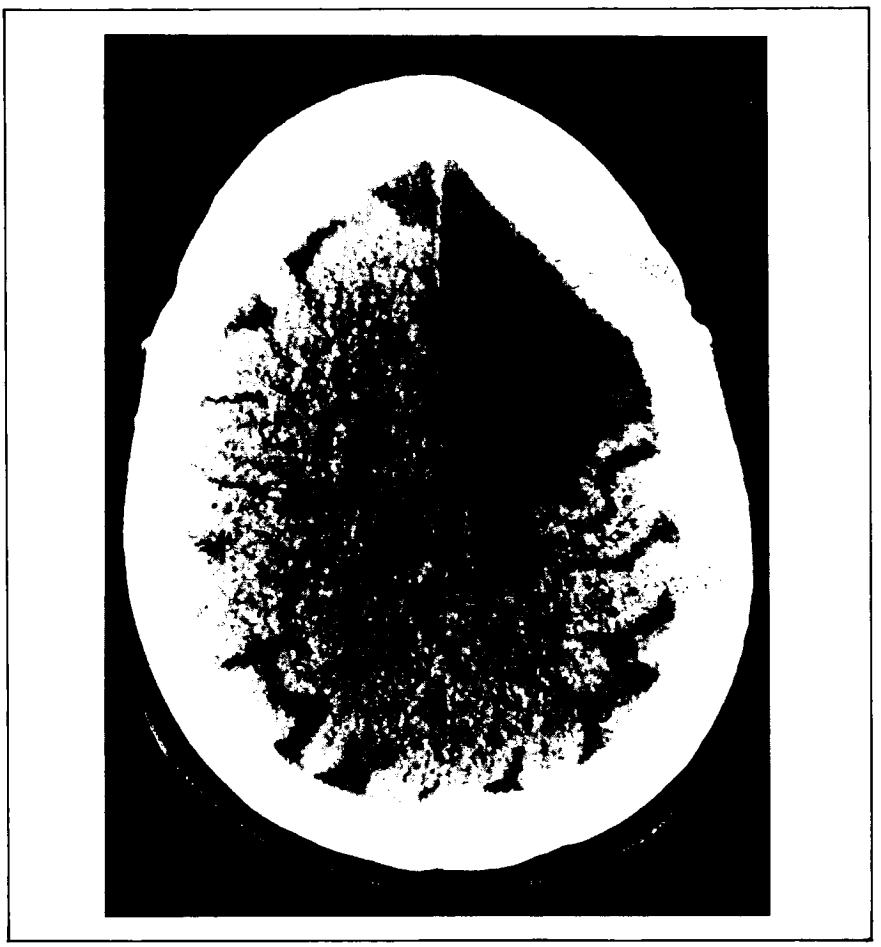

Fig 2 Cranial CT scan showing an old area of left frontal infarction. The patient's EEG is shown in Fig 1.

OTHER ELECTROENCEPHALOGRAPHIC FINDINGS

1) *Focal and persistent polymorphic delta activity* (21 patients)

Nineteen of the 20 patients with a recent cranial CT scan had an underlying structural lesion. The one patient without an associated structural lesion had presumed transient vasospasm following balloon occlusion of a caroticocavernous fistula.

2) *Bifrontal intermittent rhythmic delta activity (FIRDA)* (5 patients)

FIRDA occurred in 2 patients with epilepsy and in one with a metabolic encephalopathy, all with normal CT scans. One patient had post-stroke epilepsy, with focal zeta waves related to his previous stroke in addition to bifrontal zeta waves. One further patient had bifrontal trauma with bifrontal FIRDA and zeta waves.

ZETA WAVE CHARACTERISTICS

The morphology of zeta waves tended to be constant in a given recording. The mean duration was 794 msec (range 367 - 2500 msec) and the mean amplitude was 112 μV (range 34 - 259 μV), as measured on the longitudinal bipolar derivations. The zeta waves occurred singly, or in trains of 2 to 5, and usually with a frequency to 1 -2 per minute.

DISCUSSION

Contrary to the single previous study[2], zeta waves were found in association with a wide range of primary pathologies including closed head injury, cerebral infarction, cerebral haemorrhage, encephalitis, meningioma and cerebral secondaries. Uncommonly, bifrontal zeta waves were seen with metabolic disorders and as postictal phenomena. They were present both acutely and, at times, as a persistent residual finding. Zeta waves had a high positive predictive value for an underlying structural lesion. Some zeta-like waveforms occurred in association with FIRDA, and may represent a variation of FIRDA morphology. Excluding those with FIRDA and bifrontal zeta like waves, the positive predictive value of focal zeta waves for an underlying structural lesion was 96%.

In conclusion, zeta waves are distinctive and easily recognisable delta waves which are highly predictive of recent or past cerebral damage from a variety of causes, including cerebral infarction.

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INTRATHECAL BACLOFEN FOR SEVERE SPASTICITY: FIVE YEARS EXPERIENCE

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SUMMARY

Severe spasticity is a major problem in the rehabilitation of patients with dysfunction of the spinal cord or cerebral hemispheres. Oral baclofen is often effective. However, in patients with severe spasticity adequate control may not be obtained from oral therapy with the drug. Over the past 5 years we have developed a program for the use of intrathecal baclofen for severe spasticity, and in relation to this discuss patient assessment, practical aspects of drug administration, complications of therapy and patient benefits.

Continuous intrathecal baclofen is a safe and effective adjunct to physical therapy in the management of patients with severe spasticity.

The spasticity associated with upper motor neurone disorders may interfere not only with the ability to perform the basic activities of daily living, but also degrades quality of life through painful muscle spasms which interfere with mobility and bladder and sexual function. Therapy of this spasticity must be tailored for the individual patient. Many patients benefit functionally from their spasticity, using it to aid their gait and ability to transfer weight. However in some a degree of spasticity occurs at which the disadvantages outweigh the advantages. Treatment is then required.

The muscle spasms and increased muscle tone associated with severe spinal spasticity often respond poorly to the oral medications currently available (diazepam, baclofen and dantrolene). Although tolerance may develop to the common problem of excessive sedation from the medications, it is not

uncommon to find that patients are still significantly disabled by spasticity despite maximal acceptable doses of oral medications.

In May 1984, Penn from the Department of Neurosurgery, Rush Medical College, in Chicago, first described the effects of intermittent intrathecal administration of baclofen in humans[1]. In November 1985, the Royal Perth Hospital began a program aimed at the treatment of severe spasticity with intrathecal administration of baclofen. In this paper we describe the results of this program, highlighting in particular our methods of patient selection and evaluation, the practicalities of pump selection, the structure of our outpatient management program, the patient benefits derived and the complications of intrathecal baclofen administration.

METHODS

The intrathecal baclofen programme at Royal Perth Hospital is based in the Department of Neurology, with assistance provided by the Departments of Surgery and Anaesthetics for pump and catheter insertion.

PATIENT SELECTION

Patient selection is on an individual basis, and is determined by the following guidelines which were initially established in keeping with Ethics Committee requirements. There must be: (i) severe spasticity, (ii) frequent spontaneous spasms or limited passive movement, (iii) an inadequate response to medical treatment with maximally tolerated oral doses of diazepam, baclofen and dantrolene, alone and in combination, and (iv) a response to a test dose of intrathecal baclofen.

TEST DOSE ADMINISTRATION

A test dose of 50 μg of baclofen is given intrathecally (by lumbar injection). Patients are then assessed every one to 2 hours for 4 to 6 hours to obtain a subjective and objective impression of the effect of the intrathecal baclofen, particularly with regard to tone, spasms and functional activities such as transfers, sitting and bed mobility. If an inadequate response is obtained 75 to 100 μg test doses can then be given. Patients are usually assessed as day cases, unless other reasons for formal admission to hospital are present.

INTRATHECAL BACLOFEN DELIVERY SYSTEM

Port-a-cath intermittent baclofen administration

Port-a-cath intermittent drug delivery systems were used in the early stages of our program. These systems require intermittent percutaneous administration 2 to 4 times daily through a subcutaneous port, which connects to a catheter delivering the baclofen intrathecally. Bolus doses of baclofen were administered by the patient, spouse, carer or nursing attendant.

Continuous infusion systems for intrathecal baclofen administration

We now use this method of drug delivery exclusively and the results presented below apply to this method of baclofen administration. Five patients have received constant infusion pumps and one patient a programmable infusion pump. These pumps were implanted subcutaneously in the anterior abdominal wall under local or general anaesthesia and were connected via a subcutaneously tunnelled catheter to the subarachnoid space. Infusion pumps were refilled percutaneously, dose alteration being made by altering baclofen concentrations for the constant rate infusion pumps, and by telemetry for the programmable pump.

INTRATHECAL BACLOFEN DOSE REQUIREMENTS

Intrathecal baclofen was commenced in a dose of 250-300 µg/day. All oral drugs prescribed for spasticity or spasms were ceased, and the intrathecal baclofen dose was increased until the desired clinical response was obtained.

OUTPATIENT MANAGEMENT PROGRAM

Patients attended for reservoir refilling every 2 weeks (for some of the older pumps) to every 6 weeks (for the newer 'slower' pumps). The pumps were refilled by registered nursing staff, and patients were seen neurologically only at the usual frequency for other patients with similar conditions. Dose adjustments were made as needed, according to perceived patient requirements and clinical reassessment.

PROGRAM ASSESSMENT

Patient benefits were assessed in terms of the effectiveness of baclofen in relieving spasticity (Ashworth score[2] - Table 1) and spasms (spasm score - Table 2). Dependency levels and the social impact of intrathecal baclofen administration were also noted.

COMPLICATIONS

All technical, pharmacological and neurological complications of intrathecal baclofen infusion were recorded.

Table 1 Ashworth spasticity scores[2]

Ashworth spasticity scale (5 points)	
Grade	Degree of muscle tone
1	no increase in tone
2	slight increase in tone (catch)
3	increased tone, but passive movement easy
4	increased tone, passive movement difficult
5	rigidity in flexion or extension

Table 2 Grading scale for spasms

Spasm frequency score	
Score	Frequency of spasms
0	no spasms
1	mild spasms induced by stimulation
2	infrequent full spasms (< 1/hour)
3	spasms greater than 1/hour
4	spasms greater than 10/hour

RESULTS

PATIENT SELECTION AND TEST DOSE ADMINISTRATION

Baclofen test doses were administered mainly to patients with spinal causes for their spasticity (Table 3). Relief of spasms and spasticity occurred in all patients, although a few larger patients required 100 μg of the drug. All patients were aware of relief of spasticity and spasms, but were encouraged to try transfers and other activities of daily living to see what effect the relief of spasticity had on their level of function. Those who were still using standing transfers usually disliked the feeling of 'lack of spasticity'. Some such patients who had a baclofen test dose rejected the therapy but were more satisfied with the result of a test dose a few years later when they were using sliding transfers. Other reasons for not continuing with intrathecal baclofen infusions included the following: (i) patients with multiple sclerosis and hereditary spastic paraparesis

with contractures that limited the response to baclofen administration; (ii) a patient with Murray Valley encephalitis who had a pronounced increase in dystonia when her spasticity was reduced; (iii) a patient with a spinal ependymoma who had a good response to the baclofen test dose but who had a significant improvement in her spasticity when she stopped doing her functional electrical stimulation program. (The possibility of seeding of a tumor by the intrathecal catheter should be considered in patients with a malignant cause for their spasticity).

Table 3 Diagnoses in patients each receiving 1 - 3 doses of intrathecal baclofen

Diagnoses	Number of patients
Multiple sclerosis	5*
Traumatic quadriplegia	3**
Pontine stroke	1
Syringomyelia (Arnold Chiari)	1*
Spastic paraparesis	2*
Spinal ependymoma (post-operative)	1*
Motor neurone disease	1
Cerebral palsy (MVE)	1*
Total patients evaluated	15

*Patients not continuing with intrathecal baclofen

INTRATHECAL BACLOFEN DELIVERY SYSTEM

Port-a-cath intermittent baclofen administration

The results of intermittent baclofen administration are shown in Table 4. Four of the 5 patients developed meningitis associated with the *port-a-cath* system, necessitating its removal. Patients 1 and 2 had some success with the *port-a-cath* system but received their drug twice daily and had it administered in a nursing home situation by trained nursing staff. This was in contrast to the other patients whose baclofen was either self-administered, or administered by the patient's spouse, 4 times daily. Two patients did not continue with infusion pumps. One of these patients died and the other required nursing home care and did not wish to have any further intervention despite experiencing improvement from the intrathecal baclofen.

The *port-a-cath* system of drug delivery resulted in an unacceptable infection rate of 80%. In some overseas centres a *port-a-cath* system is used initially to allow a more prolonged trial of the effects of intrathecal baclofen given 3 to 4 times a day. If the results are satisfactory a continuous infusion method is substituted. Provided compatible systems are used, this involves changing the pump only. This method of drug delivery is useful in the short term, either for initial assessment as above, or for use in acute conditions such as tetanus. The major disadvantages of this practice, apart from the risk of infection, is the additional cost entailed.

Table 4 Patients treated with intermittent intrathecal baclofen administered through a port-a-cath 2 (Cases 1 and 2) to 4 times daily (Cases 3 - 5)

Case	Diagnosis	Age	Duration	Meningitis
1	MS	34	18 months	
2	MS*	38	18 months	Yes
3	C5 quadriplegia*	50	5 months	Yes
4	Pontine stroke	38	1 month	Yes
5	Spastic paraparesis*	31	2 months	Yes

*patients changed to continuous intrathecal baclofen infusion

Continuous infusion systems for intrathecal baclofen administration

In selecting a system for continuous intrathecal baclofen administration, the factors listed in Table 5 are taken into account. Baclofen is currently believed to be stable in solution at body temperature for 6 weeks only. This determines the interval between refills for the programmable pump, with its low flow rate. The life span of the pump is an important factor in pump selection. For the Infusaid constant infusion pump, this depends on the number of punctures made in the septum (which number, provided that the correct Heuber needles are used, approaches 1000, giving a pump life span exceeding that of the patient). The programmable pumps have a shorter life span that is determined by battery life, and has been estimated at 3 to 5 years. In view of the cost of these pumps, this is an important consideration in chronically ill patients.

INTRATHECAL BACLOFEN DOSE REQUIREMENTS

The daily requirement of intrathecal baclofen varied (Fig 1). One patient admitted taking up to 240 mg of oral baclofen per day, although she had been

prescribed significantly less. While receiving continuous intrathecal baclofen, her requirement is 0.45 mg per day. A further patient with a complete C5-6 quadriplegia who had been prescribed 90 mg of baclofen orally in combination with diazepam, has been well controlled on 1600 µg of intrathecal baclofen per day. As with oral baclofen treatment, infection should always be excluded as a cause of increased spasticity before dose increments are made.

Table 5 Comparisons between constant infusion (Infusaid 400: Medical Specialities Australia) and programmable pumps (SynchroMed: Medtronic)

	Infusion Rate Pump	
	Constant	Programmable
Number of patients	5	1
Volume	50 ml	18 ml
Flow rate	1.0 - 2.0 ml/day	0.6 ml/day (min)
Refill frequency	2 - 6 weekly	4 (24) weekly
Life span	40+ years	3 - 5 years

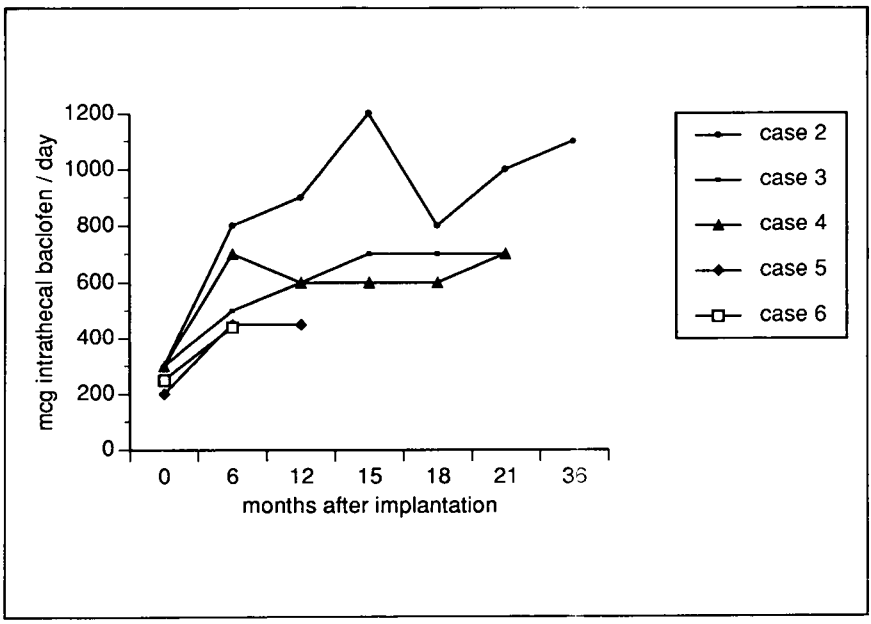

Fig 1 Daily requirements for intrathecal baclofen. Case description as in Table 6.

PROGRAM ASSESSMENT

Relief of spasticity and spasms

Relief has been almost complete in all instances. All patients improved to an Ashworth spasticity grade of 1 - 2 from a grade of 4 - 5. However, some patients preferred to retain a small amount of spasticity by reducing their bacolfen dose, to maintain their transfers or other activities at a higher level (Figs 2,3). This dose reduction usually caused the return of occasional spasms.

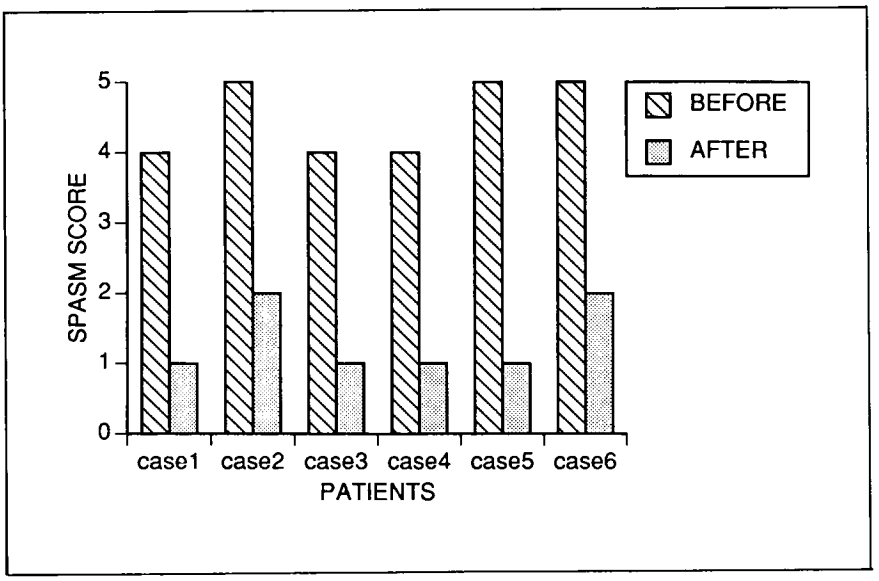

Fig 2 Ashworth spasticity scores prior to and 3 months after commencement of continuous intrathecal baclofen therapy. Case description as in Table 6.

Dependency levels - Quality of life

There was no change in dependency levels, although for all patients the performance of activities of daily living improved. For those with carers, all aspects of daily care were more easily performed without interference from spasms and spasticity. All patients and carers viewed the ability to sit in a wheelchair or lie comfortably in bed at night as of inestimable value.

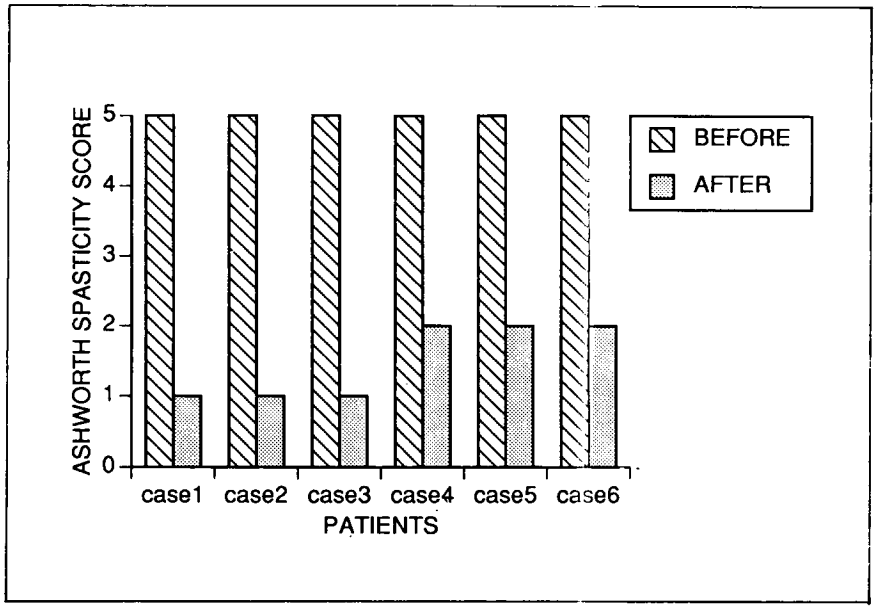

Fig 3 Spasm scores prior to and 3 months after commencement of continuous intrathecal baclofen therapy. Case description as in Table 6.

COMPLICATIONS

No patient had complications related to the test doses of intrathecal baclofen. The complications of intermittent intrathecal baclofen administration through *port-a-cath* systems have been discussed above. The complications of continuous intrathecal baclofen infusion are listed in Table 6. Technical problems related to proximal catheter displacement were most common in the earlier patients. With the improved pump fixation provided with newer models of the pump this has been less of a problem. One patient developed skin erosion and a pressure area. This patient was very cachectic and there was some migration of the pump. (We would now use a smaller pump in thin patients). Post-insertion low CSF pressure headaches were common, but did not persist. One patient had transient radicular pain after catheter insertion, probably due to irritation of nerve roots. This discomfort settled spontaneously.

Intrathecal baclofen was tolerated without adverse effects, except for transient respiratory depression in a C5-6 level quadriplegic treated with 1600 μg/day. This was associated with the intake of 8 tablets of a combination of paracetamol

(500mg) and codeine (30mg) over a 24 hour period whilst the patient suffered a urine infection. He now takes the same dose of intrathecal baclofen with no unwanted effects.

Table 6 Clinical diagnoses, pump type, duration of treatment and complications of continuous intrathecal baclofen infusion

Case	Diagnosis	Pump	Duration	Complications
1	MS	constant	22 months*	skin erosion/pressure area
2	C5QUAD	constant	42 months	proximal catheter displacement respiratory depression (see text)
3	MS	constant	35 months	nil
4	SP.PARA	constant	28 months	proximal catheter displacement mobile pump
5	MND	program.	12 months	acute radicular pain (transient)
6	MS	constant	6 months	catheter damage during insertion

MS = multiple sclerosis: C5QUAD = C5 quadriplegia: SP.PARA = spastic paraplegia: MND = motor neurone disease: * = pump removed

DISCUSSION

Baclofen is the most commonly prescribed antispasticity agent, but when it is taken orally its limited effectiveness and excessive sedation are common problems. With oral administration of the drug high systemic levels are required because of the drug's limited CSF penetration[3]. With intrathecal administration of the drug higher CSF levels are achieved with doses that may be up to 1/500th of the equivalent oral doses. Intrathecal administration improves the efficacy and reduces the side effects of therapy. The primary site of action of baclofen is spinal, where it acts on presynaptic $GABA_B$ receptors, restricting calcium influx into presynaptic terminals, leading to reduced neurotransmitter release. (Diazepam acts at $GABA_A$ receptors, further facilitating presynaptic inhibition). At higher concentrations, baclofen may also antagonise the postsynaptic actions of excitatory neurotransmitters[4]. There is also some evidence that baclofen reduces the response to noxious stimuli (analgesia) in experimental animals[5] and it has been reported to alleviate pain in spasticity[6]. Through these various actions there is a reduction in the activity of flexor reflex and pain pathways.

Intrathecal baclofen is now a proven safe and effective means of treating spasticity of cerebral or spinal origin[7,8,9]. The present authors have utilised this method of drug administration in patients not controlled by oral antispastic agents and in whom the spasticity interfered significantly with the patients' quality of life. Complications have been less frequent in recent years. This improvement is primarily related to technical improvements in infusion pumps (fixation mechanisms) and to accumulating local experience. Constant infusion pumps are now preferred, in view of their longer lifespan and mechanical simplicity. Low flow rate pumps are specifically requested from the manufacturers, allowing up to 6 weeks between pump refills.

Our findings of significant improvements in spasms, spasticity and quality of life have been supported by other studies[7,8,9,10]. Bladder function was not formally assessed in the present study, although other investigations have focussed specifically on this point. There is cystometric evidence to show that intrathecal baclofen can have a beneficial effect on bladder function[11].

ACKNOWLEDGEMENTS

Port-a-cath subcutaneous ports, Infusaid infusion pumps and Synchromed programmable pumps were supplied by Pharmacia Ltd, Medical Specialties Australia and Medtronic Australasia Pty Ltd, respectively.

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NOXIOUS HEAT HYPERALGESIA TEST INSTRUMENT

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SUMMARY

A simple feedback thermode has been developed to quantify cutaneous hyperalgesia to noxious heat. A noxious temperature set between 42°C and 60°C is applied to a test site by the subject. A resettable impedance timing circuit measures the contact duration to ±0.01s. Despite site-to-site, inter- and intra-subject variability, the test sensitivity is enhanced by comparing affected and corresponding normal skin in the same subject. This test strategy was used in 55 subjects in whom topical 0.025 to 0.05% capsaicin application provoked hyperalgesia on the forearm and foot. Capsaicin-treated sites showed a significant reduction of 52°C withdrawal latency (0.51-0.77 x normal mean; $P<0.05$). The device has been tested clinically in patients with diabetic neuropathy who had hypersensitivity to pinprick on one foot. A significant 42% difference was found between corresponding contralateral sites ($P<0.05$).

These data suggest that even mild hyperalgesia is detectable using this instrument. It provides an objective measure of hyperalgesia which can be used to assess changes in nociceptive acuity.

Although the value of experimental measurement of pain sensation thresholds has long been debated[1], particularly since the classical experiments of Head[2], the difficulties largely lie in reconciling the differences between clinical and experimental observations[3]. While clinical pain varies considerably between subjects[1], in controlled experiments Hardy *et al.*[4] showed that threshold pain is a consistent factor. Furthermore, clinical pain has an inherent threat content which is usually absent under experimental conditions[5]. By definition pain is a disagreeable sensation. However the threshold pain used in most experimental paradigms can only be considered mildly painful. In daily life, if we bump an

elbow or touch a sharp instrument to produce a threshold pain, this discomfort probably would not be considered as painful by many subjects. For these reasons it is considered that experimental tests of pain endurance may more closely reflect the experience of clinical pain than do tests of simple threshold pain[2]. This is the philosophy underlying the development of the noxious heat withdrawal latency device described here. However, because in hyperalgesia following peripheral nerve injury there is a probable contribution of peripheral nociceptor sensitisation[5,6,7], the device should be able to detect differences in pain threshold as well as in pain endurance.

METHODS

STRATEGY OF INSTRUMENT

Measurement of hyperalgesia in experimental and clinical studies has previously been difficult, but a simple instrument has now been developed to meet this purpose. This instrument measures accurately to 0.01 sec the withdrawal latency for a contact thermode set at a noxious heat between 45°C and 60°C. A lower setting (42°C to 45°C) permits allodynia to be tested. The experimental and clinical data presented here used 52°C as the noxious stimulus. This is based upon the stimulus temperature: withdrawal latency relationship described in Fig 3.

Description of Operation

The device utilises a simple heating circuit in conjunction with a feedback timing circuit to record to 0.01 second the withdrawal latency period to a noxious heat stimulus. The heating element in the probe consists of a high wattage resistor embedded in an aluminium head, regulated via a feedback-driven thermistor transistor system. The principles of operation are illustrated in the block diagram of Fig 1.

Regulated probe temperature settings can be preset to a desired noxious temperature between 45 and 60°C with the use of a series of potentiometers. To record the duration of the probe skin contact, the skin of the subject is used electronically as a high impedance feedback path. Consequently, upon application of the heated probe, the feedback loop is completed and the output of the amplifier moves positive to activate a Schmitt trigger, which in turn starts the timer. Similarly, when the probe is removed, the feedback loop is broken and the timer stops. Withdrawal latency may be recorded, the timer reset, and another measurement cycle performed when the regulated hot probe is reapplied at another site.

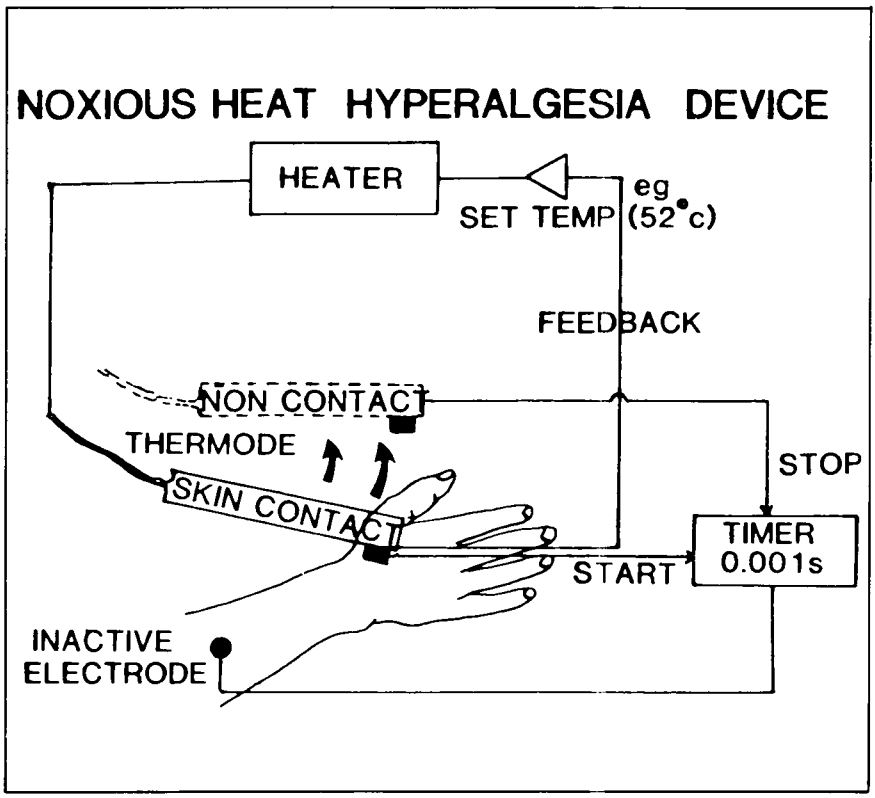

Fig 1 Block diagram showing functional principles of the noxious heat hyperalgesia device. Withdrawal latency is displayed on the digital timer, switched by the make/break of the contact circuit when the stimulus probe is placed on, or withdrawn from, the test site.

CIRCUIT DIAGRAM

The electrical circuit of the device is given in Fig 2.

EXPERIMENTAL TESTS USING CAPSAICIN PRETREATMENT

Pathophysiology

The alkaloid neurotoxin capsaicin, derived from Solanaceous plants such as Hungarian pepper, is a powerful rubefacient. Its topical application to the skin results in stimulation of peptidergic nociceptors, leading to a local burning sensation and neurogenic inflammation. In low capsaicin concentrations such as 0.025% and 0.05% cutaneous hyperalgesia is an early result, usually evident within 15 minutes of application. The inflammation (Lewis' triple response) ensues when the inflammatory

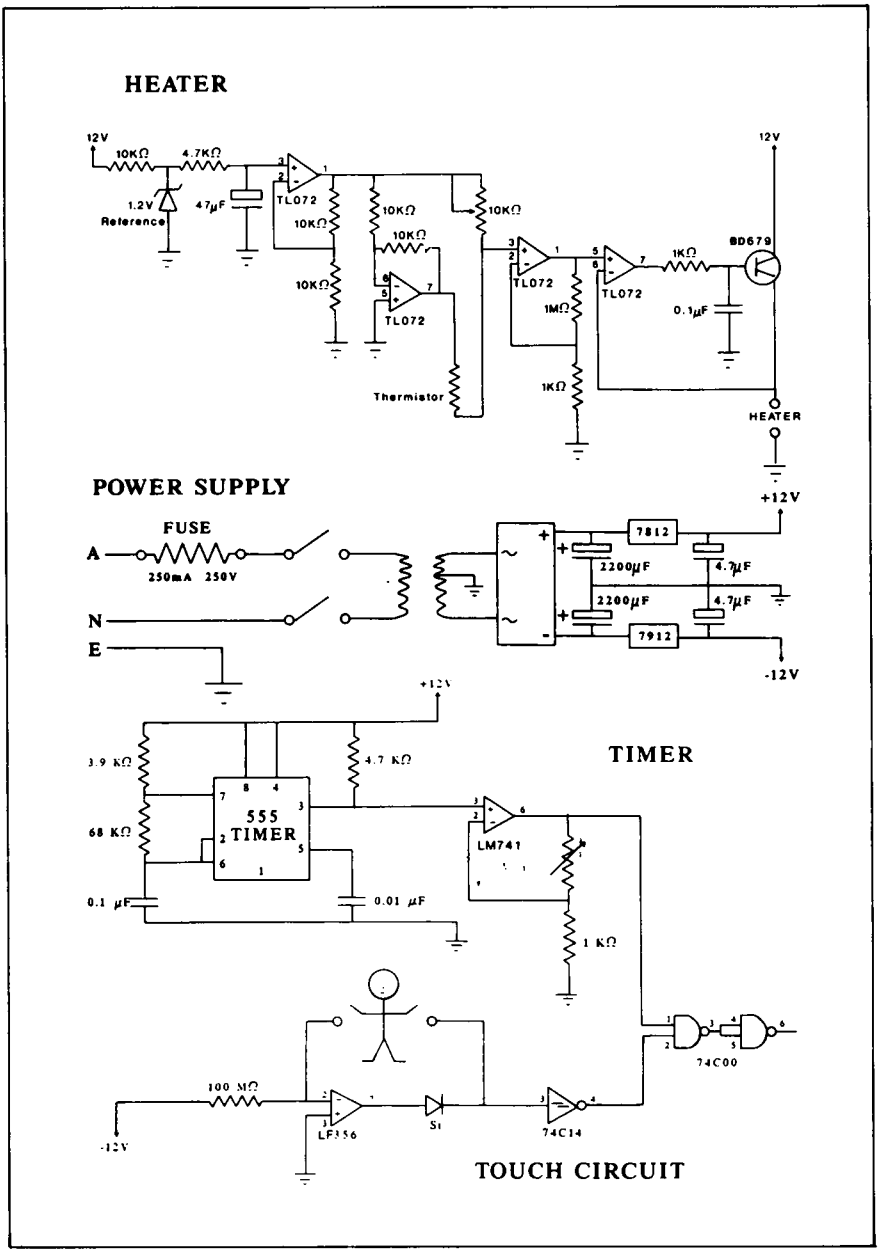

Fig 2 Circuit diagram of the noxious heat hyperalgesia test instrument.

cascade is triggered by the release of neuropeptides from nociceptors, then rapidly evolves as a result of mast cell degranulation, tachykinin release and prostaglandin synthesis[7,8]. These accumulating vasoactive compounds all sensitise nociceptors and their afferents adjacent to the zone of inflammation. This results in lowered noxious heat and mechanical pain (pinprick) thresholds and enhanced pain sensation[7,8].

SKIN TEST SITES

Because of regional differences in innervation density and epidermal thickness, a total of 10 sites was tested, comprising 3 on the anterior aspect of the forearm, the palm of the hand (one), the dorsum of the hand (2), the dorsum of the foot (3) and the foot instep (one): See Table 2, Figs 4, 5. For logistical reasons the number of capsaicin-treated subjects varied from 53 to 72 for the upper limb sites and 17 to 33 for the lower limb sites. All were consenting volunteers and the project had ethical approval from Monash University.

CLINICAL STUDIES

Hyperalgesia and allodynia are present in only a small percentage of cases of nerve trauma or disease (e.g. post- herpetic neuralgia, causalgia, reflex sympathetic dystrophy, painful symmetrical polyneuropathy in diabetes mellitus). In 17 such diabetic patients with pinprick hyperalgesia, the withdrawal latency to a 52^{0}C noxious heat was measured at several sites within the affected skin area, and at corresponding skin sites on the contralateral unaffected skin. Latency difference scores were then calculated.

RESULTS

Fig 3 shows the effects of changing the noxious stimulus temperature at the same skin site in a group of normal subjects. A non- linear relationship existed, but temperatures below 50^{0}C tended to require prolonged application (ie >60s) to elicit withdrawal, and this would prove impractical in most clinical test situations. Probe temperatures above 55^{0}C produced withdrawal latencies which were excessively short for accurate end-point determinations. The 52^{0}C noxious temperature selected in the present study elicited withdrawal latencies in the most useful range (3-8s) in most subjects.

Fig 5 shows similar histograms for the 52^{0}C noxious heat withdrawal latencies at 4 sites on the foot. Intersite latency differences are seen, with the medial instep having the longest withdrawal latency to 52 C. The 0.05% capsaicin treatment evoked shorter latencies at each site than the 0.025% capsaicin, but this trend was not statistically significant, with the smaller number of foot sites tested.

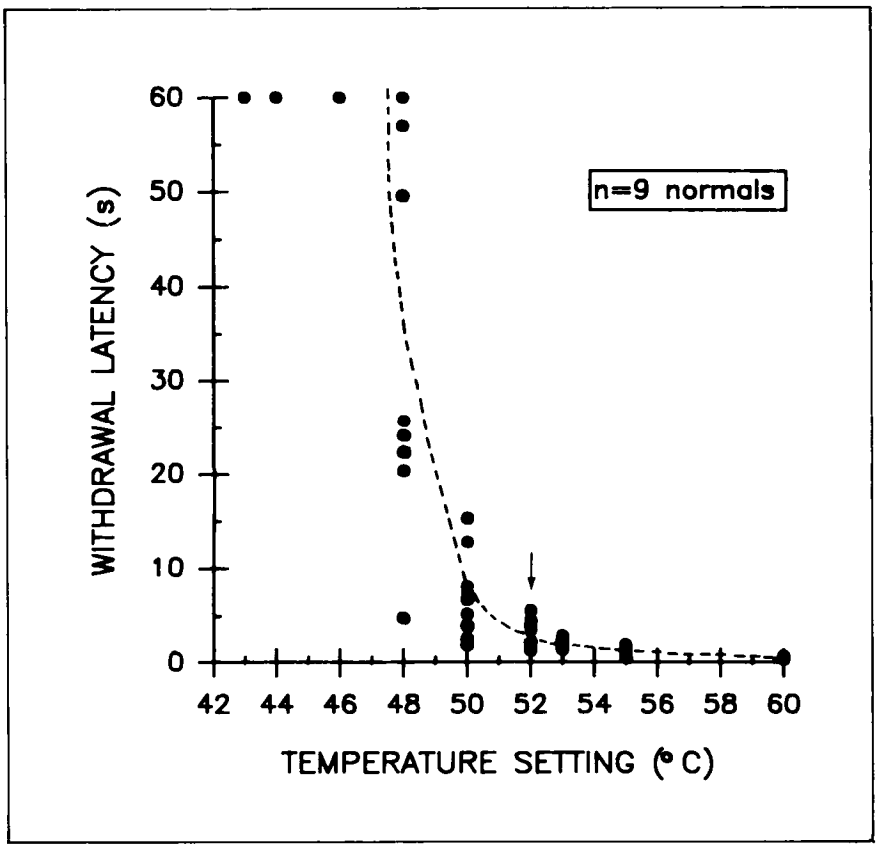

Fig 3 Showing withdrawal latency(s) after thermode contacts skin, plotted against stimulus temperature of the thermode (°C), in 9 consenting volunteers, ranging in age from 18-59 years. For lower temperatures (43,44,46°C) all subjects were instructed to terminate thermode contact after 60s probe application. For temperatures 48°C and above, all points indicate voluntary withdrawal latency when the stimulus probe temperature was perceived as painful. The least squares regression line indicates the nonlinear relationship of withdrawal latency: thermode temperature. The arrow denotes the noxious temperature 52°C chosen for experimental and clinical studies.

Clinical studies in diabetic neuropathy

In normal subjects the contralateral latency differences were small, and on average were close to zero. Shorter withdrawal latencies in diabetic patients indicate enhanced noxious heat perception. This is shown in Table 1. In these patients with hyperalgesia, the 52^{0}C withdrawal latency was, on average, 42% shorter. This is statistically significant ($P<0.05$).

Table 1 Withdrawal latencies in diabeties with unilateral pinprick hyperalgesia (17 patients). The difference between the two sides is statistically significant (P<.05).

Test site	Hyperalgesic foot		Less affected foot	
	mean ± SE	SD	mean ± SE	SD
Dorsum of foot	3.135 ± 0.227	0.937	5.382 ± 0.297	1.223

Experimental capsaicin - induced hyperalgesia

The 2 concentrations of capsaicin cream used were 0.025% and 0.05%, which corresponded to the strengths found effective in treating post-herpetic neuralgia by topical capsaicin desensitisation[8]. The results are shown as mean withdrawal latencies (seconds) and standard deviations in Table 2.

The sites at which capsaicin was applied are shown in Figs 4 and 5 in which the numbers correspond to those in Table 2.

Figs 4 and 5 display the 10 numbered sites on forearm, hand and foot at which capsaicin pretreatment provoked cutaneous hyperalgesia. Histograms show the initial 52^{0}C withdrawal latency for each site, with the latencies after 0.025% and 0.05% capsaicin being shorter in every case. In Fig 4 the extent of the forearm intersite variability is readily seen from the histograms. The mid-palm, with a mean value of 4.47s, exhibited the longest withdrawal latency for 52^{0}C, while the cubital fossa (1.61s) and the wrist (2.06s) had the shortest. In all instances, except the mid-palm site, the further reduction in withdrawal latency evoked by 0.05% capsaicin was significantly greater than that produced by 0.025% capsaicin pretreatment.

There was considerable variability within and between subjects for the withdrawal latency to 52^{0}C heat as shown by the magnitude of the standard deviations for normal skin (Table 2). In addition, there was evidence of regional differences in withdrawal latency, with the shortest latencies being
at the cubital fossa and the anterior aspects of the forearm and wrist. Longest 52^{0}C withdrawal latencies were recorded for the mid-palm and the medial instep of the foot. Using paired 'Student's' t tests for normally distributed data, the differences in the 52^{0}C withdrawal latencies at 0.025% capsaicin treated sites were significant (P<0.05), and the differences at 0.05% capsaicinised sites were also statistically significant (P<0.02).

Table 2 Experimental capsaicin hyperalgesia values for mean withdrawal latency ($\bar{x}$) ± SD (seconds) for each test site and for normal and capsaicin-treated skin 15 minutes after topical application of capsaicin. The test stimulus was 52°C heat.

Test Site	Normal skin			0.025% Capsaicin			0.05% Capsaicin		
	n	$\bar{x}$	SD	n	$\bar{x}$	SD	n	$\bar{x}$	SD
Hand dorsum radial	74	2.90	1.48	71	1.97	0.99	55	1.54	1.10
Hand dorsum ulnar	74	3.10	1.94	71	2.27	1.29	55	1.70	1.35
Midpalm	72	4.47	3.50	66	3.37	2.43	53	2.99	2.20
Wrist	75	2.06	0.99	72	1.56	0.90	55	1.23	0.60
Mid-forearm	75	2.08	1.22	72	1.49	1.03	55	1.05	0.59
Cubital fossa	75	1.61	1.12	71	1.19	0.76	55	0.86	0.50
Foot dorsum distal	34	3.77	1.67	33	2.45	1.37	21	2.11	1.44
Foot dorsum proximal	34	3.87	1.72	33	2.47	1.37	21	1.94	0.99
Lateral peroneal	20	3.44	1.12	20	2.43	1.22	17	2.54	1.04
Medial instep	25	4.32	1.46	25	3.35	1.48	19	3.11	1.34

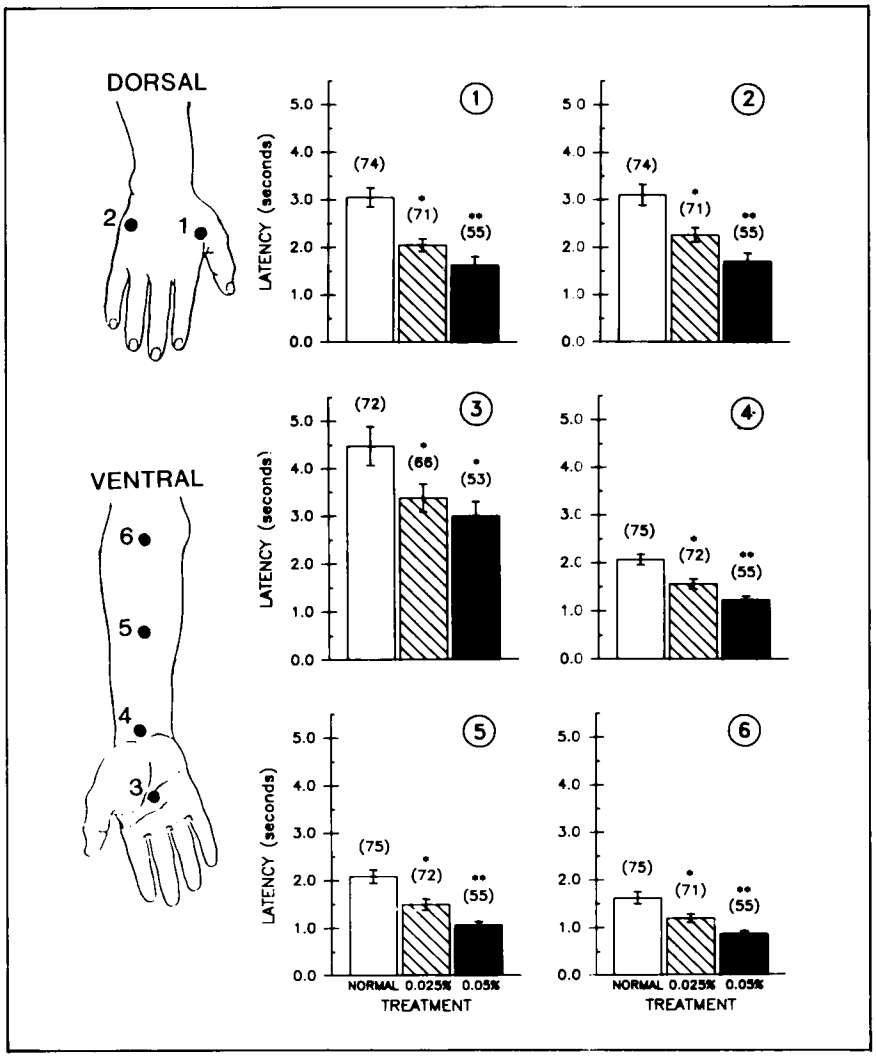

Fig 4 Showing, at left, the test sites numbered 1 to 6 on the hand and forearm at which capsaicin treatment was applied. Histograms of responses are grouped, with corresponding site numbers at top right. Mean 52°C noxious heat withdrawal latency(ies) for each site are shown as a histogram for untreated normal skin (open column), and for the same sites after 15 mins topical 0.025% capsaicin treatment (hatched) and 0.05% capsaicin (black) treatment. The number of site tests is given in parentheses for each histogram. One asterisk* denotes that withdrawal latency after capsaicin treatment is significantly different from that of the untreated site ($P<0.05$). Two asterisks** indicate that the latency after 0.05% capsaicin treatment is significantly different from that after 0.025% capsaicin.

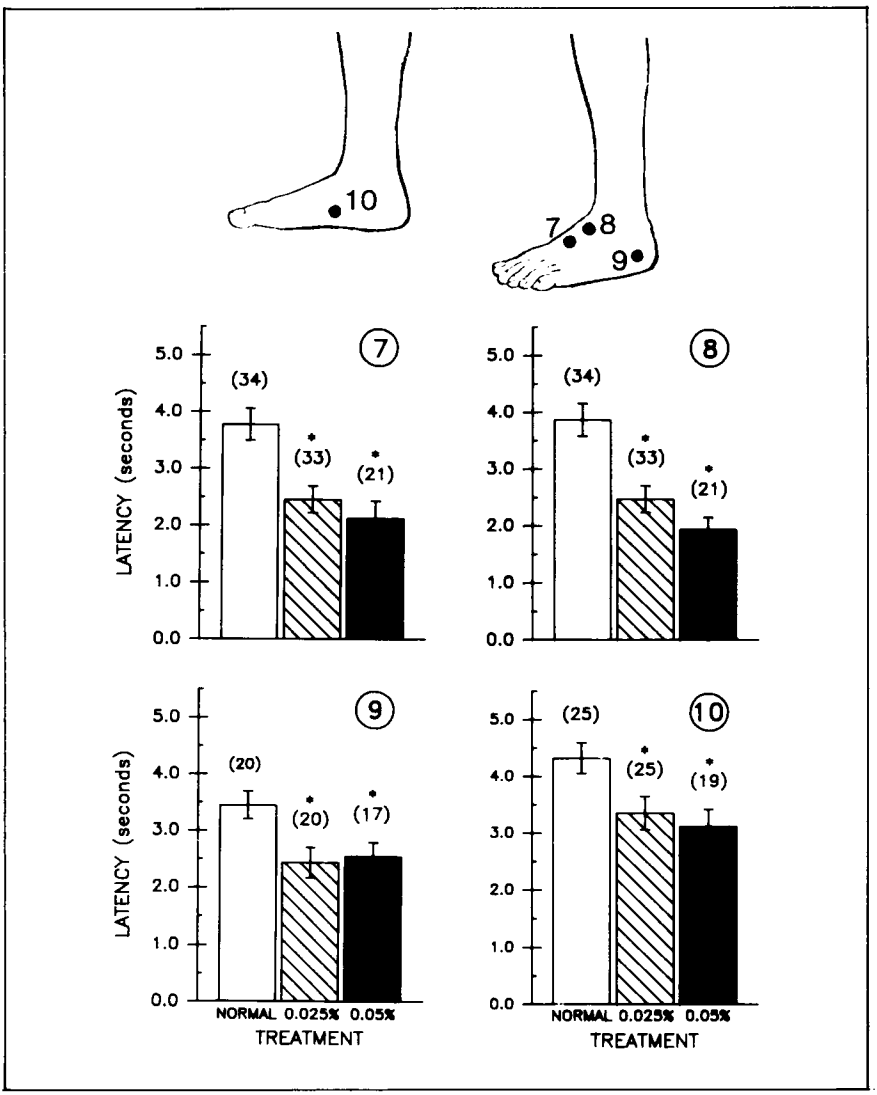

Fig 5 Showing, above, the test sites on the foot at which capsaicin treatment was applied, and clinical tests were performed in diabetic patients. The sites are numbered 7 to 10 and historgrams of the responses are grouped with the corresponding site numbers at the top right. Mean 52°C noxious heat withdrawal latency(ies) for the site is(are) shown as a histogram for untreated skin, and for the same sites after 15 mins of topical 0.025% capsaicin treatment, and 0.05% capsaicin treatment. The number of site tests performed is given in parentheses for each histogram. One asterisk* denotes that the withdrawal latency after capsaicin treatment is significantly different from that at the corresponding untreated site ($P<0.05$).

The extent of cutaneous hyperalgesia evoked by 15 minutes topical 0.025% capsaicin pretreatment ranged from a 23% to a 36% shortening of the 52°C withdrawal latency (mean 29%). Capsaicin 0.05% pretreatment had a greater effect, decreasing the 52°C withdrawal latency by 26 to 50% (mean 41%).

DISCUSSION

Several facts provide a good justification for an attempt to develop and test a clinically and experimentally useful tool for measuring cutaneous hyperalgesia. Firstly, there is still considerable debate about the pathophysiological mechanisms responsible for hyperalgesia in various experimental and clinical situations. Such a device would be a useful research tool in assessing this matter. Functional recovery after nerve injury takes place when neural regeneration occurs. This is often accompanied by hyperaesthesia or dysaesthesia[9]. Different mechanisms apply to the regeneration of small and large sensory fibres[10,11,12], at different stages of recovery following injury [13,14], and for different types of injury e.g. thermal or mechanical damage[6,11,15]. Next, mechanical injury to deeper fibro-muscular structures may be accompanied by cutaneous hyperalgesia in associated skin zones[16,17], but good measurements are difficult to obtain. Sympathetic involvement in the pathogenesis of dysaesthesia and pain following nerve injury or disease has been suggested by some investigators[18], but has been shown not to occur in relation to capsaicin-induced hyperalgesia[8,19]. Hyperalgesia in causalgia-like pain states has been carefully examined in experimental animal models[20,21], but there are difficulties in studying the clinical situations involving causalgic stump pain, reflex sympathetic dystrophy, and postherpetic neuralgia[22]. Finally, there are some difficulties in quantitation of sensory disturbances. These have been discussed by Liniger and Assal[23]. Techniques for measuring hyperalgesia deserve further discussion. Pinprick has provided a quick easy test of hyperalgesia in clinical examination, but its findings are difficult to quantify. Even the use of graded von Frey hairs or an algesiometer to demonstrate hyperaesthesia or allodynia to mechanical stimuli yield results which are not easy to reliably quantify. Noxious radiant heat withdrawal latency has proven extremely sensitive in measuring the rapid onset of cutaneous hyperalgesia in streptozotocin diabetic rats as early as 14 days after induction of the diabetes[24]. Iontophoresis of potassium or acetylcholine has been used as an excitant of nociceptive afferents[8] or for determination of pain endurance[3] in man. Noxious transcutaneous electrical nerve stimulation [25,26] has also been used as a quantitative test of nociceptor function but requires expensive equipment.

Within this range of tests from very 'low tech' pinprick and von Frey hairs to the 'high tech' laser Doppler blood flow, iontophoretic and electrical stimulating equipment, there appears to be a niche for a controlled noxious heat stimulator which is quick and simple to use but is relatively inexpensive, presently costing less than $A500 for components. The present device appears to fulfil this role. The significant and dose-dependent reduction averaging 29% in 52^{0}C withdrawal latency for 0.025% capsaicin-treated skin indicates that the device is useful in studying this experimental model of cutaneous hyperalgesia.

In the limited clinical study of 17 patients with diabetic neuropathy, quantitative sensory testing showed an average 52^{0}C withdrawal latency of 3.14 sec for the foot sites on the side with hyperalgesia to pinprick (Table 1) but an average of 5.38 sec for the less affected foot. By contrast, the average 52^{0}C withdrawal latency for the foot sites of normal subjects (Table 2) was 3.86 seconds. This difference was statistically significant ($P<0.05$) and probably corresponded to some degree of diabetic neuropathy in these 17 patients with an impaired thermal threshold for warmth and pain[23].

ACKNOWLEDGMENTS

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Instructions to Authors

Authors are requested to read carefully and comply with the following, which are changed since the 1990 volume. ***Changes since the previous volume are indicated in bold type, and are intended to reduce production costs and speed publication.***

Manuscript Preparation: **Articles should be submitted in English in double spaced typing, preferable on A4 (206mm x 294mm) paper. Two copies of all text, tables and illustrations are required.**

1. **If the typewritten text is accompanied by a 5¼ inch or 3½ inch disc running under MS-DOS and containing the full text in final form in WordPerfect format (5.0 or later version), or as an ASCII file, it will be published without cost to the authors, if judged suitable.**

2. **If only typewritten text is submitted, an attempt will be made to convert this to a WordPerfect compatible file by optical scanning, at cost to the author. Should this attempt fail, the text will be converted to WordPerfect format manually, at a higher cost to the author.**

New directions for the maximum size of illustrations will apply, as indicated later in these Instructions.

Submission Dates: **Articles may be submitted to the Editors at any time, but the date of absolute closure for receipt of articles to be considered for any year's issue will be the last day of the month in which the Annual Scientific Meeting of the Australian Association of Neurologists is held. All material submitted which has not been presented at the Meeting will be sent to referees, and if the article is judged acceptable, it will be necessary to have the final text incorporating alterations suggested by referees in the Editor's hands by the above closing date, or it will be held over to the following year.**

Subdivision of Articles: Manuscript should be prepared and paginated in the following manner.

1) Title page
2) Text pages
   - Introduction
   - Methods
   - Results
   - Discussion
3) Summary
4) Acknowledgements
5) List of references
6) Tables
7) Figures and captions
8) Footnotes

Title Page: There should be a separate title page with title, authors and institutions where the work was done, indicating city and country, and a condensed running title of not more than 50 letters including spaces. The name and address of the author to whom correspondence should be addressed should appear separately as the second page.

Summary: The summary should not exceed 150 words. It should be factual, not descriptive, and should present the reason for the study, the main findings (give specific data if possible), and the principal conclusions.

House Style: Papers reporting clinical studies or experimental work lend themselves to the sectional style of presentation and review articles also can be improved by a more limited use of this approach.

Method: Description of the experimental method should be succinct, but of sufficient detail to allow experiment to be repeated by others.

Results and Discussion: Conclusions and theoretical considerations must not appear in the results section, nor is a recapitulation of the results acceptable for the discussion section. Where relevant, a concise statement of the implications of the experimental results, should appear as a separate section.

References: References should be numbered consecutively in the order in which they are first mentioned in the text. References cited *only* in tables or in legends to figures should be numbered in accordance with a sequence established by the first identification in the text of the particular table or illustration.

Full, not abbreviated, titles of all journals should be given.

Examples of correct forms of references are given below.

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Standard journal article - (List all authors when six or less; when seven or more, list only first three and add *et al.*).
You CH, Lee KY, Chey WY, Menguy R. Electrogastrographic study of patients with unexplained nausea, bloating and vomiting. Gastroen-terology 1980; 79:311-314.

Books and Other Monographs

Personal author(s)
Eisen HN. Immunology: an introduction to molecular and cellular principles of the immune response. 5th edn. New York: Harper and Row, 1974; 406.

Chapter in a book
Weinstein L, Swartz MN. Pathogenic properties of invading micro-organisms. In: Sodeman WA Jr, Sodeman WA (eds). Pathologic physiology: mechanisms of disease. Philadelphia: W.B. Saunders, 1974; 457-472.

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Illustrations: **If they are to be mounted across the width of the page illustrations should be no wider than 110mm, and no taller than 140mm. Illustrations larger than this, up to 165 x 90mm, can be mounted along the length of a page. Illustrations larger than these dimensions will be reduced in size photographically, at the author's expense.**

Illustrations are referred to in the text by Arabic numerals (1,2 etc). Legends for illustrations should be typed on a separate sheet, numbered correspondingly and should make the illustration understandable independently of the text. If no specific mention of it is made in the text the approximate position of each illustration should be marked in the margin.

For line drawings, good-quality glossy prints or black ink drawings are requested. Symbols, abbreviations and spelling should be consistent with the text. Figures should be professionally drawn and photographed, if possible.

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The author's name, the figure number and top of the figure must be indicated (lightly) on the back of each figure.

If illustrations from previous articles or books are to be used in papers submitted, the written permission of author(s) and publisher must accompany each illustration.

Abbreviations and Symbols: Use recognised abbreviations SI symbols for units. The first time an uncommon abbreviation appears, it should be preceded by the full name for which it stands. **In general abbreviations which are not currently familiar to all neurologists, though in use within particular specialised areas, are better avoided.**

Drug names: Generic names should always be used, but if not available, brand names which take an initial capital can be used. In original articles, the maker of the study drug must be given.