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Preface

Thirty-one years ago, largely at the instigation of its then President, the late E Graeme Robertson, the Australian Association of Neurologists took the rather courageous decision to publish the proceedings of its annual scientific meetings, with the longer term aim of developing the publication into an Australian based neurology journal. The first issue of *Proceedings of the Australian Association of Neurologists* appeared as a relatively slim volume with a soft gray card cover with red lettering, under the editorship of Graeme Robertson. It reported the substance of the papers presented at the Association's meeting held in the old Sydney Hospital in Macquarie Street, in 1963.

Issues have appeared annually since, all bearing the waratah insigne of the Australian Association of Neurologists on the front cover. In 1968 the issue was published in three separate parts, to accommodate the papers of the Asian and Oceanian Congress of Neurology, which had been held in Melbourne. In the early years there was considerable concern within the Council of the Association, and among the Members, as to whether the venture could be sustained financially. Graeme Robertson had to cope with this uncertainty during the whole of his nine years of Editorship. The situation at that time was helped by annual grants from various pharmaceutical firms, and by the receipt of a Commonwealth book bounty, though this precluded converting the work into a journal. However the *Proceedings of the Australian Association of Neurologists* in those days always seemed to hover on the brink of financial disaster. There was neither the financial underpinning not the amount of publishable work available to convert it into a journal which would appear in several issues each year, and no mechanism could be found to promote it and sell it to a wider readership. None-the-less, the existence of the *Proceedings* had a very significant effect in enhancing the quality of the presentations at Association of Neurologists' scientific meetings: the exercise of preparing manuscripts in a form suitable for publication seemed to encourage organised and well planned verbal delivery of material.

Three or four years after John Tyrer took over from Graeme Robertson as Editor, George Selby managed to negotiate an arrangement whereby Adis Press became publisher for the *Proceedings,* and Adis and its successors Williams & Wilkins Adis and McLennan & Petty continued to publish the annual volume until 1990. The name *Proceedings of the Australian Association of Neurologists* was changed to *Clinical and Experimental Neurology* at the time Adis became involved, in the hope that this would make the publication appealing to a wider readership and attract more subscribers. On the whole this did not happen and, in view of rising costs, six years after John Tyrer retired from the Editorship the Australian Association of Neurologists resumed the role of publisher. Subsequent issues have been produced by means of `desk-top' publishing technology. Paradoxically, the success of the *Proceedings* (or *Clinical and Experimental Neurology*) in enhancing the reputation of Australian neurology has contributed to its failure to grow in parallel with the expansion of neurological medicine in the country.

Publication in its pages has trained a generation of embryo Australian neurologists to produce articles suitable for the scientific literature. However, having acquired that training, they have naturally enough sought to publish their more mature work in international journals which appear at shorter intervals and have a wider circulation.

The opportunity has now arisen for the Australian Association of Neurologists to tap into the Neurosurgical Society of Australia's initiative in linking itself with the new Pacific rim based *Journal of Clinical Neuroscience* edited by Professor Andrew Kaye, of Melbourne. The appearance of this journal removes much of the rationale for the continuing existence of *Clinical and Experimental Neurology* and at the same time realises the hopes of Graeme Robertson and his colleagues thirty years ago that an Australian clinical neuroscience journal would evolve. The decision has therefore been taken that the present issue of *Clinical and Experimental Neurology* will be the final one. In this last opportunity to address its readership I would like to thank my co-editors and all who have helped with the refereeing of papers and in other ways over the past decade, to pay tribute to my predecessors in the Editorship, and to wish the *Journal of Clinical Neuroscience* every success in the forthcoming years.

Mervyn Eadie
Editor

Contents

THE UNDERSTANDING OF EPILEPSY ACROSS THREE MILLENNIA

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SUMMARY

The phenomena of epilepsy have been known for at least 3000 years, the earliest recorded account being in an Akkadian text called the *Sakikku* (written around 1067-1046 BC). Over nearly all the subsequent centuries the popular belief has been that epilepsy is a disorder of supernatural origin, and to some extent such ideas have carried over into medical thought. In Western civilisation, the long dominant belief was that epilepsy was due to possession by a devil or a demon, an interpretation given authoritative support by the miracle story of the cure of the epileptic child which is recorded in all three synoptic Gospels. However, there have been many other interpretations e.g. epilepsy as a consequence of wrong doing or of lunar or magical influences. Such ideas began to die out only in the past 200 years.

From Hippocrates (*c.* 400 BC) onwards, there has been a continuing line of thought that considered epilepsy a medical condition due to natural causes. The hypotheses concerning its pathogenesis have ranged from excess phlegm in the brain, through boiling up of the vital spirits in the brain (Paracelsus), explosion of the animal spirits in the centre of the brain (Willis), heightened reflex activity at a spinal (Marshall Hall) or medullary level (Brown Séquard), to Hughlings Jackson's notion of `an occasional, an excessive, and a disorderly discharge' in part of the cerebral cortex. Among thinking men, epileptology in the past century has proved largely to be a matter of exploring the ramifications of Jackson's concepts.

The written record of man's knowledge of epilepsy extends back over at least 3000 years. There have been several major systematic accounts of the history of the disorder, notably that of Temkin[1], and numerous shorter considerations of particular aspects of its long story.

THE EARLIEST DESCRIPTION

Kinnier Wilson and Reynolds[2] recently published a translation of the cunieform text of the 25th and 26th tablets of an ancient Akkadian work, the *Sakikku*, which is believed to have been written between 1067 BC and 1046 BC. These two tablets dealt with the falling sickness, i.e. epilepsy or, as it was called in Babylonian, *miqtu*. The texts mainly dealt with the clinical phenomena, and passages such as that quoted below leave little doubt that the (unknown) writer was familiar with many of the more common manifestations of epileptic seizures. There was little attempt to interpret the nature of the events described, apart from attributing them to demonic possession, or to discuss their treatment.

> 'If at the time of his possession, while he is sitting down, his (left) eye moves to that side, a lip puckers, saliva flows from his mouth, and his hand, leg and trunk on the left side jerk (or, twitch) like a (newly)-slaughtered sheep, it is *miqtu*.'
>
> *Sakikku, 25th or 26th Tablet (1067-1046 BC)*

The publication of this material takes the record of epilepsy back half a millennium earlier than was formerly known.

THE SACRED DISEASE

One of the earliest of the Hippocratic corpus of writings was devoted to the topic of the *'Sacred Disease'*. The Hippocratic author chose this title to argue that epilepsy was in no way a sacred disease, but merely a natural disorder like other diseases. The monograph began with the assertion, in the words of Francis Adams' translation[3]:

> 'It is thus with regard to the disease called Sacred: it appears to me to be nowise more divine nor more sacred than other diseases, but has a natural cause from which it originates like other affections. Men regard its nature and cause as divine from ignorance and wonder, because it is not at all like to other diseases. And this notion of its divinity is kept up by their inability to comprehend it, and the simplicity of the mode by which it is cured, for men are freed from it by purifications and incantations.'
>
> *Hippocrates (c 500 BC): On the Sacred Disease*

The fact that 2500 years ago it was seen necessary to develop such an argument gives some indication of the popularity of the view that had already developed, attributing epilepsy to powers outside human control, be they perceived as divine, as demonic, as the outcome of astral influences, as due to magic, or

simply regarded the disorder as a retribution for wrong-doing. The Hippocratic interpretation carried the potentially critical implication that epilepsy might ultimately yield to medical treatment; on the other hand, if the disorder were of supernatural origin, men could not hope to influence it except by religious or superstitious actions.

The Hippocratic explanation of epilepsy, viz. that it was due to a superfluity of phlegm in the brain, was able to survive for centuries in the absence of the scrutiny of necropsy studies, while the observation that some instances of the disorder could be inherited remains valid today. However, the Hippocratic admission that epilepsy could be cured by purifications and incantations was scarcely to be expected of a disorder which was of natural origin.

For over 2000 years from the time of the Hippocratic writings, despite the arguments of the physicians, the general belief among ordinary people was that epilepsy had some form of supernatural cause, and there can be little doubt that such thinking was not without influence on medical minds.

RELIGIOUS INTERPRETATIONS OF EPILEPSY

The New Testament miracle story of Jesus' cure of the epileptic boy is recorded, with some differences in detail, in all three synoptic Gospels.

> 38. And, behold, a man of the company cried out, saying, Master, I beseech thee, look upon my son: for he is mine only child.
> 39. And, lo, a spirit taketh him, and he suddenly crieth out; and it teareth him that he foameth again, and bruising him hardly departeth from him.
> 40. And I besought thy disciples to cast him out: and they could not.
> 41. And Jesus answering said, O faithless and perverse generation, how long shall I be with you, and suffer you? Bring thy son hither.
> 42. And as he was yet acoming, the devil threw him down, and tare him. And Jesus rebuked the unclean spirit, and healed the child, and delivered him to his father.
>
> *Luke: Chapter 9*

The essential point, for the understanding of epilepsy in the Christian world, was that the disorder was attributed to the presence of a devil, or an unclean spirit, within the sufferer's body.

As Christianity spread over the centuries to become the dominant religion of the Western world, the enormous spiritual and moral authority of the Gospels, and

civilisation's familiarity with their contents, ensured widespread acceptance of the view that epilepsy was due to possession of the sufferer's body by an unclean spirit. Such an interpretation led to attempts to exorcise the unclean spirit e.g. Reubens' painting of St Ignatius of Loyola driving out devils from a man racked by an epileptic seizure and a woman who looks as if she may be having a pseudo-seizure. It also led to attempts to cure epilepsy by prayer, by invoking the influence of saints e.g. St Valentine, by worship of relics, by pilgrimages to shrines and by the wearing of various religious articles.

OTHER SUPERNATURAL INTERPRETATIONS

In writing on epilepsy, Aretaeus the Cappadocian[4], in the 2nd Century AD mentioned supernatural causes of the disorder other than demonic possession, and brought out the idea that epilepsy was a socially unacceptable illness.

> 'But it is also reckoned a disgraceful form of disease: for it is supposed, that it is an infliction on persons who have sinned against the Moon: and hence some have called it the Sacred Disease, and that for more reasons than one, as from the greatness of the evil, for the Greek word ιερός also signifies *great*: or because the cure of it is not human, but divine: or from the opinion that it proceeded from the entrance of a demon into the man: from some one, or all these causes together, it has been called sacred.'
>
> *Aretaeus (2nd Cent AD)*

Arising from such interpretations, a great variety of alleged cures of epilepsy were advocated, often based on rather tenuous reasoning and appearing ridiculous, if not repugnant, to the modern mind e.g. drinking the blood of gladiators, drinking urine from the shoe of someone who witnessed the sufferer's seizures.

The unclean spirit concept also developed into the idea that epilepsy might be contagious, being transmitted by the breath of the sufferer (Berthold, cited by Temkin[1]).

> And when he falls down, lies on the ground, and froths - beware of him if you value your life! Let nobody go near him, for such a terrible breath comes forth from his mouth that the person into whose mouth this breath enters may acquire the same disease.'
>
> *Berthold of Regensberg (13th Cent)*

At the time of the Renaissance Jean Fernel (1485-1558), of Paris, who Sherrington regarded as the founder of modern physiology, struggled against this idea[5].

> 'A person who has taken poison or suffers from epilepsy cannot contaminate others, either by his breath or by his contact. For this reason these diseases are different from epidemic and contagious diseases.'
>
> *Fernel, J (1577): De abditis rerum causis*

MEDICAL INTERPRETATIONS OF EPILEPSY

Ancient and Medieval Times

In the above argument Fernel was taking up the line of medical interpretation of the nature of epilepsy that had come down from Hippocrates and Galen and which had been encapsulated in the writings of Paul of Aegina[6] at the time of the end of the Ancient World (end of the 6th Century AD).

> 'Epilepsy, being a convulsion of the whole body with impairment of the leading energies, has its cause seated sometimes in the brain itself, and sometimes in its cavities. There is sometimes a pituitous and sometimes a melancholic humour. The disease also sometimes arises from sympathy with the orifice of the stomach (as happens in cholic affections, as will be stated when treating of them); and sometimes it is propagated from other parts, when a cold aura ascends to the brain, either from the leg or the fingers of the hand. It has also been seen to proceed from the uterus in females, at the time they were pregnant, for after delivery it ceased.'
>
> *Paulus Aegineta (late 6th, early 7th Cent AD)*

This account utilised the idea of 'sympathy' i.e. a disturbance in one part of the body evoking a disorder in some other part, to embrace what would now be regarded as sensory seizures of partial epilepsy, phenomena which Galen had described as an 'aura'. Orthodox medicine adhered to such interpretations of the pathogenesis of epilepsy throughout ancient and medieval times, though sometimes embellished with a superstitious overlay.

The Renaissance and Later Times

Fernel, writing at the beginnings of the ultimately successful Renaissance attempt to dispel superstition concerning epilepsy, attacked certain recommended preventative measures which reflected continuing belief in religious and supernatural notions of the nature of epilepsy.

> 'These are such as wee cannot truly say of them, wherefore and whence they have the faculties ascribed to them: for they neither arise from the temperament,

> neither from the other manifest qualities, neither from the whole substance, neither from a divine or magical power ..... Such like old wives' medicines and superstitious remedies are written figures and characters, rings, where neither the assistance of God or Spirits is implored. Let me ask you, is it not a superstitious medicine to heal the falling sickness, to carrie in writing the names of the three Kings, Gaspar, Melchior, and Balthasar, who came to worship Christ?'
>
> *Fernel, J (1577): De abditis rerum causis*

But, a little earlier than Fernel in his medical orthodoxy, a novel and radical interpretation of epilepsy had sprung up in the mind of that extraordinary and wayward peripatetic genius Philip Theophrastus Bombastus von Hohenheim (1493-1541), the self-styled Paracelsus. He attempted to interpret all events and objects in the wider world (the macrocosm) and in the human and animal body (the microcosm) in terms of the chemical knowledge of his day, and argued that God, in his benevolence, had provided chemical cures for all diseases, though it was left for man to discover them. Paracelsus believed there was a living spirit in every creature, and in all creation, and interpreted epilepsy as a consequence of a sudden abnormal boiling up of such vital spirits in the sufferer's brain[7].

> .....no living creature can exist without the *spiritus vitae*, which is the living strength of all things, as we have said in *De Spiritu Vitae*- nor is there any life (and that includes any maintenance of the *spiritus vitae*) possible without nourishment. Since everything that is alive may be affected by this disease, the illness may also be in a certain food. When such food is mixed with the *spiritus vitae*, the trouble is brought about. This is one of the causes of the disease. The boiling of the vapours in the *spiritus vitae* (but not in other humours and qualities which are also in the body) is another cause. If the *spiritus vitae* is shifted from its right disposition, it boils and effervesces, and this happens so quickly that memory and reason are destroyed. This boiling may be compared with the approach of an earthquake, which makes the whole earth tremble. Earthquakes and the falling sickness have the same causes.'
>
> *Paracelsus, T (1567): The Diseases that Deprive Man of his Reason*

While this Paracelsian view continued to locate the seat of epilepsy in the brain, as had Hippocrates, Galen and their successors, it constituted a radical departure from the 2000 years old belief that the pathogenesis of epilepsy lay in excess phlegm and perhaps ventricular obstruction. Instead, for Paracelsus epilepsy was a sudden dynamic physico-chemical event, potentially curable by chemical means.

The influence of Paracelsus was largely posthumous, as was the publication of his numerous writings. Paracelsus turned the direction of alchemy from its

centuries old preoccupation with the Philosopher's Stone, that elusive red powder that was claimed to transform base metals into gold, and instead set it seeking chemical cures for disease. Over the following century, or rather longer, Paracelsian iatrochemical thought was purged of many of its extremes[8]. One of Paracelsus' later English disciples was Thomas Willis (1621-1675), Sedleian Professor of Natural Philosophy at Oxford, a very significant figure in the English scientific revolution of the 17th Century.

Willis refined, moderated and to an extent systematised Paracelsus' rather extravagant ideas about the pathogenesis of epilepsy, when he attributed the disorder to `explosions' within the brain[9]. In various places in his writings Willis gave rather different explanations as to how the explosions produced the phenomena of epilepsy, and about the chemical basis of the explosions. It seems possible that Willis used the word `explosion' as an analogy for the energy sources and processes of energy release involved in epileptogenesis[10].

> `Wherefore it is not to be doubted, but that the heterogenous, and explosive particles are instilled from the Blood, together with the nervous juice, into the Brain; which afterwards being thrust forth, into the nervous stock, do there grow to the Spirits, and with them bring on a Convulsive disposition.'
>
> *Willis, T (1681): Of Convulsive Diseases*

> `And indeed, I think it very likely so, that the Epileptik Paroxism is stired up, from a certain suddain rarefaction, and explosion of the animal spirits, inhabiting the Brain, which are in truth the first, and immediate subject of this Disease: to wit, whereby the Brain itself is inflated, and rendered so insensible, and the nerves hanging thereto, also pulled into convulsions.'
>
> *Willis, T (1681): Of Convulsive Diseases*

> `For although we conclude, that the middle of the brain, is always the primary seat of the Epilepsia, and that from the beginning, the morbific matter is layd up wholly in that Region; yet the distemper growing grievous, this being more plentifully spread thorow the head, enlarges its bounds, so that it being strowed here and there, and far and neer stretched out, Spasmodic particles, are cast into the rest of the Brain, and also into the nervous *appendix*, like gunpowder or explosive seed, whereby it comes to passe, that at the first approach of that disorder of spirits, Convulsions follow, sometimes in these, sometimes in those parts, and not rarely thorow the whole body'.
>
> *Willis, T (1681): Of Convulsive Diseases*

Subsequent medical authorities found Willis' explosions an uncongenial concept, perhaps because they were not sympathetic to the alchemical background to the idea. They were more comfortable with the belief that brain activity

depended on the movement of the `animal spirits' within the brain (a concept Willis accepted, though he modified it with his explosions). The animal spirits progressively came to be seen as a form of brain energy. The great William Cullen (1710-1790), of Glasgow and Edinburgh, towards the end of the 18th Century, provided a cautious and circumspect interpretation of the nature of epilepsy in terms of an involuntary disturbance of cerebral energy[11].

> .....as to the proximate cause of this disease, I might say that it is an affection of the energy of the brain, which, ordinarily under the direction of the will, is here, without any concurrence of it impelled by preternatural causes; but I could go no further. For, as to what is the mechanical condition of the brain in the ordinary exertions of the will, I have no distinct knowledge, and therefore must be ignorant of the preternatural state of the energy of the brain under the irregular motions here produced.'
>
> *Cullen, W (1783): First Lines of the Practice of Physic*

By this time the growth of popular knowledge and education , the scientific revolution, and a general decline in belief in the supernatural. had ensured that the general community understanding of epilepsy was moving towards an increasing acceptance that it was a bodily disease. As Heberden wrote in his *Commentaries*[12] at the end of the 18th Century

> `The epilepsy may be called the reproach of the physicians as well as the gout; for it was well known before the writing of the most ancient medical books, and yet no certain method of cure has been discovered..... . The good sense of the world has done more than medicine towards mitigating this great evil, by lessening the imaginary part of it: for it is now generally considered in the same light with any other distemper, without adding to its malignancy by the workings of fancy or superstition. It is no longer believed to be the immediate effect of some demon's malice; nor is it regarded enough to let it dissolve public councils, and to put a stop to all business; neither is it detested with that degree of horror by the acquaintance and friends, which must have shocked the miserable patient more than the cruellest attacks of the disease.'
>
> *Heberden, W (1802): Commentaries*

The past 200 years

In the first major original English work on epilepsy since Willis, James Clowes Prichard (1786-1848), who seems to have originated the term `partial epilepsy' for seizures similar to those to which the designation is now applied, ascribed the immediate mechanism of epileptic episodes to cerebral congestion[13].

> 'The immediate cause of an attack of epilepsy, or that physical change which, in a constitution prepared by natural predisposition, or by the action of morbid circumstances, is the immediate precursor and occasion of the fit, appears to me, as I before hinted, to be a preternatural influx of blood into the vessels of the encephalon, or an unusual fulness in some part of the vascular system of that organ.'
>
> *Prichard JC (1822): A Treatise on Diseases of the Nervous System*

This interpretation was less detailed, and also less controversial, than that of Willis, but it scarcely constituted any real advance in understanding of the nature of the disorder.

The discovery of reflex action is usually attributed to Marshall Hall (1790-1857), but the whole concept was worked out earlier by Cullen's even greater predecessor in Edinburgh, Robert Whytt (1714-1766). However, Whytt used the term 'sympathy', rather than 'reflex', for the phenomena. Marshall Hall developed the idea of reflex activity into a new conception of the nature of epilepsy, which he considered was due to heightened activity in what is now called the reflex arc. Enhanced activity of the afferent side of the arc produced 'eccentric' epilepsy, enhanced activity within the spinal cord produced 'centric' epilepsy, while motor phenomena occurred from irritation of the efferent limb of the arc[14].

> '89. The *first* remark I would make is a very comprehensive one. I believe the whole order of spasmodic and convulsive diseases belongs to this, the excito-motory division of the nervous system, ...
>
> 90. Another remark is equally important. *All* their source is *one* of three parts of the excito-motory system: the first series have their origin in the spinal marrow itself, the axis or centre of the system; I shall designate these cases by the epithet *centric*: the *second* series have their sources in the excitor nerves, consequently at a distance from that centre; I shall denominate them the *eccentric*. A third series occurs, like the spasmodic tic of the seventh pair, in the course of the motor nerves.
>
> *Hall, M (1836): Lectures on the Nervous System and its Diseases*

Thus Marshall Hall moved the seat of epilepsy from its 2300 year old postulated site in the brain and transferred it to the spinal cord. Within a few years, on the basis of studies in experimental animals, Brown-Séquard (1817-1894) had moved the seat back intracranially, but took it only as far cephalad as the medulla oblongata. Brown-Séquard believed that peripheral stimuli often activated medullary excitatory mechanisms reflexly, and that the resultant medullary activity resulted in cerebral vasospasm which caused unconsciousness during seizures[15].

'Epilepsy seems to consist essentially in an increased reflex excitability of certain parts of the cerebro-spinal axis, and in a loss of the control that, in normal conditions, the will possesses over the reflex faculty. The base of the encephalon, and especially the medulla oblongata, is the most frequent seat of the increase in the reflex excitability, so that this part of the nervous system is the ordinary seat of epilepsy. The disturbance in the functions of the cerebral lobes, during and immediately after a fit, and in the interparoxysmal periods, is chiefly due to the alterations taking place in the brain during the fits. The hitherto mysterious coincidence of loss of consciousness or, in other words, loss of the function of the cerebral lobes, with an increased action of the base of the encephalon, in a complete epileptic seizure, may now be easily explained. I have tried to show that the same cause that produces the first convulsions in some muscles of the neck, the eye, the larynx, and the face, produces also a contraction of the blood vessels of the brain proper, which contraction is necessarily followed by the loss of consciousness.'

Brown-Séquard, C E (1860)

Almost contemporaneously with Brown-Séquard, Schroder van der Kolk (1797-1862), of Utrecht, published a hypothesis that epilepsy began *de novo* within the medulla, an argument he supported by citing the frequency of tongue biting during epileptic seizures. Thus the seat of epileptogenesis was moved further towards the neuraxis.

Within a decade of these attempts to locate the site of origin of epilepsy at lower levels of the nervous system and explain its phenomena in terms of altered reflex activity, the English genius of John Hughlings Jackson (1835-1911) abandoned all notion of reflex abnormality in epilepsy, and sited the pathogenesis firmly in the cerebral cortex itself, ascribing the phenomena to locally heightened neuronal irritability leading to neuronal discharging. Jackson's writing style was convoluted and hedged about with qualifications, but his famous 1870 address to the graduating students of St Andrews University contained at least two sets of pregnant passages which set down, respectively, his understanding of the nature of epilepsy, and his conviction that epilepsy could arise in the cerebral cortex[16].

'A convulsion is but a symptom, and implies only that there is an occasional, an excessive, and a disorderly discharge of nerve tissue on muscles. This discharge occurs in all degrees; it occurs with all sorts of conditions of ill health, at all ages, and under innumerable circumstances.'

Jackson, J H (1870): A Study of Convulsions

'I will not deny that disease in many parts of the encephalon "may produce epilepsy". I wish but to show that disease in the Sylvian region produces those convulsions which begin in one hand or in one side of the face, and which affect the side of the body they commence in, before the spasm spreads to the bilateral

muscles, and to the unilateral muscles of the other side.'

Jackson, J H (1870): A Study of Convulsions

In the subsequent century and a quarter, the range of clinical phenomena of epilepsy has been betted defined, the pathological and electrophysiological backgrounds better understood, and reasonably effective therapies have been developed. Yet in all this, the attempt to understand the nature of epilepsy has proved to be largely a matter of working out the ramifications and implications of Jackson's almost prophetic insights, and interpreting them in terms of growing scientific knowledge.

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THE MYSTERY OF ONE RED EAR

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SUMMARY

Flushing and a sensation of tightness or pain in one ear lobe was a presenting complaint of 3 patients. In one case the symptoms were confined to the ear, another was associated with sensory impairment in the distribution of the C_2 and C_3 segments, while the 3rd patient experienced discomfort in the area of the 1st division of the trigeminal nerve on the same side. Two out of 3 patients had evidence of hypertrophy of the ipsilateral C_{2-3} facet joint and the symptoms of the 3rd patient were improved by an ipsilateral C_{2-3} root block. A possible mechanism could be the antidromic release of vasodilator peptides from afferent nerve terminals in response to irritation of the C_3 root which supplies sensory innervation to the pinna.

Flushing of one ear, accompanied by discomfort and a feeling of warmth, is an uncommon complaint but was a presenting symptom of the 3 patients to be described.

Sudomotor fibres travel with the external carotid artery and its branches and are distributed to the skin along cutaneous nerves[1]. Sympathetic innervation of facial skin includes vasoconstrictor and vasodilator fibres[2]. Those supplying the ear are predominantly vasoconstrictor[3,4] so that flushing mediated by the sympathetic nervous system depends on the release of tonic vasoconstriction. Gustatory sweating and flushing, thought to be mediated by the parasympathetic outflow through facial and glossopharyngeal nerves, is most marked in the nose and cheek and least marked in the ear[4,5]. A 3rd mechanism to be considered is the antidromic release of vasodilator peptides. This is thought to account for the facial flush seen after the stabbing pains of tic douloureux or after thermocoagulation of the trigeminal ganglion, when it is confined to the skin areas innervated by the appropriate division or divisions of the trigeminal nerve[6], while levels of substance P and calcitonin gene-related peptide (CGRP) increase in the external jugular venous blood[7].

The cause of aural flushing in the cases to be described remains speculative.

Fig 1a Arthritic hypertrophy of left C_{2-3} facet joint. Case 1

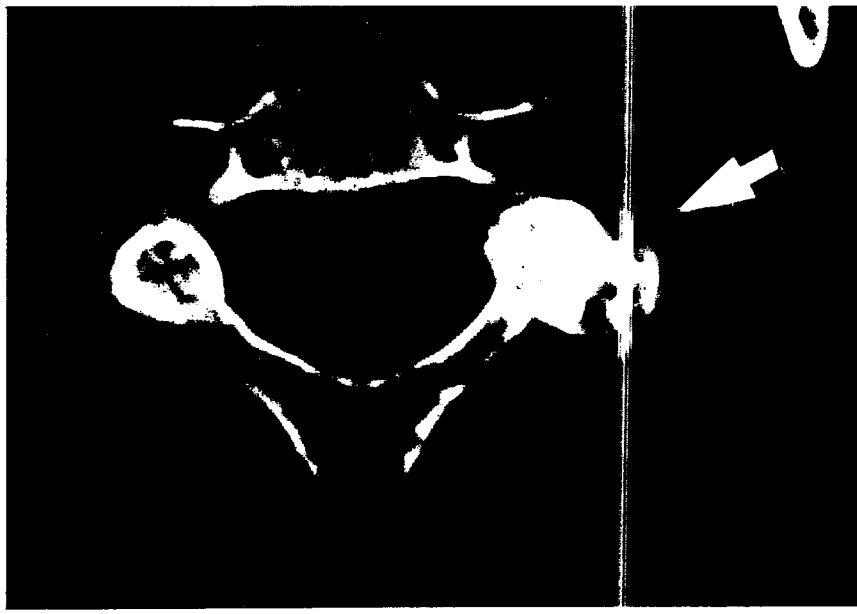

Fig 1b Arthritic hypertrophy of left C_{2-3} facet joint. Case 2

CASE REPORTS

Case 1

One night in 1979 a man aged 47 years developed a dull bilateral headache which persisted for 2 weeks. After the headache subsided, a tight sore sensation remained around his left ear, spreading to the left occipital region. This was associated with a feeling of warmth and reddening of the left ear. He was aware of numbness around his left ear, angle of jaw and occiput. He had injured his neck while playing football at the age of 30 years and when skiing 5 years later. After the last incident, he was subject to stabbing pain in the neck on abrupt movements for about 3 years. Thermography demonstrated that the left ear was 1-2°C warmer than the right.

On examination, sensation was diminished over a strip in front of the left ear, over the angle of the jaw and the left occiput, extending to a vertical line above the left ear. A CT scan demonstrated marked arthritic hypertrophy of the left C_{2-3} facet joint (Fig 1a), associated with fusion of the lateral masses of the atlas to the occiput.

In the 15 years that have elapsed since the onset, the sensations of tightness in the left ear and occiput have recurred intermittently with a feeling of warmth and perceptible redness of the ear.

Case 2

A 73 year old woman, when bending forward to pick up a heavy cooking pot felt a sudden jab of pain radiating from her left ear to the middle of her forehead. Since then, the pain has recurred on coughing, sneezing or flexing her neck while turning to the left. This stabbing pain sometimes extended from the left frontal region to her left nostril, which tingled. Eight months later, she developed a dull ache around her left ear which increased in severity 2 or 3 times each week when the left ear became distinctly hot to touch. This pain was accompanied by a feeling of fullness in the left ear and spread to the left occiput. There was no sensory loss. The jabbing pains were relieved by indomethacin 25 mg t.d.s. but the dull ache and aural flushing persisted. Twelve years before she had jarred her neck, causing neck pain which persisted intermittently for 3 years, and was eased by wearing a surgical collar.

On examination a firm mass was palpable to the left of the C_3 vertebra. There was no sensory loss over the ear or occipital region. A CT scan of the cervical spine demonstrated marked hypertrophy of the left C_{2-3} and C_{3-4} facet joints (Fig 1b). Degenerative changes were also present at lower levels.

Case 3

Fifteen months before the consultation a 37 year old man noticed a burning pain in his left ear lobe after exertion, accompanied by the sensation of heat and obvious reddening of the ear. The sensation subsided after he applied a cold pack or had a cold shower but the left ear and sometimes the adjacent part of his left cheek remained redder than the right. He avoided going out in sunlight or entering a hot environment because his left ear flushed and hurt. Four years before the onset of symptoms a skin graft had been taken from an area in

front of his left ear to be applied to his nose.

On examination, his left ear was redder than the right and the left ear lobe was warmer by 2°C, but there was no obvious sensory impairment over the affected area. His face sweated normally on exertion.

A CT scan of the cervical spine showed degeneration of the superior facet of C_4, containing gas consistent with a subchondral cyst.

The flushing and burning sensation were diminished, but not entirely prevented, by propranolol 40 mg twice daily. Local anaesthetic block of the C_2 and C_3 roots abolished the sensation in his pinna but he stated that the external auditory canal, which was not anaesthetised by the block, did not feel completely normal. For the duration of the block he could not bring on his left ear pain by exertion. Immediately after the block his left ear was still redder than the right but he said that this was not apparent when he returned to the ward after exercise.

DISCUSSION

A red ear was an interesting feature of the 3 case histories described here.

The first patient was left with unilateral aural symptoms after a prolonged generalised headache, suggesting a possible infectious origin. Sensory loss implicated the C_2 and C_3 segments while a CT scan demonstrated hypertrophy of the C_{2-3} facet joint on the appropriate side.

The 2nd patient experienced her tic-like pain on flexing her head to the left. The distribution of this pain (frontotemporal and left nostril) indicated referral to the 1st division of the trigeminal nerve. The subsequent ache around the left ear and occiput indicated involvement of the C_2 and C_3 roots. Radiographs demonstrated hypertrophy of the left C_{2-3} facet joint.

The 3rd patient experienced burning solely in his left ear lobe, accompanied by reddening of the ear. There were degenerative changes in the left C_{3-4} facet joint but not at the C_{2-3} level. His pain was abolished by a C_{2-3} block, while warmth and redness of the left ear subsided slowly.

The ears are normally cool with an average temperature of 27.8°C in a room at 18-20°C[3]. Ear temperature falls only slightly in response to body cooling. Blocking the cutaneous nerve to the ear with local anaesthetic caused an increase in temperature of more than 2°C. After body heating, ear temperature on the intact side rose to equal that of the nerve-blocked side but did not increase further in the

experiments of Blair, Glover and Roddie[3], but exceeded that of the blocked side slightly in the studies of Fox, Goldsmith and Kidd[4] so that a small component of active vasodilatation could not be excluded. Nevertheless it is clear that one mechanism for flushing of the human ear is the release of sympathetic vasoconstrictor tone. The pinna of the ear has few sweat glands and produces little sweat. A lesion of the greater auricular nerve causes only slight hypohidrosis over the temple[1], so that involvement of sympathetic fibres accompanying the nerve might easily be missed. Impairment of these fibres could lead to release of tonic vasoconstriction in the ear. However, the sympathetic supply joins the nerve only in the periphery and the clues from the patients' symptomatologies indicate involvement of the C_2 and C_3 roots rather than the greater auricular nerve.

Areas innervated by C_2 and C_3 have recently been redefined by Poletti[8] after plotting the distribution of dysaethesiae on stimulating the roots, and hypalgaesia after root decompression or anaesthetic block. The distribution of C_3 embraces the angle of the mandible and a strip on the upper neck below the mandible and the pinna, whereas C_2 innervates only the occipital area. The distribution of pain and redness of the ear in the patients described therefore lies in C_3 territory, with involvement of C_2 as well in Case 1 and radiation to C_2 and the 1st division of the trigeminal nerve in Case 2. Poletti[8] found that stimulation of the C_3 root referred pain to the ear itself, to behind the ear under the pinna, angle of the jaw and along the mandible to the chin. No patient reported referral to trigeminal areas from C_3 stimulation but referral to the 1st division is a recognised feature of C_2 root irritation. Poletti[8] made no comment about flushing of the ear, although Foerster[9] had reported in 1933 that electrical stimulation of the C_3 root caused vasodilatation of the ear, angle of the mandible and the neck on that side.

The mechanism for this antidromic response presumably involves the release of vasodilator peptides as it does in the trigeminal system[7] and could account for transient flushing following a stab of pain. Could it also account for a sustained flush accompanying constant aching of radicular origin? It is possible that an irritative lesion of the C_3 root could in some way sensitise skin afferent terminals or sympathetic vasodilator receptors so that they react excessively to heat or any painful stimulus. Some contribution from β-adrenoceptors is suggested by the partial response to propranolol in one patient. Anaesthetic blockage of the C_{2-3} root in one patient stopped the burning pain and diminished aural flushing.

ACKNOWLEDGMENTS

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INSULIN SENSITIVITY AND SENSORY NERVE FUNCTION

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SUMMARY

The central and peripheral nervous systems do not require insulin for glucose uptake. However, insulin receptors have been detected in these regions. The aim of this study was to examine peripheral sensory nerve function and its dependence on insulin using healthy non-diabetic control subjects, obese individuals, and diabetic (insulin dependent and non-insulin dependent diabetes mellitus) subjects. The results revealed that the warm and cold perception thresholds, reflecting the functional states of unmyelinated C-fibres and A-delta fibres respectively, increased with reduced insulin sensitivity and with increased fasting insulin concentrations. From such data in non-diabetic subjects with measured insulin sensitivity, it appeared that sensory nerve function was disturbed in normoglycemic but insulin resistant states, suggesting that insulin has an action on nervous tissue in addition to its effects on glucose metabolism. The mechanisms of this action remain to be elucidated.

Insulin has long been recognised as the major regulator of carbohydrate and lipid metabolism[1]. It achieves this by activating specific transport molecules which facilitate glucose uptake by cells[2]. Thus, most tissues of the body require insulin for the cellular uptake of glucose and different tissues have different types of glucose transporter molecules[3].

Skeletal muscle and adipose tissue are major targets of insulin action[3]. By contrast, the central and peripheral nervous systems do not require insulin for glucose uptake and traditionally have been considered largely insulin-insensitive. This view prevailed until about 15 years ago when insulin receptors were detected in the central nervous system[4,5] and the belief emerged that insulin may modify neural function in the brain.

About 7 years ago insulin receptors were also found in the peripheral nervous system in bovine trigeminal ganglia and autonomic superior cervical ganglia[6].

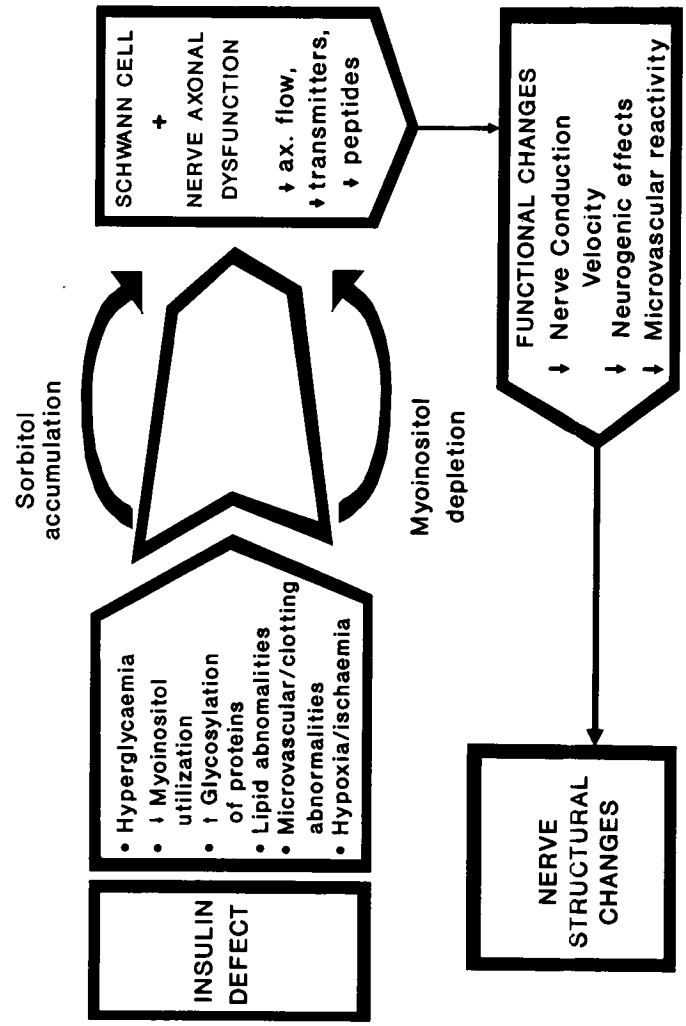

Fig 1 This flow diagram shows some of the structural and functional changes which may occur in diabetic nerves and which may result in neuropathy.

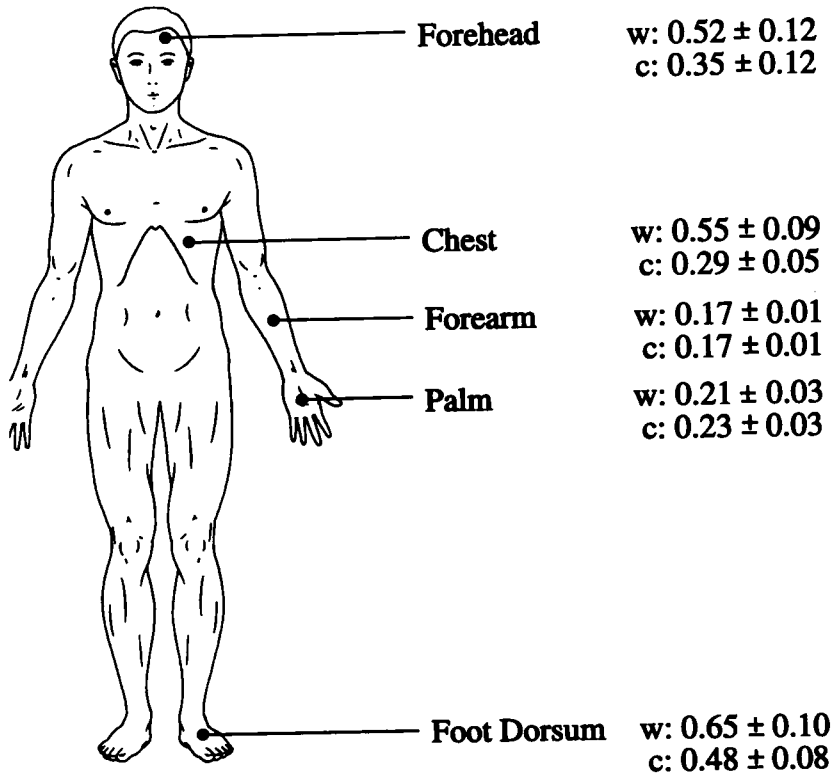

Fig 2 Site-to-site variation in the thermal perception thresholds (mean thresholds for warm and cold perception at 5 different sites, ± standard deviations).

However, their function remains unclear and no studies have investigated the question of whether insulin is necessary for normal nerve function.

The aim of the study reported below was primarily to examine the insulin-dependence of peripheral sensory nerve function. Our approach was to look at diabetes mellitus, in which there is a reduced insulin production in the case of Type 1, insulin-dependent, diabetes mellitus (IDDM) or a reduced insulin sensitivity, referred to as insulin resistance, in the case of Type 2. non-insulin-dependent, diabetes mellitus (NIDDM). Both situations lead to a rise in blood glucose levels (hyperglycemia) and are often associated with neuropathy, which may result in sensory deficits.

AETIOLOGY OF NEUROPATHY: HYPERGLYCAEMIA OR INSULIN DEFICIENCY?

Although neuropathy of various types is a relatively frequent complication of diabetes mellitus[7,8], the aetiology and underlying pathophysiology are uncertain[8,9]. Diabetes is associated with hyperglycaemia and with deficits in both insulin action and sensory nerve function, but the relative contributions of each to the genesis of the neuropathy is not clear[8].

Fig 1 diagrammatically displays some of the major structural and functional changes which have been identified in diabetic nerves. Structural changes relate mainly to the larger myelinated nerve fibres, and require biopsy and microscopy to be demonstrable. Those mechanisms by which nerve function may be disturbed are summarised in the Figure and include problems with the neural blood supply and energetics, and changes in the content, synthesis and transport of vital components within the nerve[8]. Given that all these disturbances are recognised, what is the role of insulin (if any) in these processes ?

Many of these changes are associated with hyperglycaemia which, via activation of the polyol pathway, causes distorted glucose metabolism and accumulation of alcohol-based sugars within neurons[10,11]. Consistent with this, early functional and structural disturbances to nerves have been reported to be reversible when normoglycaemia is restored with insulin[12].

However, a major problem lies in trying to separate the direct and indirect effects of insulin. That is, are the sensory nerve deficits associated with diabetes due only to the hyperglycaemia which results from the defects in insulin action or is the reduced insulin action per se also a contributing factor ?

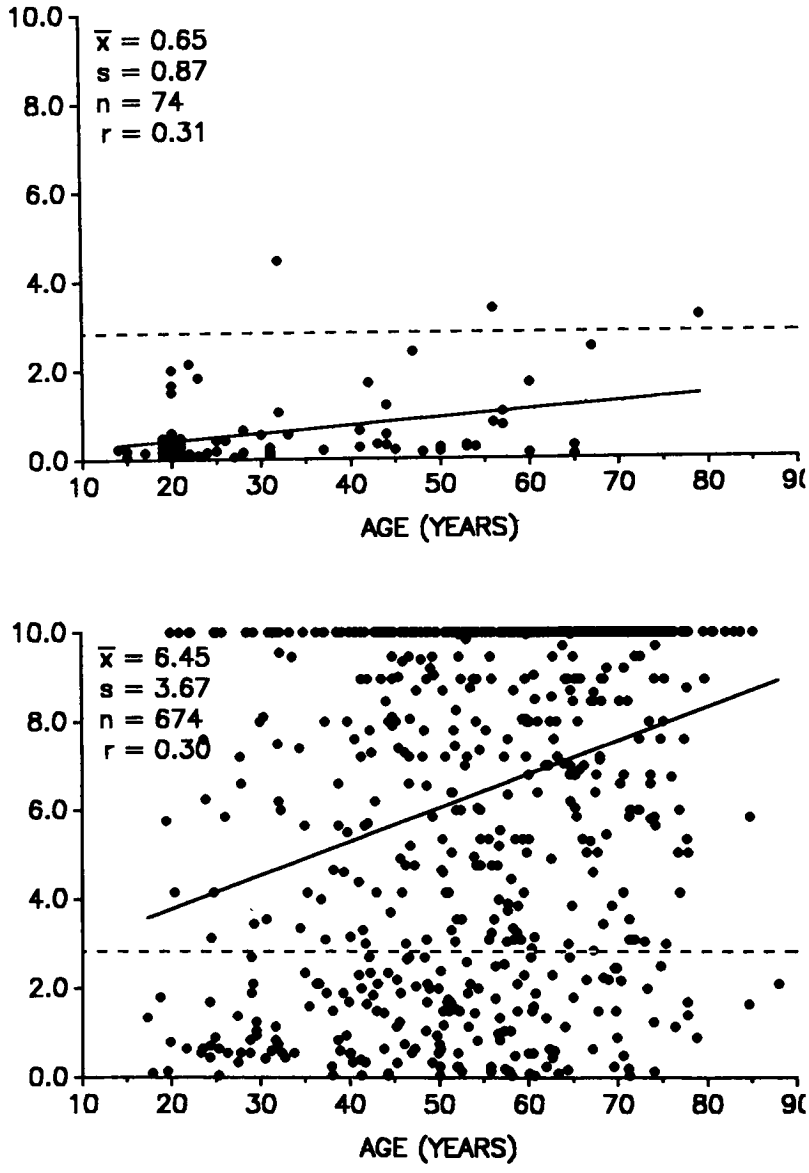

Fig 3 Scatter plots of warm thresholds on the foot dorsum (°C) for top: 74 non-diabetic, and bottom: 674 diabetic subjects of various ages.

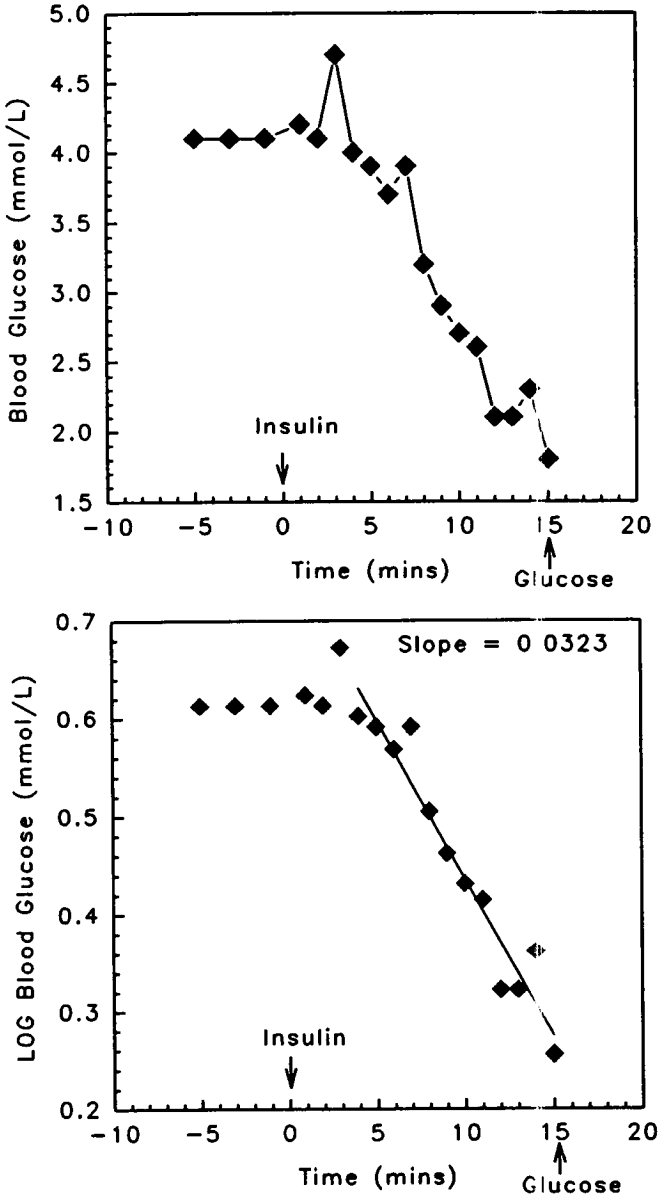

Fig 4 The short intravenous insulin tolerance test. Plot A shows the raw blood glucose values obtained from one subject during the procedure. Plot B depicts the log-transformed data with a line of best fit overlayed. The slope of this line gives the insulin sensitivity.

RESEARCH STRATEGY

In an attempt to answer this question we studied non-diabetic human subjects with defective insulin action but without the complication of hyperglycaemia. Such diabetics are difficult to find as the two disturbances usually go hand in hand. In the study, thermal sensation was measured in relation to insulin sensitivity in both lean and obese volunteers. Some useful comparisons between various groups of diabetic subjects were also made to help interpret the data.

METHODS

The experiments involved human subjects and were ethically approved.

Sensory nerve function was measured using warm and cold thermal threshold testing[13,14,15]. This was performed in 3 groups of subjects: non-diabetic; insulin dependent diabetics (IDDM); and non-insulin dependent diabetic (NIDDM), as part of routine clinical neurophysiological assessment. Insulin sensitivity was measured using a short intravenous insulin tolerance test[16,17] (IVITT) in small subgroups of the non-diabetic and NIDDM populations.

Thermal Acuity

The Medelec TTT is a microprocessor-driven device which, based on a forced choice paradigm, determines the warm or cold perception threshold. It defines this as the minimum change in temperature which the subject can reliably detect 75% of the time. This test assesses the integrity of unmyelinated C-fibres in the case of the warm test and thinly myelinated A-delta fibres in the case of a separate cold test[13,14].

Thermal thresholds vary, depending on test site[15]. Fig 2 shows the normal threshold (mean ± SD) for some different body regions. It may be seen that the forearm is more sensitive than the foot, indicated by the lower threshold value. When sensory nerve disturbances occur, they tend to progress from distal to proximal. For this reason, and also because the skin thickness varies least on the dorsum of the foot, this region was chosen as the site at which to compare subtle changes in non-diabetic subjects.

However, the foot was not an appropriate site to make subtle comparisons in diabetic subjects. Fig 3 shows the wide variability in warm threshold on the foot in diabetic subjects compared to controls. This is largely because many of the diabetic subjects tested had established neuropathy. Therefore the forearm, a less

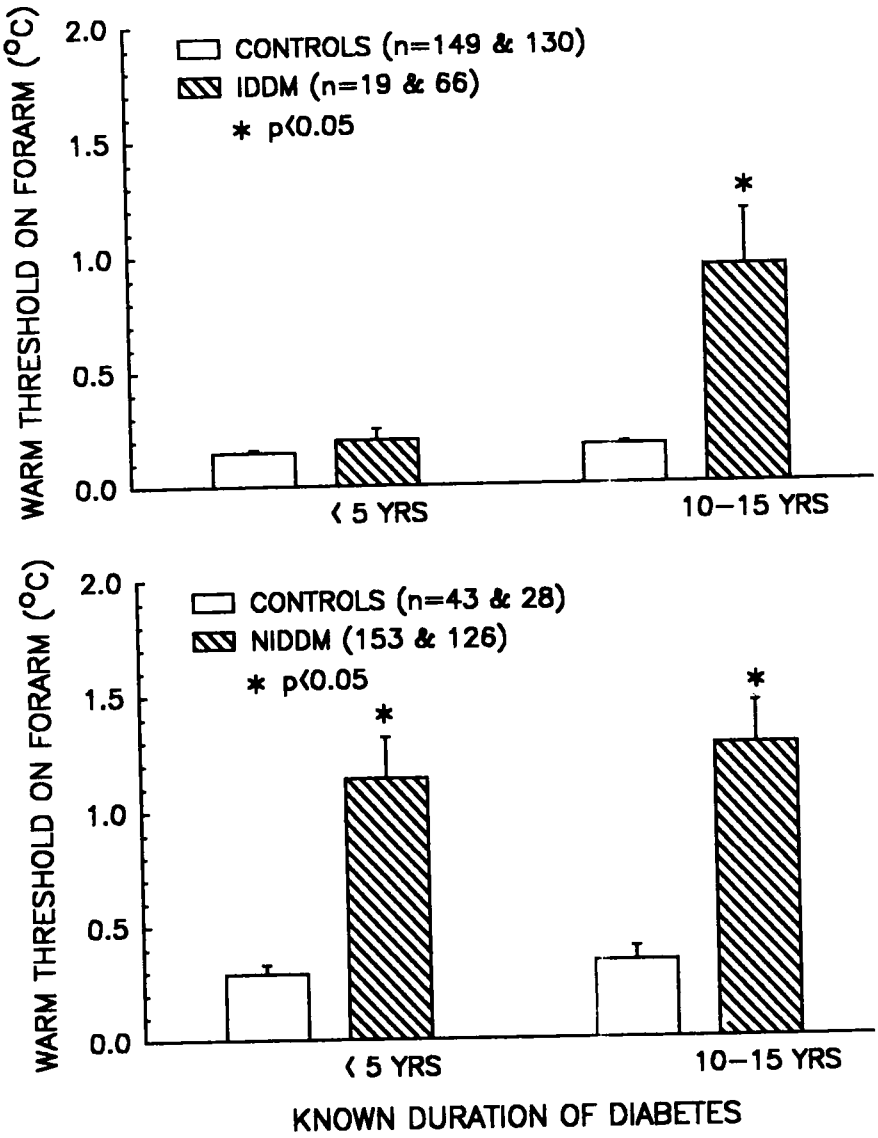

Fig 5 Forearm warm threshold data for Type 1 diabetics (upper) and Type 2 diabetic subjects (lower). Histograms (left) represent subjects with <5 years duration of diabetes; right, durations of 10-15 years; all show means and standard error bars, and asterisks indicate significant differences ($P<0.05$).

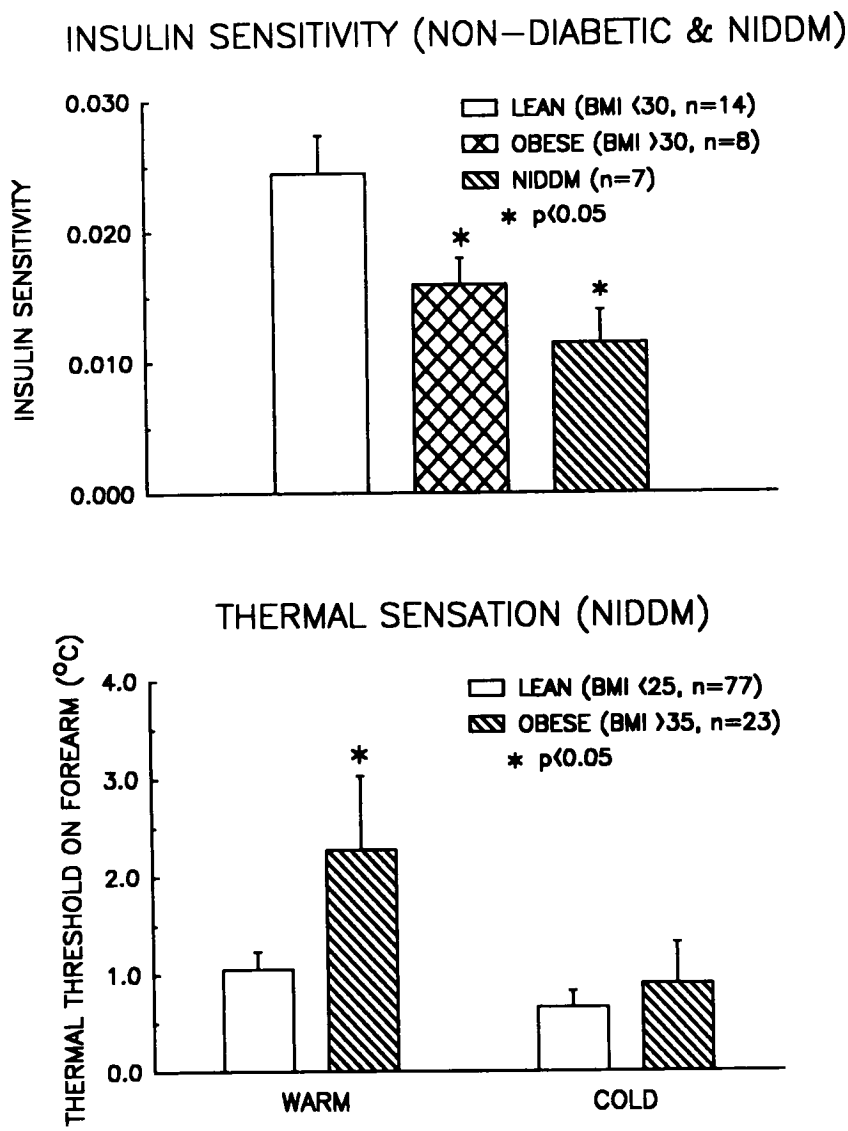

Fig 6 Upper panel - Insulin sensitivity measured by the short IVITT in 3 groups of subjects viz. lean non-diabetic subjects (open bars), obese non-diabetics (cross-hatched), and non-insulin-dependent diabetic subjects (diagonal hatched bars). Lower panel - thermal thresholds for warm and cold in lean and obese subjects with NIDDM. All histograms show means and standard errors; asterisks indicate significant differences ($P<0.05$).

common site for neuropathy to occur, was chosen for comparisons in diabetics.

Insulin Sensitivity

The short IVITT is an improved and abbreviated version of the traditional insulin tolerance test and has been previously validated against the euglycaemic clamp technique[16,17]. The result from one subject is demonstrated in Fig 4 with time on the ordinate and blood glucose level on the abscissa. In the test, after an overnight fast, the subject has a butterfly needle inserted into an antecubital vein from which blood samples are withdrawn and insulin is delivered. Three basal blood samples are taken 5, 3 and 1 min before a bolus of insulin (0.1 U/kg) is delivered. Blood samples are then taken and blood glucose levels measured every min for 15 mins, after which time the test and progressive hypoglycaemia are both terminated. The subject receives a bolus of glucose through the vein and is also fed to prevent subsequent reappearance of hypoglycaemia. After a logarithmic transformation of the glucose values a regression line is fitted from 3 min on. The slope of this line gives the insulin sensitivity. An example of such a record is shown in Fig 4B.

RESULTS

The graphs in Fig 5 show the forearm warm threshold data for groups of control, IDDM and NIDDM subjects. Hatched bars represent diabetics and open bars depict controls who are age matched to the subjects in their adjacent bars. The upper graph shows subjects with IDDM, the lower those with NIDDM. Subjects in the first group had a duration of diabetes less than 5 years, those in the second a duration of 10 to 15 years.

In the upper graph, there is a clear effect of duration of diabetes on warm perception threshold in the case of Type 1, insulin dependent diabetes. With less than 5 years since the time of diagnosis there was no significant impairment to thermal sensitivity compared to age-matched controls. In contrast, 10 to 15 years of diabetes had a significant impact on the thermal threshold.

In comparison, Type 2 (non-insulin-dependent) diabetics (in the lower panel of Fig 5) shows significant elevation of warm perception threshold compared to age matched controls within 5 years of diagnosis. This elevation is maintained in subjects with longer duration (10-15 years) diabetes, and suggests that the underlying insulin resistance and hyperinsulinaemia which occur long before diabetes is diagnosed have some impact on the function of C-fibre afferents.

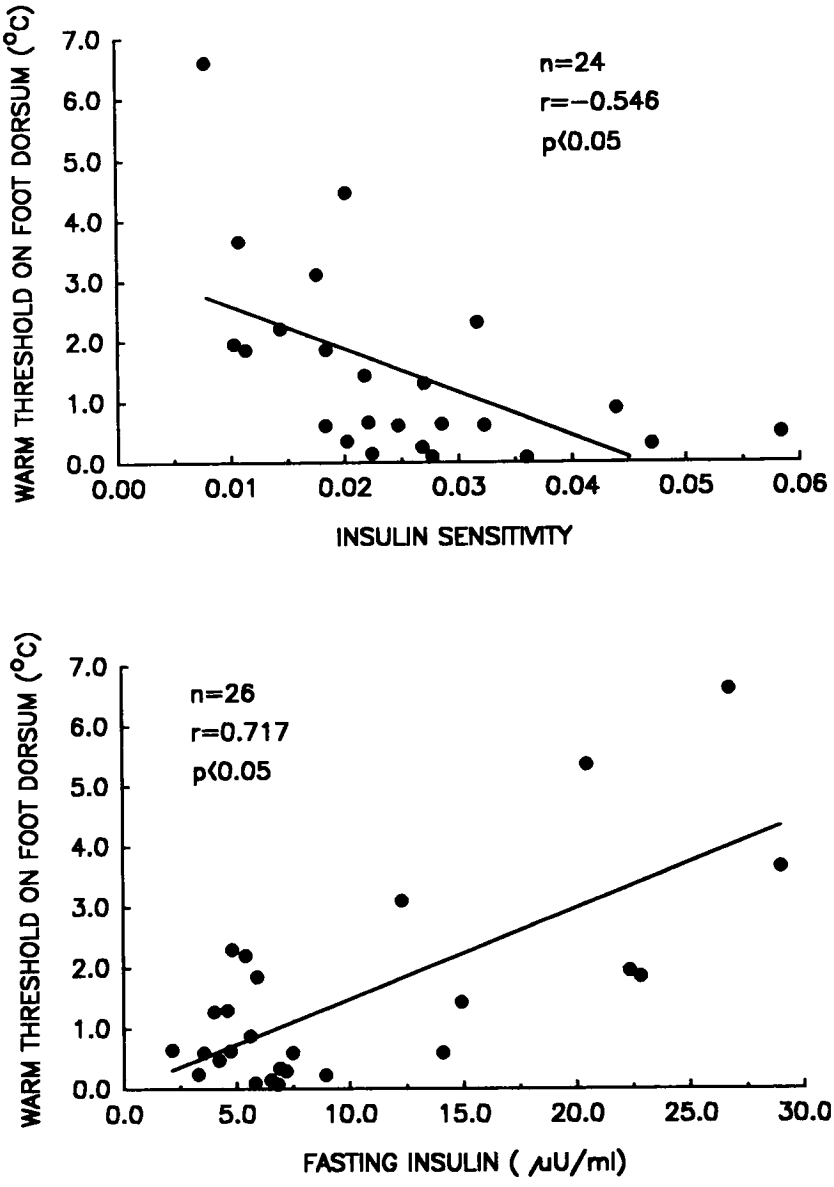

Fig 7 Correlations of warm thresholds on the foot dorsum vs insulin sensitivity (upper) and fasting insulin (lower). The correlations are both significant ($P < 0.05$) and the number of subjects and r values of the correlations are given.

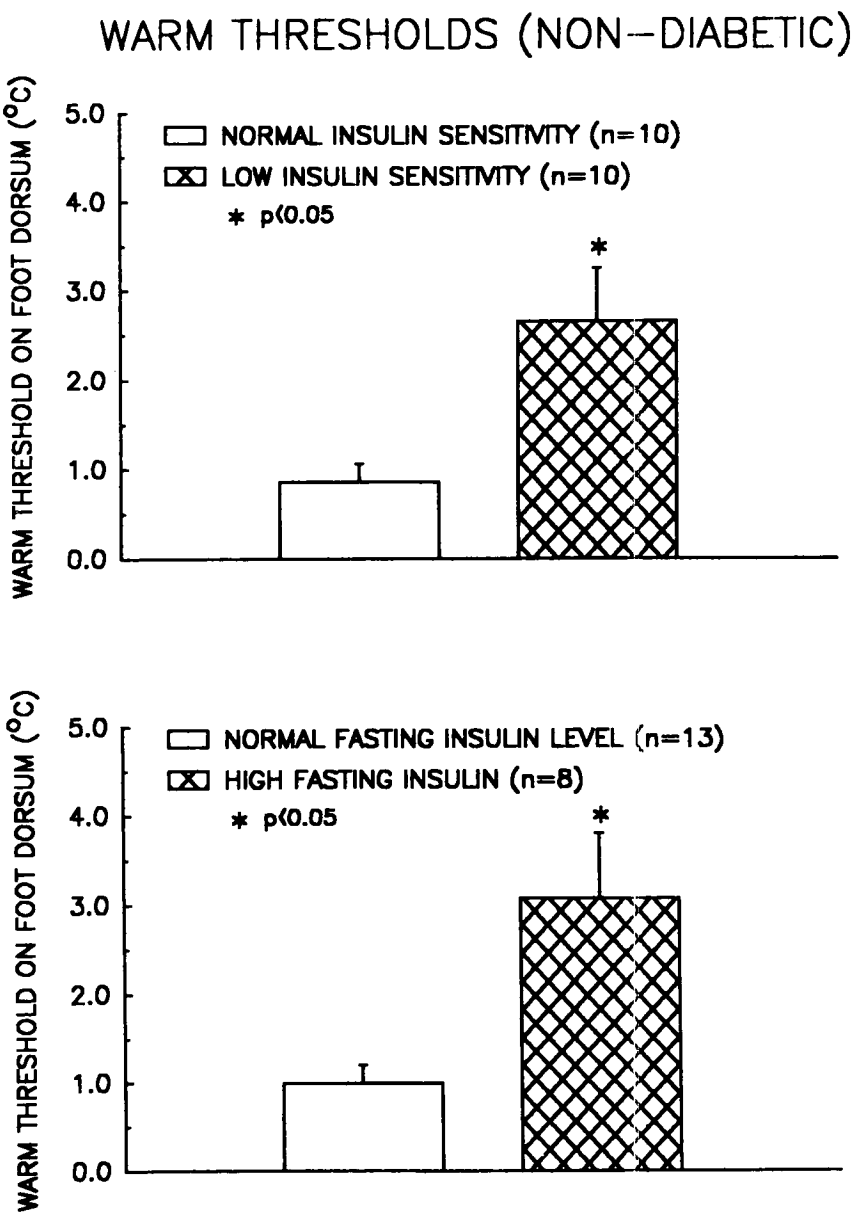

Fig 8 Warm thresholds on the foot dorsum of non-diabetic subjects shown separately in upper panel - for those with normal insulin sensitivity (open bar) and low insulin sensitivity (hatched bar). In the lower panel warm threshold data for normal (open bar) and high fasting insulin (hatched bar) are compared. Means and standard errors are shown, and asterisks flag significant differences at $P < 0.05$.

The histograms in Fig 6 (upper) depict insulin sensitivity as measured by the short IVITT in 3 groups of subjects; lean non-diabetics, obese non-diabetics and non-insulin-dependent diabetics. Insulin sensitivity as determined by this method is reduced in both non-insulin- dependent diabetic subjects and in obese members of the non-diabetic group.

Based on this result, in Fig 6 (lower) we compared thermal threshold in lean and obese NIDDM subjects. Open bars represent lean NIDDM subjects and hatched bars represent obese NIDDM subjects for warm and cold threshold on the forearm. Obese NIDDM subjects showed a more elevated warm threshold, indicating impairment of C-fibre afferents, but this factor did not seem to affect significantly the A-delta fibres, as shown by the cold threshold which was the same in lean and obese NIDDM sufferers.

Fig 7 shows correlations of warm threshold with insulin sensitivity and fasting insulin. The upper graph plots warm threshold on the foot against insulin sensitivity on the x-axis; the correlation is significant after age, height and fasting blood glucose are all considered. These factors might have affected the thermal threshold but there was no significant effect of any of them. Thus, the warm perception threshold increased with reduction in insulin sensitivity, reflecting C-fibre dysfunction with increasing insulin resistance. Unlike the diabetic patients, these subjects were not hyperglycaemic and their glucose tolerance was normal.

The lower graph in Fig 7 shows that insulin resistant non-diabetic subjects tended to have a higher fasting plasma insulin level than those with normal insulin sensitivity. This was because insulin resistance is generally accompanied by a compensatory increase in insulin release.

As with insulin resistance, there was a significant correlation between fasting insulin level and the warm threshold on the foot. That is, the higher the fasting insulin level the greater the impairment of sensory nerve function.

Warm threshold is plotted versus insulin sensitivity and fasting insulin level in Fig 8. In this Fig, and in Fig 9, the non-diabetic subjects were divided into sub-groups with normal and low insulin sensitivity in the upper graph and normal and high fasting insulin levels in the lower graph. When warm threshold on the foot was compared in these sub-groups, the subjects with low insulin sensitivity showed elevated thresholds and thus reduced sensitivity for warm stimuli on the foot, compared to age matched controls. Similarly, when the group was subdivided into subjects with normal and high fasting insulin levels, the latter also showed sensory nerve dysfunction compared with age-matched controls.

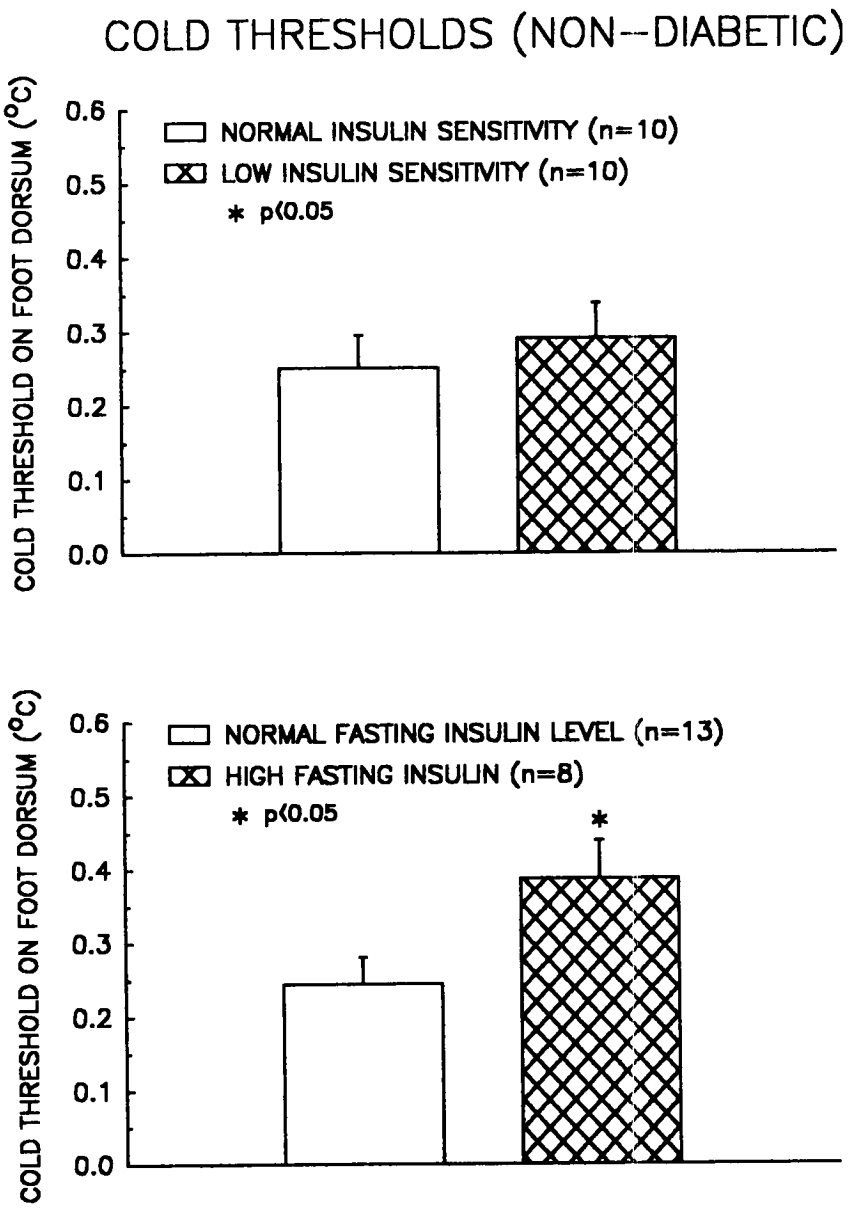

Fig 9 The same comparisons as in Fig 8, but for cold thresholds on the dorsum of the foot.

Fig 9 shows the same comparisons in the previous Fig, but for cold threshold on the foot. Unlike the warm threshold, low insulin sensitivity did not significantly alter cold perception. However the group with elevated fasting insulin levels showed some impairment to cold sensation suggesting that this measure may be more sensitive and relevant than insulin resistance itself when looking at the neural effects of insulin.

DISCUSSION

Interpretation of the results relates to the basic differences in carbohydrate metabolism between the various groups of subjects that were studied. The primary defect in Type 1 diabetes mellitus (IDDM) is insulin deficiency due to the destruction of pancreatic β-cells or failure of their function. Hyperglycaemia results and its onset and that of the associated symptoms is relatively sudden.

In contrast, since Himsworth & Kerr[18] first described the 2 different types of diabetes it has been demonstrated that the primary defect in Type 2 diabetes (NIDDM) is reduced insulin sensitivity or insulin resistance. Insulin resistance is partly compensated for by the pancreatic secretion of more insulin and hence high circulating insulin levels occur (hyperinsulinaemia). There is also a β-cell defect such that there is eventual exhaustion of this system and the islets can no longer produce enough insulin to compensate for the insulin resistance, so that hyperglycemia ensues. Therefore the onset of Type 2 diabetes is more insidious than Type 1 and insulin resistance may be present in the pre-diabetic state for a long time before hyperglycaemia sets in. This is particularly the case in obese NIDDM individuals[19].

In people without diabetes who are obese, insulin resistance also occurs[19,20]. However their blood glucose and glucose tolerance are usually normal because they are able to produce enough insulin to compensate for the insulin resistance. They hence have high circulating insulin levels and this hyperinsulinaemia can in turn contribute to the insulin resistance. This vicious cycle can eventually lead to β-cell exhaustion. Thus obesity is a major risk factor for developing NIDDM[19].

Clinical observations in Fig 5 point to a clear adverse impact of diabetes of both types on thermal acuity, and therefore on small sensory fibre function. In Type 1 diabetes, durations less than 5 years did not significantly affect thermal perception, although 10 to 15 years of diabetes did significantly impair warm acuity. By contrast, in Type 2 diabetes compared with age-matched controls, both the short (5 years) and longer (10-15 years) durations of diabetes were associated

with elevated warm perception thresholds.

Because obesity is associated with reduced insulin sensitivity[19] (see Fig 6) age-matched leanness and obesity in non-diabetic subjects and subjects with NIDDM were compared. These further clinically derived data suggested an effect of insulin resistance *per se* on the function of unmyelinated afferents. However, the conclusions that can be drawn from these data are still limited by the fact that some of the subjects were diabetic and therefore hyperglycaemia was still an important confounding factor in interpreting the pathophysiology of the deficits seen.

In contrast to this, the data of Fig 7 relate to non-diabetic subjects in whom both thermal threshold and insulin sensitivity were measured. They were normoglycaemic so that their blood glucose level was not a relevant factor. In these subjects who had normal glucose tolerances and were normoglycaemic, the warm perception threshold increased with reduction in insulin sensitivity. Furthermore, the fasting insulin concentration is an indicator of insulin resistance[20,21] and this correlation was also reflected in C-thermal nerve fibre dysfunction when correlated with insulin resistance.

In Fig 8 (for warm acuity), and in Fig 9 (for cold acuity), histograms illustrate data derived from non-diabetic subjects with measured insulin sensitivity and fasting insulin levels. Because hyperglycaemia was not a confounding factor the findings are also easier to interpret. They highlight the dependence of small thermal sensory nerve function upon normal insulin action. Warm perception threshold seemed a more sensitive indicator than cold perception (Fig 8, compared with Fig 9).

Although nerves do not require insulin for glucose uptake, insulin receptors have been shown to exist on peripheral nerves[7]. This poses the central question - is insulin essential for normal nerve function? In summarising the results of this study, it appeared that sensory nerve function is disturbed in normoglycaemic but insulin resistant states. This suggested a role for insulin apart from its effects on glucose metabolism in maintaining normal nerve function. Further, the disturbance appeared to be greater in unmyelinated C-afferents mediating warmth, than in the larger A-delta fibres which mediate cold. Finally, a high fasting insulin level appeared to be more closely associated with sensory nerve dysfunction than was insulin resistance *per se*.

An immediate corollary to these findings and the resultant conclusions is to consider possible sites and mechanisms by which insulin resistance and/or hyperinsulinaemia may exert their influences. For example, in muscle, which is

completely insulin-dependent for glucose uptake, there are several postulated sites for insulin resistance to occur between insulin binding to its receptor and the process of glucose entering the cell[22,23,24].

Since the early reports of the production of insulin resistance by hyperinsulinaemia in man[22], studies have proposed an insulin-induced postreceptor defect in the glucose transport system of adipocytes[25], or decreased insulin receptor biosynthesis and mRNA levels[26] as the primary mechanism. Certainly the phenomenon has been adequately confirmed[27], and the different effects of prolonged pulsatile hyperinsulinaemia in humans have proved important[28].

Whatever the mechanisms of insulin resistance prove to be, it may be the high circulating insulin levels which result from this that produce the observed effects on nerve function by down-regulating insulin receptors[25,26] on sensory nerves. The major prerequisite for this hypothesis to become more tenable would be to demonstrate insulin receptors on peripheral sensory nerves. This matter is being addressed in current insulin receptor binding studies. A further difficulty is that while insulin receptors have been shown to exist on sensory nerves, no studies have compared the density of these receptors in normo- and hyper-insulinaemic states. This is now being undertaken by comparing the density of insulin receptors in the sensory nerves and ganglia of animal models of NIDDM such as Zucker and Israeli sand rats.

Two final criticisms of the present study could be advanced: firstly, the short IVITT method of assessing insulin sensitivity may not be as absolutely certain as the euglycaemic clamp[29], although the IVITT method has been validated against this method[16,17]. Secondly, the measurement of fasting plasma insulin levels by radioimmunoassay as an indicator of hyperinsulinaemia (and therefore insulin resistance) may be open to errors arising from cross-reactivity of insulin antibodies with proinsulins[30]. The RIA used in the present study was only minimally affected in this way.

Thus, there is no clear answer yet as to whether the insulin deficiency or insulin resistance is the primary cause of NIDDM[31]. Correspondingly, there is no indication yet as to the respective roles of insulin resistance and deficiency in causing sensory nerve dysfunction.

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RESPONSE TO L-DOPA AND EVOLUTION OF MOTOR FLUCTUATIONS IN THE EARLY PHASE OF TREATMENT OF PARKINSON'S DISEASE

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SUMMARY

Twenty patients with Parkinson's disease were studied during the early phase of L-dopa treatment to clarify the development and progression of Parkinsonian motor fluctuations. Two patients had developed symptomatic motor fluctuations of moderate severity and another 3 had mild fluctuations. Both the initial response to L-dopa and the amplitude of response to a L-dopa test dose after a mean follow up period of 30 months were significantly greater for the fluctuating patients compared with those without fluctuation ($p < 0.05$). Although severe motor fluctuations do not usually develop until a number of years of L-dopa treatment have elapsed, this study shows that motor fluctuations can be detected quite early in the disease course and tend to appear in those patients who respond best to L-dopa.

L-dopa is the most effective pharmacological treatment for Parkinson's disease. Although most patients improve when treatment is commenced, many gradually develop unstable and fluctuating responses to L-dopa over subsequent years. This phenomenon is often referred to as a 'complication' of long-term L-dopa treatment. Both the mechanisms which lead to the development of motor fluctuations and the best management of pharmacological therapy to prevent or delay them are controversial.

Many currently held concepts of the natural history of motor fluctuations are based on cross-sectional evaluation of groups of Parkinsonian patients, extrapolating from these data to reach conclusions about changes in response to L-dopa that accompany disease progression. This study attempts to clarify the evolution of motor fluctuations over the early phase of L-dopa treatment by longitudinal evaluation of motor response to L-dopa in patients taking standard L-dopa/decarboxylase inhibitor medication.

MATERIALS AND METHODS

Patients

Twenty patients with Parkinson's disease were studied during the early phase of L-dopa treatment. All patients who had been referred by their general practitioner for neurological consultation to one of the authors (PK) between 1988 and 1992 and who met the following criteria were included in the study:

(i) clinical features consistent with the United Kingdom Parkinson's Disease Brain Bank definition of idiopathic Parkinson's disease[1] at their time of presentation,

(ii) not taking pharmacological treatment for Parkinson's disease when first seen, and

(iii) a follow up period of at least 12 months after initiation of L-dopa medication.

Twelve male and 8 female patients were studied. Their mean age was 66 years and the mean period between their onset of motor symptoms and the commencement of L-dopa treatment was 22 months. Over the follow up period all patients received a standard L-dopa/carbidopa preparation. Three patients were also treated with a slow release L-dopa formulation but dopamine receptor agonists, selegiline, anticholinergics and amantidine were not used.

Methods

Standard clinical practice in each case was to start L-dopa 100mg/ carbidopa 25mg tablets at low dose and to increase the dose gradually as tolerated until a satisfactory response occurred, as judged by perceptions of patients and their relatives and by objective motor assessment. The mean L-dopa daily dose when treatment was judged to be optimal was 430mg.

Modified Webster scale scoring[2] was performed before starting treatment and when optimum L-dopa therapy was in use. Patients were reviewed at 2 to 3 monthly periods after initiation of treatment and the best modified Webster score recorded over the first 6 months on optimum L-dopa dosage was used to calculate the initial motor response to L-dopa. After a mean follow up period of 30 months, a test dose of 2 L-dopa 100mg/carbidopa 25mg tablets was given in the morning while fasting after withholding of anti-parkinsonian medication. Four patients were not available for this follow-up test dose evaluation (2 dead, one severely disabled in a nursing home).

The amplitude of the motor response was defined as the pre-treatment minus post-treatment modified Webster scale score.

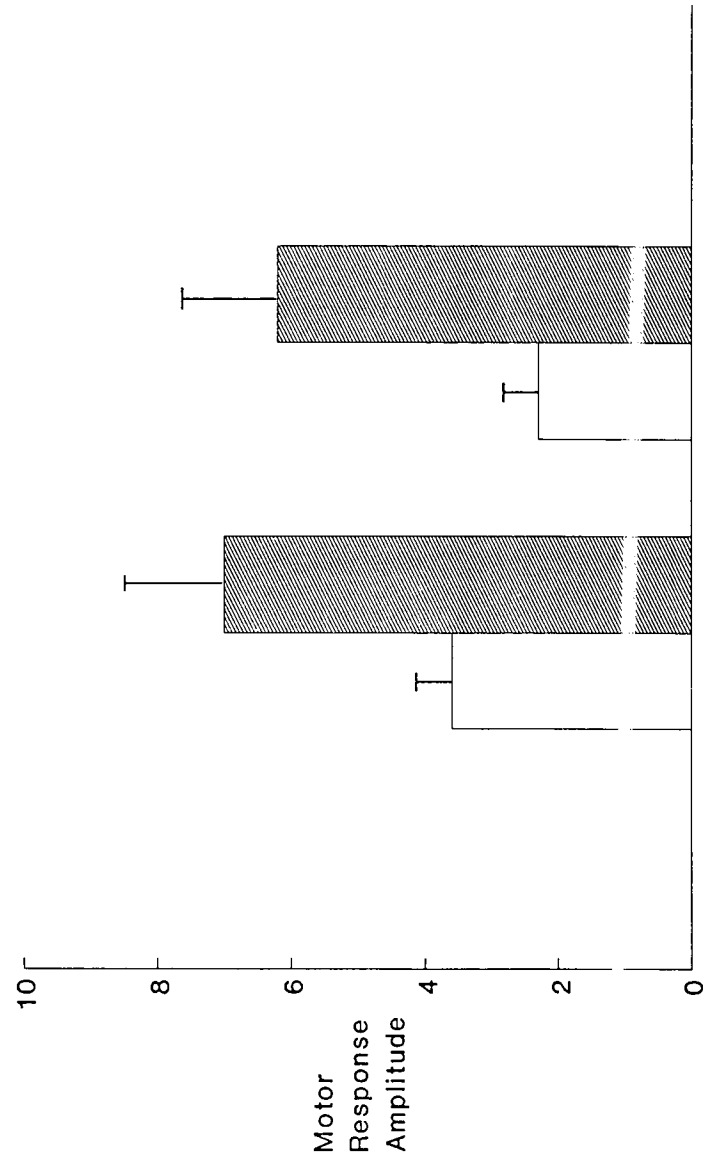

Fig 1 Magnitude of initial response to L-dopa treatment and amplitude of response to follow-up test L-dopa dose in patients with stable control of motor symptoms at follow up (plain bars) and in patients who had developed symptomatic motor fluctuations (shaded bars).

The following simple qualitative scale was used to define the severity of symptomatic motor fluctuations:
Mild: Patient aware of changes in motor performance in relation to L-dopa doses but no significant change in functional motor status due to fluctuations; mild 'on' phase dyskinesia may be present;
Moderate: Alterations in motor performance interfering with tasks of daily living during phases of decline in medication response;
Severe: 'on-off' fluctuations with incapacitating 'off' phase diability.

RESULTS

The mean pre-treatment Webster score was 12.1 and this fell to 7.6 when patients received an optimum L-dopa dose. The mean L-dopa test dose scores were 11.3 (pre-dose) and 7.8 (post-dose). By this time 2 patients had developed symptomatic motor fluctuations of moderate severity and another 3 had mild fluctuations. All had mild dyskinesia and a further 4 had developed dyskinesia although their response to L-dopa was otherwise stable. Both the initial response to L-dopa treatment and the amplitude of the response to the L-dopa test dose were significantly greater ($p<0.05$) for the fluctuating patients compared with those without fluctuations (Fig 1).

The 2 cases with greatest fluctuations each noticed the onset of fluctuation within several weeks of commencing L-dopa. These patients each described mild 'wearing-off' effects of the motor response to L-dopa medication which occurred 3 to 4 hours post-dose. Within 6 months, mild dyskinetic involuntary movements could be observed. These patients had the greatest improvement in disability score on commencing treatment and the greatest amplitude of response to the L-dopa test dose.

DISCUSSION

Although severe motor fluctuations usually do not develop until a number of years of L-dopa therapy have elapsed, mild but detectable motor fluctuations are present quite early in the disease course in many patients. This finding is consistent with previous estimates that motor fluctuations develop at a rate of approximately 10% per L-dopa treatment year[3]. The patients who showed the greatest degree of response on starting L-dopa therapy are those most likely to develop motor fluctuations with disease progression.

The clinical effects of motor fluctuations do not become significant until 'off' phase disability becomes severe and obvious dyskinesia accompanies motor responses to L-dopa. Both of these developments are caused by advanced nigral cell loss and increasing reliance on pharmacological stimulation of dopamine receptors.

A fluctuating motor response to L-dopa may develop once disease progression has reduced endogenous striatal dopamine production to a critical level in patients who retain the capacity to respond strongly to pharmacological striatal dopamine receptor stimulation.

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HUNTINGTON'S DISEASE IN HONG KONG CHINESE: EPIDEMIOLOGY AND CLINICAL PICTURE

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SUMMARY

In a territory-wide survey of Huntington's disease (HD) in the Chinese population of Hong Kong, 20 patients from 11 families were identified from 1984 to 1991, giving a low period prevalence of 3.7 per 10^6 population. Six patients had died by 1991, hence the point prevalence was even lower, being 2.5 per 10^6 population. The male to female ratio was 3:1. No paternal transmission effect on the age of onset was observed. Apart from these differences, the clinical and pathological features were similar to those seen in the West.

Huntington's disease (HD) has been described in many parts of the world. Initially, it was thought that most cases in North and South America, South Africa and Australia could be traced to a northwestern European founder[1]. More recently, HD has been shown to arise as independent mutations in families, since affected individuals were found to have expanded trinucleotide repeats at the 5' end of the Huntington gene (IT5)[2], which was inherited from an intermediate size repeat allele in the parental generation[3]. In the Chinese, HD was first described in Mainland China in 1959[4], and later in Hong Kong in 1962[5]. Because of the lack of systematic surveys, the disease prevalence is unknown in Mainland China where only 66 cases had been reported up to 1990[6]. Moreover, very few reports have described the disease in its various stages and autopsy studies are even rarer. Hence, a territory-wide investigation of HD was undertaken among Hong Kong Chinese to study the epidemiology, clinical and pathological features.

PATIENTS AND METHODS

Patients with HD who were alive between 1st January 1984 and 31st December 1991 were identified via the following means. A computer search was carried out in major hospitals and an announcement was made in the Newsletter of the Hong Kong Medical Association asking all doctors to contribute suspected or confirmed cases of HD for study. In addition, neurologists and psychiatrists from all major hospitals and centres were contacted in person. The records of all identified cases were reviewed and each patient was examined by at least one neurologist and one psychiatrist. Family members were interviewed and pedigrees reconstructed. HD was diagnosed on the basis of a positive family history, plus an insidious progressive disorder comprising chorea and disorders of voluntary movement and cognition and often psychiatric disturbances[7]. Neurological disorders which may mimic HD (e.g. senile or benign familial chorea) were excluded by their non-progressive nature, while Wilson's disease and neuroacanthocytosis were excluded by normal serum copper and ceruloplasmin levels and peripheral blood smear examinations. Caudate atrophy on computed tomography (CT) of the brain was considered supportive of the diagnosis. Autopsy confirmation was obtained in 2 patients. DNA analysis was performed on all those patient who were alive at the time of study, and the results will be reported separately.

RESULTS

Twenty Chinese patients (15 males, 5 females) from 11 families were identified. As the average Chinese population in Hong Kong during this period was 5.44 million, the period prevalence was 3.7 per 10^6 population. By the prevalence date (31st December 1991), 6 patients had died, and the Chinese population then was 5.55 million. Hence the point prevalence was 2.5 per 10^6 population. The average incidence was 0.46 and the average mortality 0.14 per 10^6 population per year respectively.

The patients' clinical data are summarized in Table 1. The mean age of onset for all patients was 37.6 years (range 20 to 52), and 37.9 and 36.8 years in the 15 paternally transmitted and in the 5 maternally transmitted cases respectively. In the 6 patients who died, the age of death varied from 29 to 60 years and the mean duration of illness was 8.2 years (range 7 to 9). For those still alive, the duration of illness varied from 1 to 23 years. The initial symptom was chorea in 12 patients (60%) and psychiatric disturbance in 8 (40%). The chorea was of insidious onset and progressive, usually affecting the face, neck or upper limbs first and then

becoming more generalised. Abnormalities of voluntary movements of the eyes and of fine motor coordination, speech and gait were also frequently present. Severe dysarthria, dysphagia, dystonia, rigidity and bradykinesia were seen in patients with advanced disease. Four patients had generalised hyperreflexia or ankle clonus but none had Babinski's sign. Progressive cognitive impairment was present in all patients except one who had early disease. The most common psychiatric features were irritability and aggression, followed by depression, anxiety, suicidal attempts, obsessive compulsive behaviour and hypersexuality. The terminal events were pneumonia in 5 patients and bilateral subdural haematomas in one.

CT of brain showed the typical changes of caudate head atrophy with dilatation of the frontal horns of the lateral ventricles in 14 patients. In Cases 7, 13 and 16, CT studies performed 2 years after onset were normal. Autopsy in 2 patients showed typical changes of HD, viz. severe atrophy and neuronal loss in the corpus striatum (particularly the caudate nuclei) with astrocytic proliferation and fibrillary gliosis (Fig 1).

DISCUSSION

As this study was not a door-to-door population survey, the possibility of under-diagnosis and under-reporting certainly exists. Hence, our prevalence and incidence figures must be regarded as minimum estimates. However, we believe our data reflect the epidemiology of HD in Hong Kong Chinese reasonably well because of the vigorous efforts in tracing cases. Excluding those areas with a very high prevalence, most western countries have a prevalence of about 40-100 per 10^6 population. The prevalence of HD in our series is therefore low compared to occidentals, but similar to the Japanese figures of 1.1 to 4.5 per million[8]. Further, the disease is seldom reported in Mainland China. Thus, the available evidence suggests that there is an over ten-fold difference in the prevalence of HD between orientals and occidentals. Based on the geographical distribution of HD cases in China, we have postulated that Chinese HD may be inherited from European traders[6], but the hypothesis needs substantiating evidence from genetic studies. A predominance of male patients was found in the present study and the Mainland China series[6]. It is interesting that paternal transmission of the disease was more common and apparently was not more often associated with an earlier age of onset, as occurred in Caucasian series[1].

The initial symptom was chorea in 12 patients (60%) and psychiatric disturbance in 8 patients (40%), resulting in referral to neurologist and psychiatrist

Table 1 Summary of the clinical data

Case	1	2	3	4	5	6	7	8	9	10
Initials	HKY	HKW	SHT	SR	SS	TKK	TKK	NMF	NWH	TCP
Family	Ia	Ia	Ib	II	II	III	III	IV	V	VI
Sex	M	M	M	M	F	M	M	M	M	M
Age	34*	29*	43	44*	44	48*	41	27*	44	55
Occupation	artisan	artisan	guard	computer engineer	nurse	seaman	watchman	store-keeper	baker	barber
Age at onset	25	20	41	36	38	40	39	20	43	40
Origin	GD	GD	GD	JS	JS	GD	GD	GD	GD	JS
Inheritance	AD	AD	AD	AD	AD	AD	AD	AD	AD	AD
Transmission	mat	mat	pat	pat	pat	pat	pat	pat	pat	mat
Initial symptom	C	C	P	C	C	C	C	P	P	P
Chorea	+	+	+	+	+	+	+	+	+	+
Cognitive decline	+	+	+	+	+	+	+	+	+	+
Psychiatric symptom	I,A,X	I,A,X	D,I,A,I, Su Se	I,X	I,A	I,A	I	D,I,Su	D,I,Su	
CT	CA	CA	CA	CA	CA	CA	N	CA	CA	CA
Cause of death	pneu	pneu		SH		pneu		pneu		
Post-mortem	+	ND		ND		+		ND		

Abbreviations: A=aggression; AD=autosomal dominant; C=chorea; CA=caudate atrophy; CT=computed tomography; D=depression; F=female; GD=Guangdong; HB=Hebei; I=irritability; JS=Jiangsu; M=male; mat=maternal; N=normal; ND=not done; OC=obsessive compulsive behaviour; P=psychiatric; pat=paternal; pneu=pneumonia; Se=hypersexuality; SH=subdural haematoma; Su=suicide attempts; X=anxiety; *Age at death

Case Initials	11 LLM	12 WCM	13 WCF	14 MSC	15 CYC	16 LWP	17 TSP	18 TYL	19 TSY	20 TSW
Family	VII	VIII	VIII	IX	X	X	XI	XI	XI	XI
Sex	F	M	M	M	F	M	F	M	F	M
Age	32	40	41	60*	68	48	40	52	48	43
Occupation	factory worker	hawker	watchman	sales	housewife	cook	teacher	mechanic	teacher	mechanical engineer
Age at onset	21	39	39	52	45	45	37	47	43	42
Origin	GD	GD	GD	GD	GD	GD	HB	HB	HB	HB
Inheritance	AD	AD	AD	AD	AD	AD	AD	AD	AD	AD
Transmission	mat	pat	pat	pat	pat	mat	pat	pat	pat	pat
Initial symptom	P	C	C	C	C	C	C	P	P	C
Chorea	+	+	+	+	+	+	+	+	+	+
Cognitive decline	+	+	+	+	+	+	+	+	+	-
Psychiatric symptom	I,A	I	D,I	I,A	I,A	D	I,OC	OC	X	X
CT	CA	CA	N	ND	ND	N	CA	CA	CA	ND
Cause of death				pneu						
Post-mortem				ND						

Abbreviations: A=aggression; AD=autosomal dominant; C=chorea; CA=caudate atrophy; CT=computed tomography; D=depression; F=female; GD=Guangdong; HB=Hebei; I=irritability; JS=Jiangsu; M=male; mat=maternal; N=normal; ND=not done; OC=obsessive compulsive behaviour; P=psychiatric; pat=paternal; pneu=pneumonia; Se=hypersexuality; SH=subdural haematoma; Su=suicide attempts; X=anxiety; *Age at death

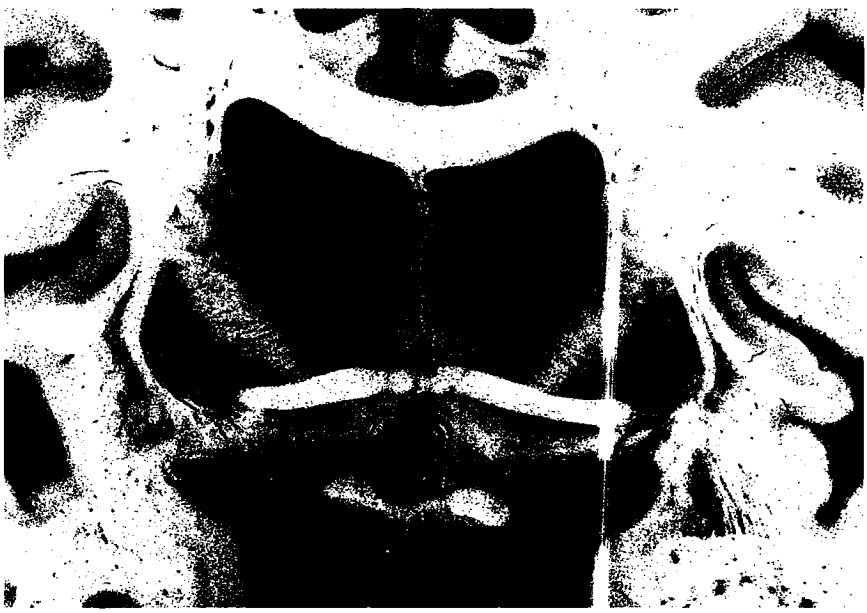

Fig 1a Autopsy findings of Patient 1
Close up view of coronal section of brain at the level of the optic chiasma. There is severe symmetrical shrinkage of the caudate nuclei, with compensatory dilatation of the anterior horns of the lateral ventricles.

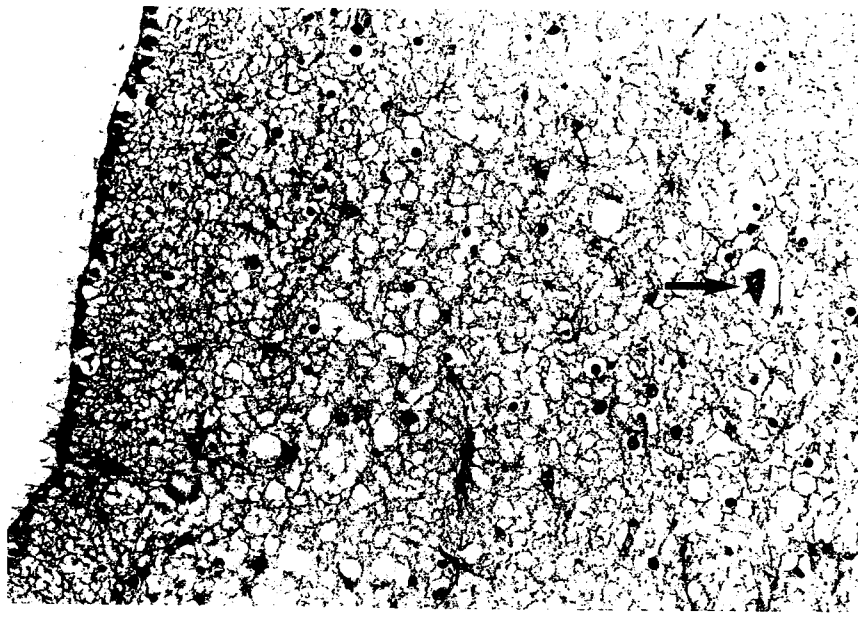

Fig 1b Autopsy findings of Patient 1
Caudate nucleus showing a spongy state due to almost complete disappearance of small neurons but occasional large ones are still present (arrow). Proliferation of astrocytes is most noticeable deep to the subependymal layer. H&E x 200

respectively. The other features, including abnormalities of saccadic eye movements, fine motor coordination, speech and gait, were also common and may precede the development of chorea. Progressive cognitive impairment was present in all patients except Case 20 who was seen at an early stage. It is noteworthy that some HD patients could have above average intelligence before the onset of illness, as illustrated by Cases 4 and 20 who worked as computer and mechanical engineers respectively. Psychiatric manifestations, aggression and irritability were found in all patients.

In our two autopsy cases, typical pathological features of HD were present. Since up to 15% of cases reported as HD may be misdiagnosed, pathological confirmation should be obtained whenever possible[7]. In addition, knowledge of the definitive pathology provides a strong basis for genetic counselling and predictive testing. Recent studies have provided new insight about clinico-pathologic correlation. Chorea and other abnormal movements are attributed to early degeneration of the striatal projections to the substantial nigra reticulata and the lateral globus pallidus, whereas rigidity and bradykinesia correlate with late degeneration of the striatal projections to the medial globus pallidus[9]. However, the pathological substrate responsible for the pyramidal tract signs remains undefined.

Our study shows that HD is rare amongst Hong Kong Chinese. Apart from the male predominance and the lack of a paternal transmission effect on the age of onset, the clinical and pathological features of the disorder are similar to those described elsewhere. It has been suggested that the Japanese cases may have a Dutch origin[1] since the Japanese HD gene has been shown to be linked to similar DNA markers with similar recombination scores as the HD gene in the West[10]. Although Dutch, Portuguese and English traders were known to have settlements in this region, mutation analysis will be needed to determine whether the disease in Chinese and Caucasians has a common origin. The recent identification of the HD gene containing a trinucleotide repeat at the distal short area of chromosome 4 is a major advance in our understanding of this hereditary disorder[2]. If the molecular correlate of paternally-transmitted cases is true, Chinese HD patients should have a larger number of trinucleotide repeats and an earlier onset of disease[11]. However, within the small patient number in the present study, a paternal transmission effect on the age of disease onset is not obvious. DNA studies on the HD patients which are currently underway will hopefully elucidate these points.

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ISAAC'S SYNDROME: REPORT OF A CASE RESPONDING TO VALPROIC ACID

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SUMMARY

Isaac's syndrome is an uncommon, but distressing, condition of spontaneous abnormal muscle activity caused by neuronal hyperexcitability possibly due to damage to slow potassium channels. The underlying aetiology may be peripheral nerve damage from a wide variety of causes, including autoimmune disease. We report a case that failed to respond to carbamazepine or phenytoin but responded dramatically to valproic acid. Thus, valproic acid may be an effective treatment for Isaac's syndrome where these other drugs have failed.

Isaac's syndrome (neuromyotonia) is characterised by spontaneous muscle activity with cramps often associated with myokymia, pseudomyotonia and excessive sweating[1]. EMGs show typical features that distinguish it from other causes of visible myokymia and muscle cramps[1]. Denny-Brown and Foley[2] first described the syndrome as 'undulating myokymia' in 1948 and it was later (1961) further defined by Isaac[3] who called it 'the syndrome of continuous muscle fibre activity'. Current evidence suggests it is a disorder of peripheral nerves[1] and some cases may have an autoimmune basis[4]. Carbamazepine and phenytoin are effective treatments in some patients[5] while resistant cases may respond to plasmapheresis and immunosuppression[1]. We report a patient with Isaac's syndrome associated with an idiopathic peripheral neuropathy, in whom trials of treatment with carbamazepine, phenytoin and steroids were unsuccessful, but in whom valproic acid dramatically improved the symptoms. We believe this to be the first report of valproic acid being effective in Isaac's syndrome where these other drugs have failed.

CASE HISTORY

A 63 year old man presented with a 12 month history of disabling muscle cramps predominantly affecting the legs, forearms, intercostal and abdominal muscles. Initially the cramps would occur only after heavy exercise but by the time of presentation could

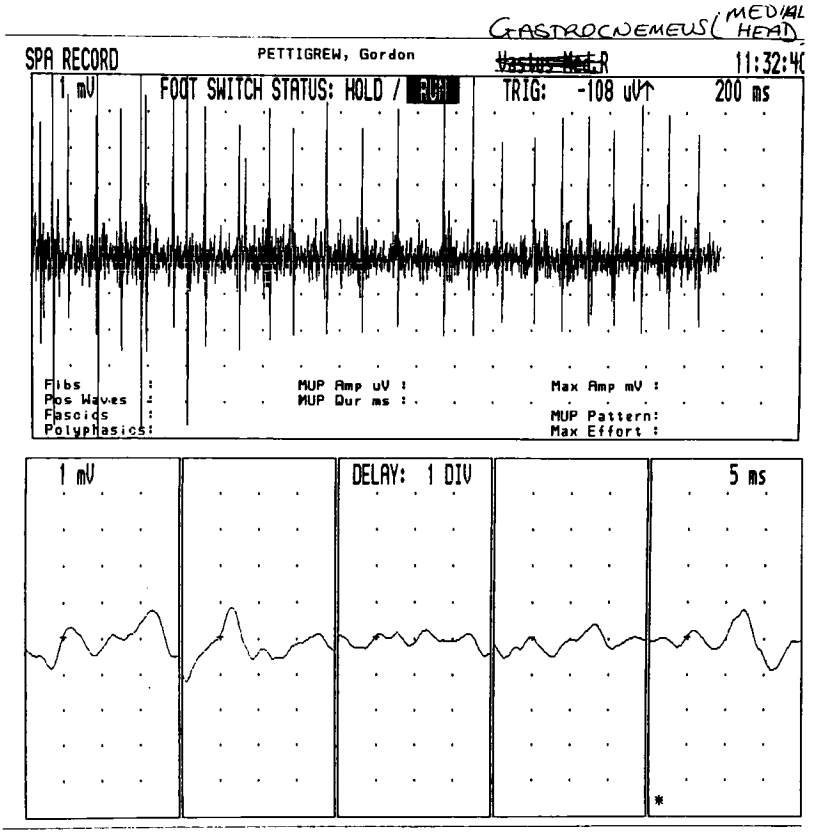

Fig 1a EMG from a patient with Isaac's syndrome during spontaneous muscle cramps. Right gastrocnemius: high amplitude low frequency motor units with very high frequency low amplitude background units.

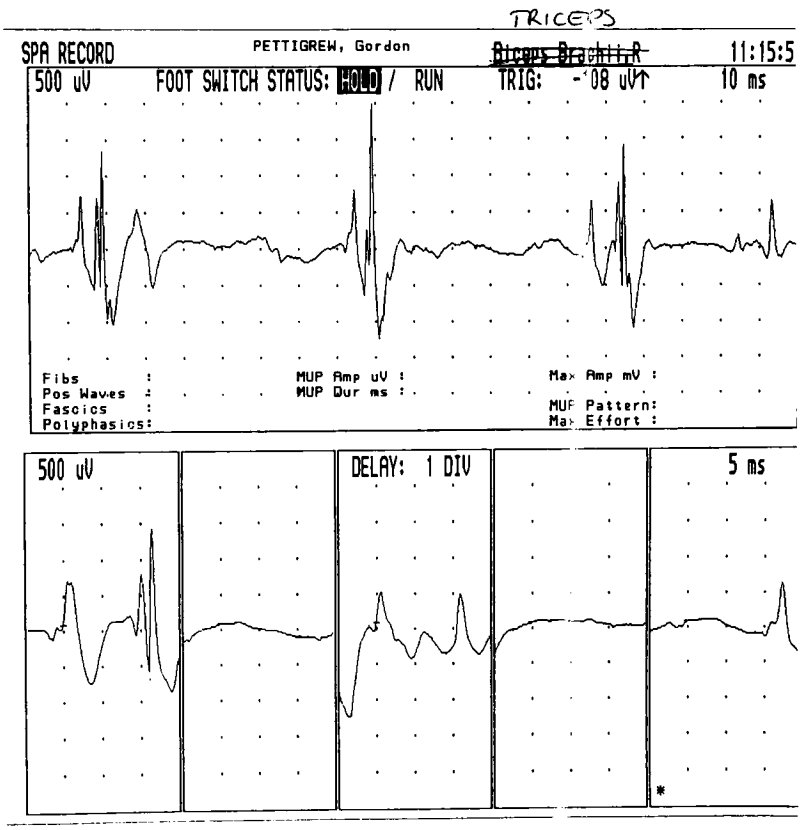

Fig 1b EMG from a patient with Isaac's syndrome during spontaneous muscle cramps. Right triceps: regularly firing doublet unit.

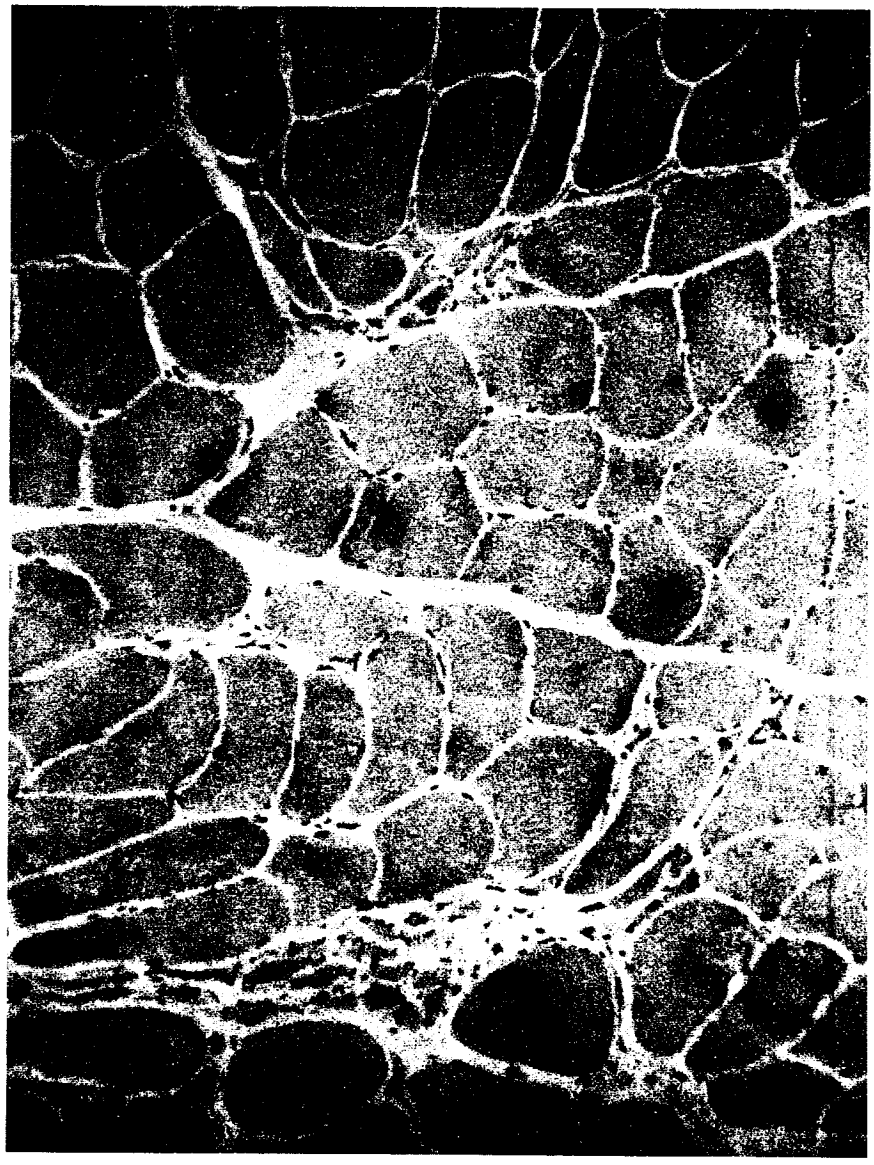

Fig 2a Muscle biopsy of right gastrocnemius from a patient with Isaac's syndrome. H.&E. paraffin section demonstrating large fibre atrophy.

Fig 2b Muscle biopsy of right gastrocnemius from a patient with Isaac's syndrome. ATPase stain demonstrating moderately severe fibre grouping.

come on after walking only 10 to 20 metres and sometimes resulted in falls. They would also occur at rest (especially during sleep) and be induced by sustained muscle contraction. The cramps were associated with considerable pain and could last up to 5 mins. Mild lethargy and malaise and some slight distal numbness and paraesthesia were also reported. Trials of diazepam, carbamazepine, phenytoin, magnesium supplements and high dose steroids had failed to improve the symptoms.

His other medical problems included steroid dependent chronic airways disease for which he had several hospital admissions over the past year. At the time of presentation he was smoking 3 cigarettes and drinking 3 glasses of beer per day but in the past his intake of both had been much heavier. There was no family history of neuromuscular disease.

On examination he was a lean middle-aged man with no muscle wasting, fasciculation or visible myokymia. After a short period of walking, prominent cramping developed in his calves with forced inversion of his feet. Cramps which lasted up to several minutes could also be induced in the arms by sustained contraction, but there was no clinical evidence of myotonia. Hip flexion was mildly weakened but otherwise power was normal. Reflexes were generally suppressed but elicitable with reinforcement except for the ankle jerks. Muscle tone was normal. Light touch and pain sensation were mildly decreased distally to above the ankles and wrists bilaterally, but proprioception and vibration were intact. There were no other neurological abnormalities and general examination revealed some changes of chronic airways disease but was otherwise unremarkable.

Investigations revealed a normal serum creatine kinase, full blood examination, erythrocyte sedimentation rate, vitamin B_{12}, folate, electrolytes, calcium, phosphate and magnesium levels. Chest x-ray, and CT of chest and abdomen were unremarkable. Auto-antibodies, including glutamic acid decarboxylase, were negative. Nerve conduction studies revealed a mild generalised reduction in motor amplitudes and conduction velocities and low sensory amplitudes. Electromyography (EMG) showed a mild excess of polyphasia and a few scattered fasciculations in all muscles sampled. During a cramp (right triceps and gastrocnemius muscles) continuous motor activity, including duplets and multiplets with high intra-burst frequency, was observed and gradually subsided over 1 to 2 mins (Fig 1). Muscle biopsy showed significant fibre atrophy and some type grouping suggesting a chronic neuropathic process of some duration (Fig 2).

Valproic acid therapy was commenced at a dose of 200 mg 3 times daily with abolition of the cramps which was maintained at 8 months follow up.

DISCUSSION

Clinically and electophysiologically our patient fulfils the criteria for Isaac's syndrome (neuromyotonia) which has been defined clinically by

spontaneously occurring muscle activity with cramps that can be triggered by voluntary or induced muscle activity and which persists during sleep[1]. Visible myokymia, paramyotonia and excessive sweating were not present in our case but are not required for the diagnosis. EMGs of the abnormal muscle activity characteristically show doublet, triplet or multiplet single motor unit discharges with a high intra-burst frequency (40-200 per sec) and sampling of resting muscles often show fibrillation potentials and fasciculations[1].

Isaac's syndrome needs to be distinguished from other conditions with abnormal muscle activity. In the stiff-man syndrome the abnormal muscle activity does not show the high frequency discharges and disappears during sleep, while antibodies to glutamic acid decarboxylase may be present[6]. EMGs in the more benign cramp-fasciculation syndrome do not show fibrillation potentials or prominent fasciculations[7]. Localised myokymia due to radiation or demyelination is distinguishable by its lack of a generalised distribution and by the regular periodicity of the abnormal discharges[1].

As in our patient, Isaac's syndrome may be associated with either acquired or inherited peripheral neuropathies[1,8]. The abnormal muscle activity is abolished by curare and in most patients persists despite peripheral nerve block suggesting a distal peripheral nerve origin[3]. However in some patients it is reduced or abolished by peripheral nerve block[1], and in one patient by epidural anaesthesia[9], suggesting that it can originate from any site along the nerve.

There is good evidence that in some patients there may be an autoimmune mechanism involved in Isaac's syndrome[4]. There is an association with autoimmune disease (especially myasthenia gravis), with malignancies that are known to be associated with autoimmune diseases (thymoma and lung cancer) and with penicillamine therapy[1]. Oligoclonal bands are often found in the CSF and the symptoms may improve with plasmapheresis and immunosuppression[1,4]. Recent animal experiments have suggested autoantibodies to neuronal slow potassium channels as a cause of the nerve hyperexcitability[4]. Damage to these channels may also be the mechanism for the myotonia in the non-immune mediated instances e.g. peripheral neuropathies[8].

Carbamazepine and phenytoin have commonly been reported to improve the symptoms and decrease the electomyographic abnormal muscle activity in neuromyotonia, but are ineffective in some patients and in others may require high dosage associated with significant side effects[1,5]. Our patient failed to show any improvement with phenytoin, carbamazepine or steroids but had a dramatic response to valproic acid. A previous report found valproic acid to be as

effective as phenytoin and carbamazepine with minimal side effects but did not show its effectiveness in patients in whom other drugs have failed[5]. Valproic acid, like the other two anticonvulsants, acts to decrease the peripheral nerve firing threshold, at least in part by interfering with voltage dependant inward sodium and calcium channels. However valproic acid has recently been shown to also increase the amplitude of the late potassium outward currents which have been implicated in the aetiology of Isaac's syndrome[11]. In some resistant cases plasmapheresis or immunosuppression may be helpful[1].

ACKNOWLEDGMENTS

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ROUTINE USE OF LAMOTRIGINE, A NEW ANTI-EPILEPTIC MEDICATION, AND THE VALUE OF MEASURING ITS BLOOD LEVELS

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SUMMARY

Lamotrigine (LTG) has recently been approved for marketing in Australia as add-on therapy in resistant partial seizure disorders. Early reports cited a therapeutic blood level for LTG of 1-3 mg/L (4-12 μmol/L). Aspects of routine patient care with LTG, devoid of the restrictions of trial protocols, are discussed. Forty-five patients commenced therapy but 15 discontinued LTG. Of the remaining 30 patients, 9 became seizure free, 3 from the *de novo* trial in focal epilepsy and 6 with generalised epilepsy. Global evaluation of patients showed mild to moderate improvement for those with focal epilepsy and moderate to marked improvement for those with generalised epilepsy. Blood levels of LTG did not provide clinically useful information.

Lamotrigine (LTG) is a phenyltriazine derivative, chemically unrelated to other anti-epileptic medications (AEM), which recently has been approved for marketing in Australia as add-on therapy in resistant partial seizure disorders. It was launched, in Australia, in February 1994 at a national conference at which the local experience with LTG was reviewed[1].

The mode of action of LTG is reported to be via stabilization of presynaptic neuronal membranes by blockade of voltage-dependent sodium channels, thereby reducing release of excitatory neurotransmitters (especially glutamate and aspartate)[2]. Early reports cited a therapeutic blood level for LTG of 1-3 mg/L[3] (which is equivalent to 4-12 μmol/L - the units used locally in Sydney). Later studies have cast doubt on this relationship between blood level and clinical efficacy[4-6].

Australians have had compassionate access to LTG by way of the 'Individual Patient Use' and later the 'Special Access Scheme' (SAS). This allowed a less rigorous approach to use of the drug, without the rigidity of research trial protocols and more closely resembling the approach used in

routine patient care in clinical practice. This meant that the use of medication was not restricted to one identified seizure type and incremental changes in LTG dosages were at the discretion of the treating physician. SAS use of LTG dictated that the patient must be refractory to other available AEMs, thereby establishing those patients treated to be a sample of people in whom epilepsy had been most difficult to control.

The account that follows reviews a sample of 45 patients treated with LTG via the SAS and examines the clinical efficacy and the role of LTG blood level determination in routine patient care.

PATIENTS AND METHODS

Patients who attended an out-patient service which had been involved in early Australian trials of LTG were offered SAS use of LTG, when other agents had failed to provide sufficient seizure control. A small number of patients who had completed double-blind controlled trial studies of LTG were offered post-trial SAS use of LTG. Within the context of routine patient care with LTG, 4 patients who presented *de novo* with epilepsy and were part of a monotherapy open label clinical trial have been included in the analysis as their management was similar to that of the SAS patients.

The patients' records were reviewed by a pharmacologist (K.S.) who was not directly involved in the care of those patients who used LTG via the SAS. The pharmacologist's audit defined demographic data, seizure type, use of other AEMs, LTG dosage and LTG drug level reports and evaluated the efficacy of the therapy for each patient.

Blood levels of LTG were assessed by the Department of Biochemistry at Royal Prince Alfred Hospital in Sydney and were measured using high pressure liquid chromotography; the results were reported in micromoles per litre (μmol/L).

As part of the SAS protocol, all patients were monitored by their attending physician as appropriate and a global evaluation was carried out at 6 monthly intervals. Global scores were defined as: 1 = marked deterioration; 2 = moderate deterioration; 3 = mild deterioration; 4 = no change; 5 = mild improvement; 6 = moderate improvement and 7 = marked improvement. Patients were also monitored for adverse reactions.

Table 1 Epilepsy type, daily dose and blood lamotrigine level for patients who became seizure free on lamotrigine

Patient	Epilepsy type	LTG (mg) dose	Level (μmol/L)
IS *	F	100	4.5 ± 1.8
SD	G	200	20.9 ± 4.2
Msh *	F	100	6.5 ± 0.8
MK	G	200	50.3 ± 7.5
MB	G	200	26.8 ± 2.5
DS	G	100	-
IH *	F	200	-
DF	G	100	-
Ska	G	150	11.5 ± 2.6

* These patients presented *de novo* with epilepsy
G = Generalised epilepsy
F = Focal epilepsy

RESULTS

Forty-five (45) patients comprised the initial study population; 15 of these discontinued LTG treatment. Nine patients (20%) stopped taking LTG due to lack of efficacy. One patient stopped LTG because of unwanted effects (diplopia). One patient who had been seizure free on LTG monotherapy for more than 2 years stopped medication as she planned a further pregnancy. One patient was reclassified as having pseudo-seizures and LTG was ceased. The remaining 3 patients who ceased therapy (7%) were lost to follow up. This left 30 patients still taking LTG at the time of evaluation.

One patient developed a rash sufficient to justify withdrawal of LTG but was successfully rechallenged using a slower dose escalation regimen and has continued taking LTG with a greater than 50% reduction in seizures.

Of those patients who ceased LTG but were available for 6 months follow up assessment, 8 showed no change (global score 4), one had deteriorated significantly (global score 2), one had improved marginally (global score 5) and in the patient in whom adverse events had caused cessation of LTG there was significant improvement in seizure control, with a global score of 6.

Table 2 Epilepsy type, lamotrigine daily dose and blood lamotrigine level for patients still experiencing seizures while on lamotrigine

Patient	Epilepsy Type	LTG (mg) dose	Level (µmol/L)
HJ	G	150	36.7 ± 17.8
MSi	F	400	15.1 ± 2.8
		450	26.9 ± 6.5
BR	F	200	14.9 ± 2.7
KQ +	G	200	32.4 ± 4.9
SP	G	150	14.8 ± 3.4
		200	13.7 ± 5.0
JL +§	F	250	7.2 ± 1.2
		350	19.8 ± 14.6
JA	F	200	25.1 ± 8.6
VG +	F	100	8.8 ± 5.1
LH	F	500	13.6 ± 3.4
AM	G	100	10.8 ± 4.9
		200	27.1 ± 8.9
JN	G	250	27.4 ± 8.9
		350	35.1 ± 2.1
AS	G	150	24.4 ± 8.3
AP +¶	G		-
MW	F	200	14.0 ± 4.3
TC +	F	500	6.2 ± 0.7
TG	G	100	10.9 ± 4.6
JH +¶	G		-
SKe¶	G		-
JK	F	250	27.1 ± 0.4
		300	28.1 ± 11.0
DS ¶	G		-
MR¶	G		-

\+ These patients had a greater than 50% reduction in seizures

§ This patient has had successful temporal lobectomy and values quoted predate surgery; he remains on LTG

¶ LTG blood levels were either not measured or measured only on one occasion thus providing insufficient data to justify reporting mean values

G = Generalised epilepsy

F = Focal epilepsy

The remaining 30 patients comprised 20 males and 10 females, with an age range of 11 to 57 years (mean 29.6 ± 11.2 years).

Of these patients, 3 had been involved in a study of LTG as monotherapy with *de novo* presentation of epilepsy (as had the patient cited above who had been seizure-free for 2 years). Two of the patients had continued SAS use of LTG after a placebo-controlled cross-over study of LTG in primarily generalised epilepsy. Both were seizure-free at the time of evaluation (there was a requirement for at least 6 seizures per month at recruitment into the trial).

Two other patients, still taking LTG, had been part of a placebo-controlled cross-over study of LTG as add-on therapy for resistant focal epilepsy and both had gained a greater than 50% reduction in seizures (one of these patients was receiving LTG monotherapy at entry into the present study). Of the remaining 23 patients, 16 had generalised epilepsy (including 6 with the Lennox-Gastaut syndrome) and 7 had focal epilepsy.

Twenty-four of the total 30 patients underwent global evaluation at both 6 months and one year; of the 24, 13 had focal epilepsy and 11 had generalised epilepsy. Mean global evaluation score for the patients with focal epilepsy was 5.8 ± 1 units at 6 months and 5.9 ± 1 units at one year. For patients with generalised epilepsy the mean global evaluation score at 6 months was 6 ± 0.8 units and at one year was 6.4 ± 0.7 units.

Of the 30 patients, 9 (30%) were seizure free at the time of assessment. Of the 9, 3 had *de novo* focal epilepsy and 6 had generalised epilepsy (2 with the Lennox-Gastaut syndrome). This 9 comprised 20% of the original 45 persons exposed to LTG.

Of the 30 patients, 4 were receiving LTG monotherapy, 9 were taking one other AEM (7 valproate (VPA), 2 phenytoin (PHT)); 15 were receiving 2 other AEMs (carbamazepine (CBZ) plus VPA in 10, PHT plus VPA in 1, CBZ plus clonazepam in 1, vigabatrin plus VPA in 1, VPA plus primidone in 1); and 2 patients were receiving 3 other AEMs (although one of these was using the third AEM only as 'pulse therapy' in the catamenial period).

Daily dosages of LTG ranged from 100-600 mg (mean 227 ± 114 mg) and random LTG blood levels ranged from 3.4 - 60.1 μmol/L with durations of exposure to LTG ranging from 0.5 to 5.6 years (mean 2.2 ± 1.3 years).

The 9 patients who were seizure-free were assessed separately (Table 1).

Of the 9, the 5 who had more than a single blood level determination on a defined LTG dosage, had mean levels which ranged from 4.5 μmol/L to 50.3 μmol/L. Drug levels at set LTG dosages in the remaining 21 patients were also assessed (Table 2).

DISCUSSION

This paper has described the use of LTG in clinical practice rather than in the more rigorously controlled situations of research therapeutic trials. The treated patients were considered fairly representative of the general population of difficult-to-manage patients with epilepsy. While the numbers involved are small there are clear trends. No patients, within the observation period, demonstrated serious adverse events. Of the 45 patients included in the initial sample, 20% had no benefit from LTG but only one patient (2%) had sufficient adverse events to require cessation of the drug.

Three of the 30 patients were *de novo* epilepsy sufferers and could not be considered as difficult-to-manage. They showed a good response to LTG, suggesting that LTG may prove an effective first line medication in the treatment of epilepsy.

Six patients, all of whom were classified as having generalised epilepsy, were seizure free at the time of assessment, suggesting that LTG may be a very effective agent in the treatment of generalised epilepsy, in particular refractory generalised epilepsy. The global evaluation scores at 6 months (reflecting moderate to marked improvement) for generalised epilepsy were higher than for focal epilepsy (mild to moderate improvement). There was no indication of a reduction in these scores 6 months later.

When looking at those patients who were seizure free, in whom drug levels were taken on more than one occasion, it could be seen that there was no adequately demonstrated therapeutic range. Three patients were within the previously cited therapeutic range of 4-12 μmol/L but 3 patients were well beyond that range with one patient, MK, having a blood LTG concentration 4 times the upper limit of the previously reported therapeutic range.

Review of the levels provided for those patients with greater than 50% reduction in seizures (Table 2) also failed to demonstrate a therapeutic range.

Evaluation of the data demonstrated that VPA was the other AEM most

commonly used in conjunction with LTG. This is not surprising as the majority of patients in the study population had generalised epilepsies for which VPA is currently held to be the most effective agent. It was also not surprising to find that 10 of the 15 patients receiving 2 other AEMs were taking combination therapy of CBZ and VPA as these are the favoured first line medications in the current approach in the treatment of epilepsy[7].

Rash, the most commonly reported adverse event with LTG[8,9] was reported only in one patient and rechallenge with slower introduction of the drug allowed the patient to continue on LTG without problem and with good therapeutic efficacy.

In conclusion, these results suggest that LTG has wider range of efficacy than merely for the partial seizures of focal epilepsy for which marketing approval in Australia has been given. The results further demonstrate that LTG blood level determination provides little indication as to the drug's efficacy or to the risk of adverse events. It follows that the final decision as to the amount of LTG to be prescribed must be based on clinical judgment as to the balance between efficacy and adverse events in the patient.

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RHINOCEREBRAL MUCORMYCOSIS PRESENTING AS PERIORBITAL CELLULITIS WITH BLINDNESS: REPORT OF 2 CASES

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SUMMARY

Two cases of rhinocerebral mucormycosis in elderly, non-ketotic diabetics who were initially diagnosed and treated for bacterial periorbital cellulitis are reported. Both presented with a short history of periorbital pain and swelling followed rapidly by complete ophthalmoplegia and blindness. By the time of correct diagnosis, both cases were advanced with lower cranial nerve involvement, CT evidence of ophthalmic artery and cavernous sinus thrombosis and, in one, internal carotid artery invasion (demonstrated on MR angiography) with resultant cerebral infarction. One patient was treated with intravenous amphotericin B but died within a few days. The second patient had aggressive surgical resection and survived with significant residual morbidity. These cases illustrate that mucormycosis should be excluded in any diabetic patient presenting with orbital cellulitis, especially when there is early visual loss. Early aggressive treatment with surgery and antifungal agents is often successful whereas the outcome is almost universally fatal when the diagnosis is delayed.

Mucormycosis is an uncommon fulminant necrotizing saprophytic fungal infection caused by organisms of the order *Mucorales*, the most common species involved being *Rhizopus*, *Mucor* and *Absidia*[1]. *Mucoraceae* are ubiquitous in the environment and grow as molds on fruit and bread[2]. They enter the body through skin or mucosa and cause invasive disease in patients with predisposing conditions[3]. The most common form is rhinocerebral mucormycosis which occurs predominantly in diabetics (especially with ketoacidosis)[3] but may also occur in otherwise healthy people[4]. The infection begins in a nasal sinus and spreads to the paranasal sinuses then invades along blood vessels to involve the retro-orbital region, the cranial nerves and the brain[3]. Untreated, it is almost invariably rapidly fatal[5]. However, recent series have reported that with early diagnosis and aggressive treatment a significant proportion of patients can be saved[1,3]. We report 2 patients with rhinocerebral mucormycosis who were initially diagnosed as having bacterial periorbital cellulitis.

CASE HISTORIES

Case 1

A 79 year old man with a 20 year history of poorly controlled type II diabetes mellitus managed with diet and oral hypoglycaemics was admitted to another metropolitan hospital with a 4 day history of progressive visual loss in the right eye with associated periorbital pain and swelling. Over the following day, right facial numbness and weakness developed and the patient became increasingly confused, febrile and hyperglycaemic (but non-ketotic). CT showed right periorbital swelling and right optic nerve thickening but no paranasal sinus abnormality. A diagnosis of fulminant periorbital cellulitis, probably bacterial, was made and he was transferred to St. Vincent's Hospital for further management. On arrival, he was alert but moderately confused and febrile (38.7°C.). There was marked right periorbital swelling and chemosis, a fixed dilated right pupil with no perception of light and complete ophthalmoplegia. Fundoscopy of the right eye was consistent with a central retinal artery occlusion. Sensation was impaired in the distribution of the 1st and 2nd branches of the right trigeminal nerve and there was a marked right facial paresis. The remainder of the cranial nerves and oto-laryngeal examination were normal.

Investigations revealed a venous blood glucose of 73 mmol/L; the cerebrospinal fluid (CSF) contained 137 x 10^6/L white blood cells (WBC) (70% polymorphonuclear cells) with a protein content of 0.70 g/L and a glucose content of 13.6 mmol/L with no organisms on microscopy or culture. Intravenous antibiotics, full heparinization, and an insulin infusion were commenced. The possibility of infection with mucormycosis was thought unlikely in view of the apparently normal paranasal sinuses and an initial apparent response to treatment.

However, on the 3rd day of admission his condition again deteriorated with increasing confusion, high fever, development of left eye involvement with periorbital inflammation, visual impairment, ophthalmoplegia, and impaired left ophthalmic nerve sensation. CT scan with double dose contrast suggested bilateral cavernous sinus thrombosis (Fig 1). Intravenous amphotericin B and streptokinase infusions were commenced. The patient continued to deteriorate and died on the 6th day after admission.

Post mortem examination showed necrotizing inflammation of the retro-orbital tissues with involvement of the cavernous sinus bilaterally by mucormycosis. *Rhizopus* species was cultured from retro-orbital tissues on the right. There was widespread inflammation and infarction of nerves and vessels in the cavernous sinus bilaterally, invasion of the siphon of the right internal carotid artery by fungus with extension of hyphae into the right ophthalmic artery and the intracerebral portion of the cartoid artery. The adventitia of the left internal carotid artery was infiltrated by *mucor*. The right optic nerve was infarcted with invasion by fungi along its entire length up to and including the optic chiasm. The right globe was removed for examination, and this showed a posterior area of multifocal scleral necrosis and inflammation with fungal hyphae, but the retina and choroid were intact. Examination of the brain showed an acute purulent meningitis over the base of the brain and infiltration of the right VII cranial nerve by mucormycosis. Old cerebral cortical and bilateral lacunar

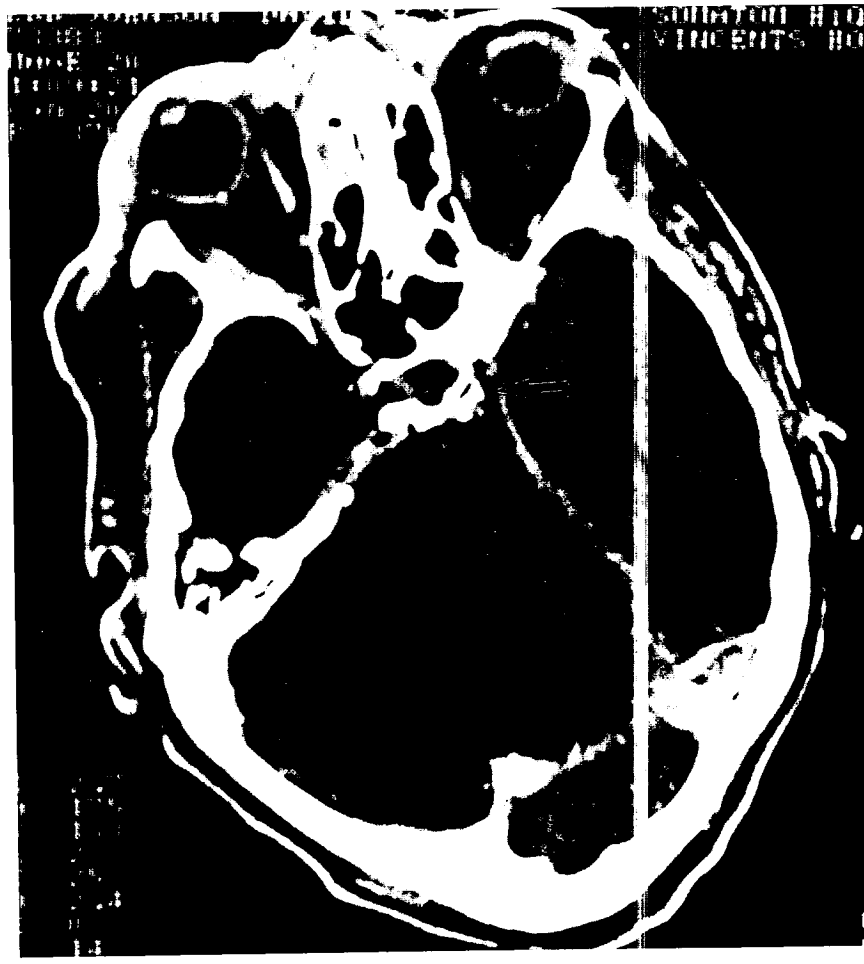

Fig 1(a) CT scan of Case 1 demonstrating lack of enhancement of the cavernous sinus bilaterally with double dose contrast.

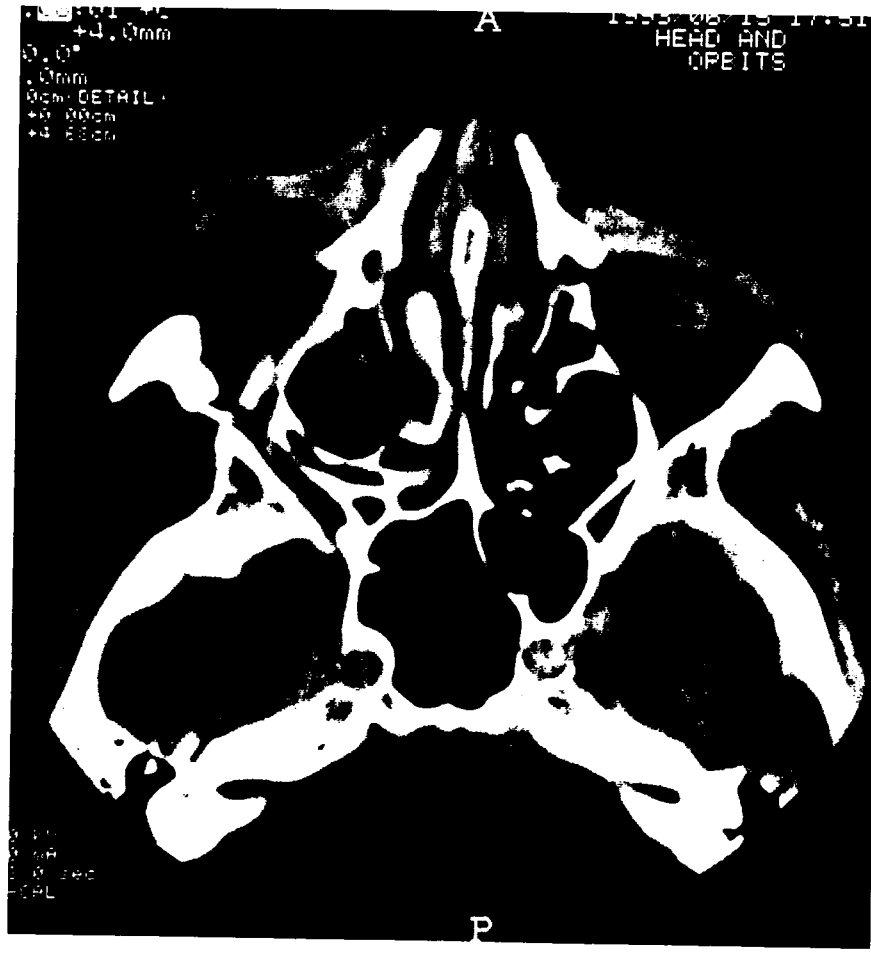

Fig 1(b) CT scan of Case 1 demonstrating the absence of changes in the paranasal sinuses.

infarcts were noted. The general autopsy examination showed extensive bronchopneumonia, old myocardial infarction, diabetic nephropathy and acute renal tubular necrosis.

Case 2

A 69 year old woman, with an 18 year history of type II diabetes mellitus currently treated with 190 U of insulin per day, was transferred to another metropolitan hospital from a rural base hospital. She had been admitted one day previously with a one week history of left nasal 'stuffiness' followed by 2 days of left periorbital pain and swelling with diplopia and then rapid loss of vision in the left eye. She was febrile and hyperglycaemic (but non-ketotic) and had marked left periorbital inflammation with a fixed dilated pupil, no light perception, and complete left ophthalmoplegia. Sensation was impaired in the 1st and 2nd divisions of the left trigeminal nerve. CT showed marked left periorbital swelling with mucosal thickening and fluid in the left sphenoid and ethmoid sinuses. Left external ethmoidotomy showed mucosal swelling and some pus but no necrosis. Microbiological investigations revealed a light growth of *Staphylococcus epidermidis*. Mucormycosis was considered unlikely and she was treated for a bacterial periorbital cellulitis with intravenous antibacterials and an insulin infusion. There was some improvement over the next 3 days but she then deteriorated and developed left facial weakness and early right periorbital inflammation with visual impairment. She was transferred to St. Vincent's Hospital for further management.

On arrival, she was febrile (38.5°C) and moderately confused. In addition to the signs noted above, there was moderate right arm weakness. A repeat contrast enhanced head CT scan was suggestive of left, and possibly right, cavernous sinus thrombosis. CSF examination revealed 300 x 10^6WBC/L (33% polymorphonuclear), 15 x 10^6 red cells, protein 0.64 g/L, glucose 2.7 mmol/L with no organisms detected on microscopy or culture. An exploration of the external ethmoid and sphenoid sinuses showed marked mucosal oedema and moderate pus but no necrosis. Biopsies showed necrotizing suppurative and granulomatous inflammation with fungal hyphae in thrombosed vessels. Culture revealed *Rhizopus* species.

Amphotericin and heparin infusions were commenced postoperatively with some initial improvement. Two days later her condition deteriorated with increasing periorbital swelling, fever and the development of right arm weakness and receptive dysphasia. Left orbital exenteration was performed and the pathology showed extensive multifocal necrosis with fungal hyphae in the retro-orbital tissues including nerves, fat and extra-ocular muscles. There was widespread intraneural invasion by hyphae and occasional vessels with necrotizing fungal vasculitis. The entire orbital course of the optic nerve showed exudative leptomeningitis and multifocal necrotizing inflammation due to fungi. The retina was normal. Culture of the middle turbinate grew *Rhizopus* species.

MRI of the head demonstrated marked swelling and contrast enhancement of the left periorbital tissues and paranasal sinuses, and multiple small ischaemic lesions in the left parietal lobe. MR angiography was suggestive of left ophthalmic artery thrombosis. Intra-cavernous and proximal portions of the left internal carotid artery were narrowed and

Fig 2(a) MRI scan of Case 2. T_1 image demonstrating thickening and narrowing of left carotid artery wall from fungal invasion (large arrows) and marked periorbital inflammation and invasion of medial orbital wall (small arrow).

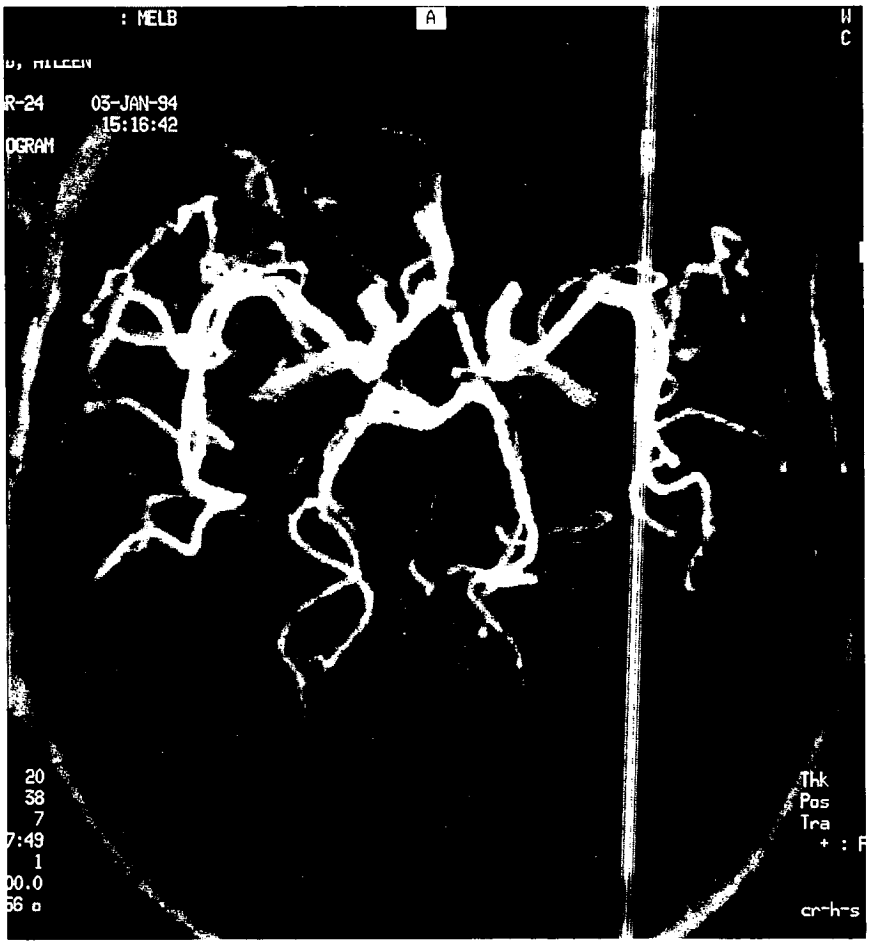

Fig 2(b) MRI scan of Case 2. MRA demonstrating the right ophthalmic artery (arrowed) which is absent on the left.

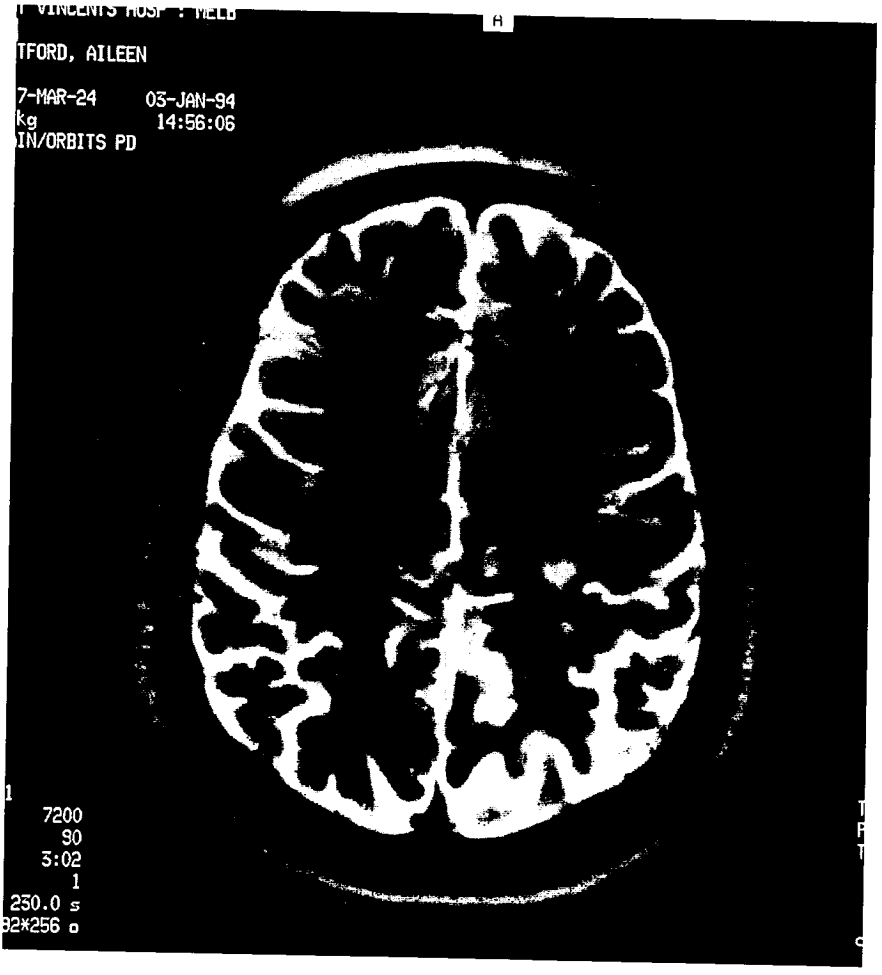

Fig 2(c) T_2 image demonstrating multiple small left cerebral infarcts.

irregular, consistent with fungal invasion (Fig 2).

The patient slowly, but steadily, improved and antibacterials were ceased after 2 weeks. Intravenous amphotericin was continued at 50 mg per day for 10 weeks to a total dose of 3 grams. At the time of transfer back to her local country hospital for rehabilitation, a moderate dysphasia and profound right arm weakness were still present.

DISCUSSION

Mucormycosis accounts for 5% to 15% of fungal infections in the immuno-compromised host[6] and an increasing incidence of the disorder has been found in a number of recent series[3]. The most common types are rhinocerebral, pulmonary, gastrointestinal, skin and soft tissue, and disseminated[3]. The rhinocerebral form is the most common and occurs predominantly in diabetics in the presence of ketoacidosis[1]. Both our cases were diabetics with a history of poor diabetic control but neither had ketoacidosis.

In typical rhinocerebral mucormycosis infection 3 stages are described, viz. rhinosinusal, rhino-ocular and rhinocerebral[7]. The disease may remain confined to the first 2 stages in non-diabetics but often rapidly progresses to the cerebral stage in diabetics[3]. *Mucor* is particularly prone to invade and spread along blood vessels resulting in thrombosis, haemorrhage and extensive tissue necrosis[8]. Involvement of the ophthalmic artery, the cavernous sinus and the internal carotid artery is common[1] and was present in our cases. Cranial nerves are progressively infarcted as the infection spreads, usually initially affecting the optic, oculomotor, trochlear and abducens nerves, then often the trigeminal nerve, and less commonly the facial nerve[9].

Our patients presented typically, with short histories of unilateral periorbital pain and swelling with associated fever and then rapidly developed ophthalmoplegia and blindness. Early visual loss from retinal artery occlusion is common and is a distinguishing feature from pyogenic cavernous sinus thrombosis where this is uncommon and occurs late[9]. The presence of a dark nasal discharge and intranasal or palatal necrotic eschar are highly suggestive features of infection with mucormycosis[9]. The absence of these features in our cases contributed to the delay in diagnosis. However, in some series these features were present in fewer than 50% of cases[1,9].

CT scanning demonstrates mucosal thickening in the nasal fossa or paranasal sinuses in almost all patients with rhinocerebral mucormycosis[10] and the absence of this on the first scan in Case 1 is a highly unusual feature which contributed to

the delay in diagnosis. Evidence of deep tissue invasion is found in about half the cases and bony destruction in a minority[10]. The lack of enhancement of the ophthalmic artery by contrast may be a relatively specific sign of orbital apex involvement by mucormycosis[11] which, retrospectively, was present in both our cases. Cavernous sinus thrombosis was suggested in both patients on CT by failure of the sinuses to enhance with contrast (Fig 2). This diagnosis was confirmed pathologically in Case 1. MRI was performed in Case 2 and clearly demonstrated thrombosis of the ophthalmic artery as well as invasion of the intracavernous and proximal intradural portions of the internal carotid artery. Cerebral infarction may be difficult to distinquish from fungal abscess on CT as oedema is often minimal and ring enhancement may be absent[10]. The MRI was helpful in making the differentiation.

Infections with other organisms including Gram negative bacilli (especially *Pseudomonas*) and aspergillosis can present in a similiar manner to *Mucor*[8]. Definitive diagnosis of mucormycosis relies on histological and microbiological examination of biopsy (usually nasal or paranasal sinus mucosa) or post-mortem specimens. The diagnostic finding is invasion through vessel walls by broad, non-septate fungal hyphae[2]. Cultures of swabs, CSF and biopsy material are often negative[12].

Rhinocerebral mucormycosis was previously almost uniformly rapidly fatal[5]. However, over the last 20 years the prognosis has markedly improved with reported survival rates of up to 89%[3,13]. This has resulted both from earlier diagnosis and from aggressive treatment with stabilization of blood glucose, intravenous anti-fungal agents and surgical resection[3]. Aggressive surgical clearance of as much infected and necrotic tissue as possible (usually including eye enucleation when there is orbital involvement as in Case 2) is probably the most important aspect of management[8]. Antifungals used alone, as in Case 1, are usually insufficient. Amphotericin B commencing at a daily dose of 1-1.5 mg/kg is the only antifungal agent with proven efficacy *in vivo*[8], although there is little agreement about the required total dose required with reports varying from 2 to 4 grams[1,9]. Unfortunately patients with advanced disease at the time of commencement of treatment, as in our 2 cases, still have a very poor prognosis[6] and therefore early diagnosis is critical.

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PRIMARY CEREBRAL ABSCESS DUE TO *NOCARDIA ASTEROIDES* PRESENTING AS STROKE

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SUMMARY

Nocardial cerebral abscess, an uncommon condition, is usually secondary to a septic focus elsewhere in the body. We report a 44-year-old Chinese male patient who had primary nocardial cerebral abscesses due to *Nocardia asteroides* which presented with stroke-like episodes. He improved spontaneously between these episodes. The diagnosis was reached only after a contrast CT brain study and microbiological examination of specimens obtained during craniotomy. An early contrast CT study is important in avoiding any delay in diagnosis and treatment of this serious condition.

Nocardial cerebral abscess accounts for 1% of brain abscesses[1,2]. It is an uncommon but serious infection, with a case fatality rate of 80%[3]. Early diagnosis and vigorous treatment may improve the outcome. It usually occurs in immuno-compromised patients who have an extracranial primary focus of infection, for example, in the lung as an indolent pulmonary infection[4]. In contrast, primary nocardial cerebral abscess is uncommon[5]. The clinical presentation of nocardial cerebral abscess is subacute and progressive, with the symptoms and signs of an expanding intracranial mass[2]. We report here a case of primary nocardial cerebral abscess with an unusual presentation.

CASE HISTORY

A 44-year-old Chinese man had been followed up regularly by both a haematologist and a neurologist for 8 years because of secondary polycythaemia and 2 episodes of lacunar stroke. He had consumed 40 cigarettes and 10 pints of beer every day for 20 years. The secondary polycythaemia was treated by regular venesections. Three years before, his haemoglobin levels became stabilized at around 15 gm% without active treatment. Within

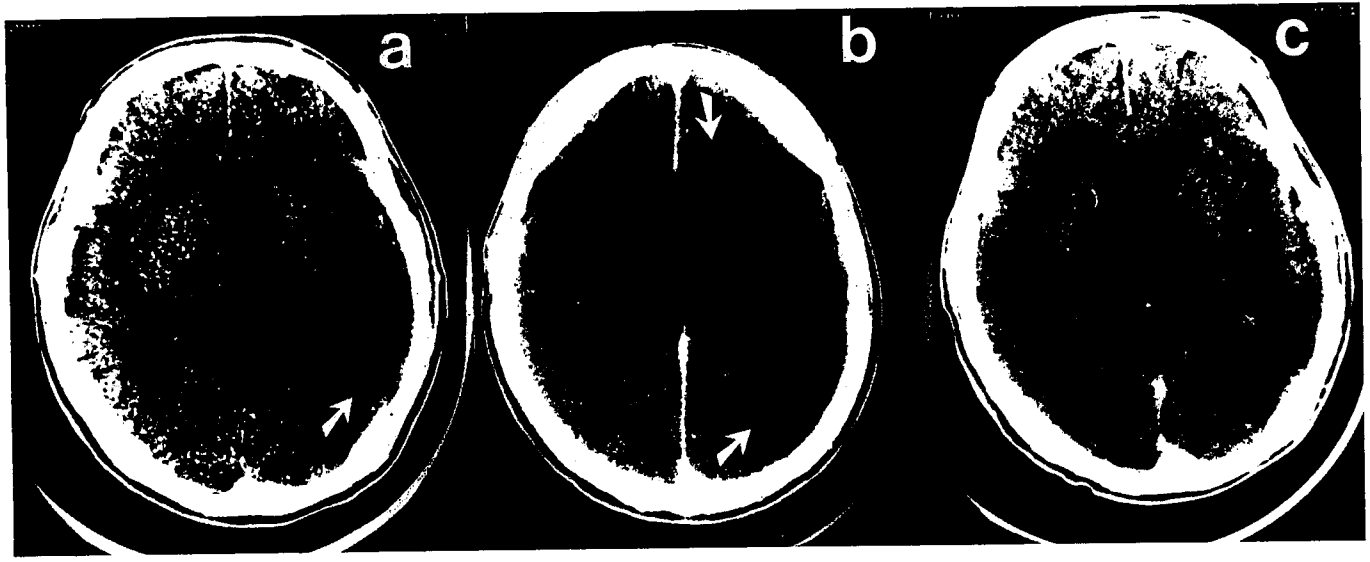

Fig 1 (a) Plain CT of brain. The arrow points to a hypodense lesion in the left temporal lobe.
(b) Contrast CT of brain. The arrow points to two ring enhancing lesions with surrounding oedema in the left hemisphere; there is also oedema in the right posterior region.
(c) Contrast CT of brain one month later. There is marked reduction in the size of the abscesses and in the amount of oedema.

the past year, he had been admitted because of acute upper gastrointestinal bleeding. The bleeding was severe and his haemoglobin level dropped to 7.7 gm%. Upper endoscopy revealed a bleeding chronic gastric ulcer. He was given appropriate treatment and discharged. One month later, he had 2 generalized seizures with loss of consciousness. Physical examination revealed retrograde amnesia. He was afebrile. Computed tomography (CT) of the brain showed a hypodense area in the left posterior temporal region (Fig 1a). Electroencephalography was normal. The diagnosis of recurrent cerebral infarction complicated by secondary seizures was made. One week later, he had developed another generalized seizure followed by global dysphasia. Repeat CT of the brain showed identical findings. He was investigated for preventable causes of ischemic stroke and prescribed phenytoin and ticlopidine. His speech improved dramatically with speech therapy. A contrast CT brain study was arranged but the appointment was still pending when, 2 weeks later, he deteriorated acutely after a further generalized seizure.

Examination revealed a dense right hemiplegia and worsening global dysphasia. An urgent contrast CT brain study showed a lesion with ring enhancement and surrounding oedema in the left temporoparietal region, and a similar lesion within the oedematous left frontal region (Fig 1b); there was another lesion in the right posterior parietal region in higher cuts. He became febrile with neck stiffness and a positive Kernig's sign. He was treated for multifocal pyogenic cerebral abscesses with cefotaxime, soluble penicillin and metronidazole. Two craniotomies were performed with aspiration of pus from and instillation of amikacin into the abscesses. Smear and culture of pus and the abscess wall identified *Nocardia asteroides*. The antibiotic regimen was therefore changed to intravenous cotrimoxazole 1.44 gm every 6 hours. Later intravenous ciprofloxacin, 200 mg every 12 hours was added. Serial CT of the brain showed definite improvement (Fig 1c). However, his right hemiplegia and global dysphasia persisted.

Human immunodeficiency virus serology was repeatedly negative and there was no laboratory evidence of impaired cellular immunity. His B-lymphocyte count and immunoglobulin levels were abnormally low. These findings suggested common variable immunodeficiency. Intravenous immunoglobulin G was therefore added to the treatment regimen. On review of his record, contrast CT of brain provided the first suggestion of an infection and the serial chest X-ray examinations were normal.

DISCUSSION

Our patient's presentation was unusual because initially it resembled that of recurrent ischemic stroke on a background of alcoholism, smoking, polycythaemia and previous strokes. Seizures as a complication are not uncommon in acute stroke, occurring in 11% of stroke patients with no previous history of seizures[6]. About 1/3rd occur within the first 2 weeks, 90% of these within the first day[7]. In acute ischemic stroke, we avoided contrast CT brain studies because contrast injection may increase the cerebral oedema and cause a systemic reaction. Later in the

patient's management, we ordered a contrast CT brain study because of the atypical features comprising repeated stroke-like episodes and recurrent seizures within a short period. However, our CT service could not provide an early appointment. It is important to carry out an early contrast CT of the brain in stroke patients with atypical presentations. Retrospectively, the stroke-like episodes in the patient were most likely to have been the result of cerebritis. The initial spontaneous improvement in the dysphasia, however, was more suggestive of stroke than cerebral abscess. Absence of an extracranial focus of infection precluded the possibility of microbiological examination of clinical specimens other than pus from the cerebral abscess. The patient's subsequent deterioration was acute, suggesting pyogenic cerebral abscess with meningitis. Microbiological examination of specimens obtained during the craniotomies provided the true diagnosis. The finding of common variable immunodeficiency was probably an incidental one because cellular immunity is regarded as important in nocardiosis[3,8,9].

Nocardial organisms are obligatory aerobic, gram-positive, acid-fast, filamentous bacteria[8]. They exist in soil as saprophytes and were first recognized as pathogens in cattle by M.E. Nocard in 1888. Nocardiosis affects immuno-compromised and immunocompetent patients, *Nocardia asteroides* being the most frequently implicated species[5]. It is an opportunistic infection in about 2/3rd of the cases. The underlying conditions include malignancies such as lymphoma and leukaemia, chronic pulmonary disease, acquired immunodeficiency syndrome, use of immunosuppressants or corticosteroids, and other causes of cellular immunodeficiency[8,9,10]. In 1890, Eppinger described the first case of nocardial cerebral abscess in man. This was an invariably fatal condition until Krueger and colleague reported the first survivor in 1954[11]. The lung was the primary site of nocardial infection in 75% of the reported patients[9]. One-quarter of the patients had central nervous system (CNS) involvement but cerebral abscess has usually been secondary to a primary focus elsewhere. In 7% of patients, cerebral abscess is the primary infection; nocardial meningitis *per se* is rare[5,12]. Other sites affected include bone, joint, heart valve, muscle, lymph node, thyroid gland, adrenal gland, prostate and skin[8]. In an immunocompromised patient with symptoms and signs of an expanding intracranial mass, nocardial cerebral abscess should be considered. If there are pulmonary or cutaneous lesions, these extracranial sites are accessible for collection of specimens. However, gram staining alone may not be diagnostic and culture may take up to 4 weeks to produce results so that the microbiology laboratory must be informed of the possibility of nocardial infection[8,9]. For primary nocardial cerebral abscess, a delay in diagnosis is common. A high index of suspicion, an appropriate neuro-imaging study, early neurosurgical intervention and careful microbiological examination carried out on collected specimens are essential to achieve an early diagnosis. The cerebrospinal fluid may be normal or

may show a neutrophil pleocytosis, a low glucose, and an elevated protein level; gram stains of the CSF are invariably negative[12]. Culture of CSF, showing some or all of the aforementioned abnormalities, may be positive in up to 75% of cases but culture takes 3 weeks or more to produce results[8,12]. Therefore early neurosurgical intervention is important to obtain specimens and to decompress the abscess.

Krone and colleagues suggested factors that may affect the prognosis of patients with nocardial cerebral abscess[3]. Favourable factors include the absence of systemic disorder, a single lesion, an early diagnosis, the use of antinocardial chemotherapy, and early surgical evacuation. Poor prognostic factors include the presence of underlying predisposing conditions, the presence of multiple lesions, a delay in diagnosis, the use of nonspecific antibiotics, and the presence of inoperable abscesses. Cotrimoxazole, ciprofloxacin, combination of tienam and amikacin, cefotaxime, 'Augmentin' and minocycline are effective antinocardial drugs[3,8]. The consensus is to operate early if surgery is needed and to use a combination of 2 antinocardial agents for a prolonged period of up to one year for immunocompetent patients with disseminated or CNS infection[8]. The optimal duration of treatment for immunocompromised patients is uncertain: some authors have advocated long term maintenance therapy[9].

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ALZHEIMER'S DISEASE AND ALZHEIMER-TYPE OF CEREBRAL DEGENERATIONS IN CHINESE

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SUMMARY

The incidence of Alzheimer's disease has been suggested to be low in Chinese but there have been few histological studies of the disease and of Alzheimer-related changes in Chinese. In this study, brains from 8 cases of Alzheimer's disease and 27 non-demented elderly Chinese individuals were examined comprehensively. Dementia was excluded in the latter by careful retrospective interviews with relatives. Histological sections were taken from standardised areas and quantitative analysis of neuritic plaques, neurofibrillary tangles and diffuse plaques was carried out with 3 histological methods: microwave modification of Bielschowsky, Bodian and βA4 protein immunostaining. There were conspicuous differences in the amounts of neurofibrillary tangles and neuritic plaques seen between the demented and non-demented groups. In the latter, the amount of Alzheimer-related changes appeared to be much smaller than in corresponding studies among Western populations. Diffuse plaques were not found to be a good histological marker for dementia.

Alzheimer's disease (AD) is the leading cause of dementia among the elderly in Western countries, where the prevalence of severe dementia attributable to AD is estimated at 1 to 6% of the general population over the age of 65 years.[1-3] The incidence of AD is often thought to be low in Hong Kong,[4-5] but there have been no definitive clinical or pathological studies. In China, the disease obviously exists and there have been a few epidemiological surveys[6-8]. The prevalence of dementia in the general Chinese population appears lower than that in the West.[8] In the English literature, there has been no description of the pathological changes of Alzheimer's disease in persons of Chinese origin. We previously looked at Alzheimer-type cortical degenerations in normal autopsy brains in Hong Kong, 97% of the population of which is Chinese.[9] However, the techniques employed, Congo-red and Bodian stains will be regarded as somewhat inadequate as there

Table 1 Interview questionnaire for relatives

AUTOPSY No. _____ SEX: F / M Age: _____

1. Impaired Memory:
   - People Y / N
   - Place Y / N
   - Domestic Affairs Y / N
   - Other _____ Y / N

2. Disorientation in Date / Time / Space ? Y / N

3. Poor Physical State:
   - Self-Care
   - Continence
     - Urine Y / N
     - Bowel Y / N
   - Mobile: Unaided / with aid / Immobile

4. Abnormal Behaviour:
   - Emotional Lability
   - Aggression
   - Depression
   - Wanderings
   - Others: _____

5. PMH :
   - Cerebrovascular Disease
   - Hypertension
   - IHD
   - Heart Failure

Frequency of occurrence Grade
1 = occasionally
2 = Frequently
3 = Most of the time

Reliability of History
Person giving history:
- Lives with patient
- Sees him / her often
- Only see patient very occasionally
- Intelligent / Average / Dull
- Cooperative / Uncooperative

Assessment: Dementia is probably Present / Suspicious / Absent

Discard because of dubious history
Other illness _____

have been recent advances in the histological techniques used in the examination of Alzheimer's brains. Also, cases of Alzheimer's disease were not included in this previous study and the number of areas of the brain examined was small.

In the present study, we report the morphological changes of 8 cases of Alzheimer's disease in Chinese. We also examined the brains of 27 non-demented elderly Chinese individuals from unselected autopsies, seeking similar changes. In addition to neuritic plaques and neurofibrillary tangles, we studied the prevalence of diffuse plaques in these groups. Histological methods and methodologies closely similar to those proposed for use in standardised protocols in the West were employed.[10-12]

MATERIALS AND METHODS

Eight cases of Alzheimer's disease were analyzed from our autopsy and consultation files. Their demographic details were: Case 1 F/77 years, Case 2 F/78 years, Case 3 F/76 years, Case 4 F/74 years, Case 5 F/77 years, Case 6 F/84 years, Case 7 M/67 years, Case 8 F/84 years. All died of non-neurological causes except patient 7 who died of a lobar haemorrhage due to congophilic angiopathy. There was a pre-morbid history of dementia of various severities in all cases. In addition, a group of non-demented elderly patients from non-selected consecutive autopsies was examined. In order to minimise the risk that cases of subclinical dementia might have been included, the case records were scrutinised carefully for the absence of signs and symptoms of dementing illnesses, and close relatives of these patients were interviewed when they came to collect the bodies. A questionnaire was structured which was modified from the methods of Blessed *et al*[13] (Table 1). Information was obtained from relatives in continuous contact with the patients. Enquiries were made into the mental status of the patients, including their memory, orientation, pattern of daily living, past history of strokes, physical state and personality. The data were not scored as only cases which were clearly devoid of signs and symptoms of dementia were included. Cases where the source of information was unclear or the history suggested mental deterioration were excluded. Of these 27 cases, there were 12 men and 15 women. Their ages ranged from 60 to 93 years (average 73 years). None had died of neurological disease.

At brain cutting after 2 weeks of fixation in 20% formalin, blocks of the following areas were taken from all cases from the left side: entorhinal cortex, superior temporal gyrus, inferior parietal lobule, middle frontal gyrus, amygdaloid body and the medial occipital lobe, according to the recommendations of Mirra[12] and Braak and Braak[14]. The following histological techniques were performed for every block: Bodian, microwave modification of Bielschowsky[15] and βA4 protein

immunostaining (Boehringer, 1/30). For immunostaining, the avidin-biotin-peroxidase complex (ABC) method was used on formalin-fixed paraffin-embedded material pretreated with 90% formic acid.[16] All sections were initially scanned for the areas of the cortex which contained the highest density of degenerative changes. Afterwards, quantitation of the degenerative changes was conducted over the same areas in different preparations by counting at x200 magnification over 10 fields of 500 x 500 μm with an eyepiece graticle. Sections processed by all 3 methods were counted for neurofibrillary tangles, neuritic plaques and diffuse plaques. For both types of plaques, only positively labelled plaques measuring more than 30 μm were counted. For tangles, the counting included ghost neurons but not dystrophic neurites. The highest scores for any preparation were recorded. The presence of vascular amyloid was noted but not quantified. The results were expressed per mm^2 to conform to the methodology described by Khachaturian.[10]

RESULTS

The results of quantitation of neuritic plaques, neurofibrillary tangles and diffuse plaques in Alzheimer's disease patients as well as non-demented people are shown (Tables 2-7). The quantities of neuritic plaques and neurofibrillary tangles seen in AD patients far exceeded those observed in non-demented individuals. In AD patients, the quantities of neuritic plaques exceeded the recommended minimal criteria[10-12]. The quantities of neurofibrillary tangles were also generally consistent with the diagnostic criteria.[12] All cases had neuritic plaques and tangles in some sites in the cerebral cortex. However, the distribution of neurofibrillary tangles seemed more scattered and patchy than that of neuritic plaques and there were several sites with no or only small numbers of tangles. As regards non-demented individuals, 7 cases (25%) possessed neuritic plaques and 13 (48%) contained some tangles.

All except 2 cases (Cases 1 and 8) of Alzheimer's disease exhibited amyloid deposits in blood vessels, in the usual distribution in the superficial and cortical small vessels over the parietal and occipital lobes. None of the non-demented cases showed βA4 staining of the blood vessels.

In general, we have found that the Bielschowsky technique was more sensitive in detecting diffuse plaques while βA4 protein immunostaining demonstrated more neuritic plaques. The Bodian method showed more tangles than the Bielschowsky, and they were not demonstrated by βA4 protein immunostaining in this series.[17] Although quantitative comparison between the different stains has not been carried out in this study, the findings are generally similar to the results of other authors[11,12,18].

Table 2 Distribution of neuritic plaques in Chinese Alzheimer's disease patients (per mm²). (Figures in brackets: standard errors of mean)

Case	Entorhinal cortex	Temporal lobe	Amygdaloid body	Frontal lobe	Occipital lobe	Parietal lobe	Average
1	18.6	70.4	40	48	50	36	43.8
2	20.4	19.6	9.6	14	19.6	14	16.2
3	24.8	20.8	18.8	23.2	48	.. 14.4	25
4	14.4	23.6	19.2	23.2	22.8	20.8	20.7
5	23.2	21.6	34	31.6	16.4	36.8	27.3
6	12.4	18.8	10.4	1.2	2.4	0	7.5
7	18.4	14.4	8.8	15.2	11.6	14.4	13.8
8	21.2	20	8.8	14.8	9.6	11.2	14.3
Mean	19.2 (1.5)	26.2 (6.4)	18.7 (4.3)	21.4 (4.9)	22.6 (6.2)	18.5 (4.4)	21.1 (4.0)

DISCUSSION

Neuritic plaques and neurofibrillary tangles are the histological hallmarks of Alzheimer's disease.[19] Although minimal histological criteria for the diagnosis of Alzheimer's disease have been agreed upon,[10-12] problems with these morphological criteria persist.[19] As can be seen from Table 1, for Alzheimer's disease in persons of Chinese origin, the overall average of the neuritic plaque counts in different areas of the brain was 21 per mm². Together with a clinical history of dementia, this is in keeping with the consensus criteria for the diagnosis of Alzheimer's disease[10-12]. However, there was some variation in the distribution of these lesions, with occasional histological sections containing much smaller numbers of neuritic plaques. As regards neurofibrillary tangles, there was more controversy and the consensus criteria were less clearcut[10-12] as cases of Alzheimer's disease, especially those in the elderly, are known in which there have been only few or no tangles in the neocortex[15,19,20,21,22]. This is also reflected in Cases 5 and 6 in the series, where tangles were not as numerous as in the other cases.

As regards patients who were not demented, less than half the brains contained neuritic plaques and neurofibrillary tangles. The number of abnormalities was small: there was an overall average of 1 neuritic plaque and 1

Table 3 Distribution of neuritic plaques in non-demented Chinese patients (per mm^2. (Figures in brackets: standard errors of mean)

Cases	Entorhinal cortex	Temporal lobe	Amygdaloid body	Frontal lobe	Occipital lobe	Parietal lobe	Average
9	0	0	0	0	0	0	0
10	0	0	0	0	0	0	0
11	0	0	0	0	0	0	0
12	0	0	0	0	0	0	0
13	0	0.8	0	0	0	0.4	0.2
14	0	0	0	0	0	0	0
15	4	0.4	0.8	0	1.2	0	1.1
16	0	0	0	0	0	0	0
17	0	0	0	0	0	0	0
18	0	0.4	0	0	0	0.8	0.2
19	0	0	0	0	0	0	0
20	0	0	0	0	0	0	0
21	0	0	0	0	0	0	0
22	0	0	0	0	0	0	0
23	0	0	0	0	0	0	0
24	0	0	0	0	0	0	0
25	0	0	0	0	0	0	0
26	1.6	0	0.8	0	2	0	0.7
27	0	0	0	0	0	0	0
28	4.8	0	0	0	0	0	0.8
29	19.2	6.8	8	26.6	10	18.4	14.8
30	0	0	0	0	0	0	0
31	4	6.8	4.8	18	8.8	18.4	10.1
32	0	0	0	0	0	0	0
33	0	0	0	0	0	0	0
34	0	0	0	0	0	0	0
35	0	0	0	0	0	0	0
Mean	1.2 (0.7)	0.6 (0.3)	0.5 (0.3)	1.7 (1.2)	0.8 (0.5)	1.4 (0.9)	1.0 (0.6)

Table 4 Distribution of neurofibrillary tangles in Chinese Alzheimer's disease patients (per mm^2). (Figures in brackets: standard errors of mean)

Case	Entorhinal cortex	Temporal lobe	Amygdaloid body	Frontal lobe	Occipital lobe	Parietal lobe	Average
1	52	29.6	56	68.8	50.4	44.8	50.3
2	33.6	8	27.6	16.8	12	11.2	18.2
3	25.6	1.6	15.6	2.4	6.4	8	9.9
4	28	11.8	12.8	0	6	4.8	10.1
5	9.2	1.2	1.2	0	2	2.8	2.7
6	18	2.4	5.6	0	0	2.4	4.7
7	15.6	14.4	13.6	10.8	10.4	11.6	12.7
8	21.2	20	8.8	14.8	9.6	11.2	14.3
Mean	25.4 (4.7)	11.1 (3.6)	17.7 (6.1)	14.2 (8.2)	12.1 (5.7)	12.1 (4.9)	15.4 (5.3)

neurofibrillary tangle per mm^2. It is well known that tangles and plaques are found in the cerebral cortex with normal ageing. It is believed that by the 7th decade 50% to 70% of people show some tangles and plaques[18,23,24,25]. There have been many studies of the normal elderly brain in Western populations. Table 8 lists selectively those studies which employed methodologies similar to ours. Although variation in methodology does not allow precise statistical comparisons and there was a wide spectrum in those studies, it appears that the incidence of neuritic plaques and tangles is less among elderly Chinese patients than in Westerners, and when these lesions are present, their numbers are smaller. Moreover, the techniques employed in this study are probably more sensitive than some of the older histological methods employed in previous investigations. It is noteworthy that another group from Hong Kong working on surgically evacuated cerebral haematomas has shown that the incidence of congophilic angiopathy, a condition closely associated with Alzheimer's type changes in the brain, was only 8.5%, much lower than the corresponding figures obtained in the West[26]. Unfortunately, neither histological or psychiatric examination of these cases was performed. The finding of this study, that there is a lower incidence of Alzheimer's type changes than in the West, is consistent with results of the previous investigation.

In this study, there were occasional instances of non-demented persons where the plaque or tangle counts were high (Cases 9 and 29). However, it is well

Table 5 Distribution of neurofibrillary tangles in non-demented Chinese patients (per mm²). (Figures in brackets: standard errors of mean)

Case	Entorhinal cortex	Temporal lobe	Amygdaloid body	Frontal lobe	Occipital lobe	Parietal lobe	Average
9	16.8	11.2	3.2	0	0	0	5.2
10	0	0	0	0	0	0	0
11	0	0	0	0	0	0	0
12	0	0	0	0	0	0	0
13	0.4	0	0	0	0.4	0	0.1
14	0	0	0	0	0	0	0
15	0.8	0.8	0	0	0	0	0.3
16	0	0	0	0	0	0	0
17	0	0	0	0	0	0	0
18	0	0.8	2.4	0	0	0	0.54
19	0	0	0	0	0	0	0
20	0.8	0	0	0	0	0	0.1
21	0	0	0	0	0	0	0
22	0	0	0	0	0	0	0
23	1.6	0	0	0	0	0	0.3
24	0	0	0	0	0	0	0
25	0	0	0	0	0	0	0
26	7.2	6.4	0.8	2	0	0	2.7
27	0.8	0.8	0	0.8	0	0	0.4
28	1.6	5.2	3.2	0	0	0	1.7
29	23.6	4.8	20.8	0	4.8	0	9
30	0	0	0	0	0	0	0
31	15.6	2.4	0	0	0	0	3
32	2	1.2	0	0	0	0	0.5
33	0	0	0	0	0	0	0
34	7.2	8.8	0	0	0	0	2.7
35	0	0	0	0	0	0	0
Mean	2.9 (1.2)	1.6 (0.6)	1.1 (0.8)	0.1 (0.1)	0.2 (0.2)	0 (0)	1.0 (0.4)

Table 6 Distribution of diffuse plaques in Chinese Alzheimer's disease patients (per mm²). (Figures in brackets: standard errors of mean)

Case	Entorhinal cortex	Temporal lobe	Amygdaloid body	Frontal lobe	Occipital lobe	Parietal lobe	Average
1	0	12	0.8	5.6	1.6	2.4	3.7
2	2	1.6	1.6	0	0	0	0.9
3	2.4	4.8	2	2	12	9.6	2.7
4	7.2	6	0	11.2	0	15.2	6.6
5	6.8	0	0	0	0	0	1.1
6	1.6	2	1.6	1.2	2.4	0	1.5
7	2.8	4	1.6	0.8	2	3.2	2.4
8	1.6	0	0.8	0.4	2	4.8	1.6
Mean	3.0 (0.9)	3.8 (1.4)	1.1 (0.3)	2.7 (1.4)	2.5 (1.4)	4.4 (1.9)	2.6 (0.7)

documented among Western populations that there are cases of mentally normal individuals with plaque and tangle counts which are normally found in Alzheimer's disease[19,27-30]. Whether these represent subclinical cases of Alzheimer's disease which might have evolved into full-blown dementia had the patients not died earlier of other causes remains to be determined. In this series, this possibility has been reduced by careful retrospective interview with close relatives, confirming the absence of dementia at the time of death.

Notwithstanding the relative rarity of neuritic plaques and neurofibrillary tangles, diffuse plaques were not uncommonly encountered in the non-demented group. Diffuse plaques are focal deposits of βA4 protein or argyrophylic materials which lack both a dense core and dystrophic neurites. They are found in patients with Alzheimer's disease as well as in non-demented individuals and their significance relative to the mature, neuritic plaques remains uncertain[19,31-33]. There is at present no convincing evidence that these diffuse plaques actually transform to the neuritic plaques and their presence may be regarded as a consequence of pathological ageing[19,31-33]. The findings of this study are certainly in keeping with this concept: such plaques were found in both Alzheimer's disease and in non-demented elderly individuals and there was no significant difference in their numbers between the two groups.

Table 7 Distribution of diffuse plaques in non-demented Chinese patients (per mm²). (Figures in brackets: standard errors of mean)

Case	Entorhinal cortex	Temporal lobe	Amygdaloid body	Frontal lobe	Occipital lobe	Parietal lobe	Average
9	0	0	0	0	6	0	1
10	0	2	0	0	0	0	0.3
11	0	0	0	0	0	0	0
12	0	0	0	0	0	0	0
13	8.8	14	0	10.4	0.4	6.8	6.7
14	0	0	0	0	0	0	0
15	0	6.8	1.6	8	0	0	2.7
16	0	0	0	0.4	0	0	0.1
17	0	0	0	6	1.2	2.4	1.6
18	0	10	0	6.4	7.2	3.6	4.5
19	0	0	0	0	0	0	0
20	0	0	7.2	0	0	0	1.2
21	7.2	0	0	0	0	0	1.2
22	0	8.8	0	0	0	0	1.5
23	1	0	0	0	0	0	0.2
24	2.4	6	0.8	0	0	0	1.5
25	23.2	29.2	26.4	22.4	24	20.8	24.3
26	2.4	2.4	4.8	8	10	0	4.6
27	1.6	0.8	1.6	6.4	4	8.8	3.9
28	0.8	1.6	2	3.2	0	1.6	1.5
29	2.4	10	1.6	6.8	3.2	12	6
30	0	4.4	0	0	0	0	0.7
31	10	10.8	2.8	16	6.4	4.4	8.4
32	8.4	7.2	2	1.6	3.2	2.8	4.2
33	0	0	0	0	0	0	0
34	16.8	8.4	6	0	0	0	5.2
35	0	0	0	0	0	0	0
Mean	3.1 (1.1)	4.5 (1.3)	2.1 (1.0)	3.5 (1.1)	2.4 (1.0)	2.3 (0.9)	3.0 (0.9)

Table 8 Comparison of Alzheimer-type changes in non-demented elderly Caucasians and Chinese

Author	Cases examined	% with tangles	% with NP	Average tangle score*	Average plaque score*
Tomlinson *et al* (1968)[35]	28	61%	79%	NA	3.3
Tomlinson (1972)[29]	28	54%	79&	NA	5 (median)
Tomlinson & Henderson (1976)[36]	28	58%	79%	NA	1-5 (median)
Ulrich *et al* (1982)[37]	100	75%	-	NA	-
Mann *et al* (1987)[24]	22	73%	64%	3.6	5.9
Lamy *et al* (1988)[18]	15	100%	93%	19.13	15.91
Mann *et al* (1990)[28]	20	100%	90%	-	2.11
Arriagada *et al* (1992)[38]	21	100%	52%	2.2	0.35
Giannakopoulas *et al* (1993)[39]	24	100%	83%	17.2	4.0
This series	27	48%	26%	1.0	1.0

* Averages are mean scores per mm^2 unless otherwise stated; it is uncertain if all 3 series authored by Tomlinson refer to the same cases; NA: not applicable; NP: neuritic plaques. Only patients over the age of 60 are included in this Table.

There has been little information on the effects of racial difference on the incidences of Alzheimer's disease or Alzheimer-related changes in different ageing populations. The incidence of dementing illness in the elderly Chinese population has been estimated as between 0.46% and 4.6%, which is lower than corresponding estimates in the West, although the actual incidence still remains somewhat controversial.[8] Interestingly, the incidence of such changes among Japanese appear to be similar to that in the West[23,34]. This study showed that the incidence of Alzheimer-related changes in the ageing brain may be low in Hong Kong Chinese. Hopefully, our results will be confirmed by larger and more exhaustive studies. However, the pathological changes in cases of Alzheimer's disease in this Chinese population appear similar to those of the West.

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