A case of pandysautonomia with associated sensory ganglionopathy

Since Young et al. described a patient with acute loss of sympathetic and parasympathetic functions in 1969, many similar cases have been reported as being acute idiopathic autonomic neuropathy. Apart from acute cholinergic neuropathy, there are four types of acute idiopathic autonomic neuropathy, classified according to somatic nerve involvement: acute pandysautonomia, which has minimal or no motor or sensory dysfunction; acute autonomic sensory and motor neuropathy, involving both autonomic sensory neuropathy and severe motor and sensory impairment. Despite minimal or no sensory disturbance, reduction of myelinated fibres in biopsied sural nerve has been found in several cases with acute pandysautonomia. However, the exact site of pathological involvement in the sensory system remains unknown, because postmortem examinations have seldom been performed. We report a case of acute pandysautonomia with no evidence of significant somatic nerve involvement, accompanied by dorsal root ganglionopathy shown by postmortem examinations.

An 18 year old male student experienced low grade fever, vomiting, and tingling pain in the limbs on 26 February 1987. Orthostatic syncopy occurred three times on the next day. Difficulty in emptying the bladder, alternating diarrhoea and constipation, and lack of sweating over the whole body developed rapidly. He was admitted to the Third Department of Internal Medicine, Medical College of Oita on 24 April 1987. On physical examination, he weighed 46 kg, with a recent weight loss of 14 kg. Blood pressure was 108/78 mm Hg in the supine position and 90/58 when standing. Defective sweating, urinary bladder symptoms, and impotence. No sensory symptoms and signs were found. Nerve conduction studies were normal. The leg fractures were difficult to heal, and he underwent orthopaedic surgery several times. Although nerve conduction studies again disclosed no abnormality, he developed severe pneumonia and died of respiratory failure at the age of 25 in 1994.

On necropsy 10 hours after death, the brain weighed 1440 g, and no tumour was found in any part. The most prominent finding was located in the lumbar (L5) dorsal root ganglia. There was a marked reduction in the number of ganglionocytes, whereas clusters of satellite cells were easily seen (figure A). The dorsal columns of the spinal cord showed a loss of myelinated fibres (figure B). No other detectable changes were present in the CNS including the brainstem, the intermediolateral nucleus of the thoracic spinal cord, and Onuf's nucleus. The celiac ganglia showed no abnormalities, but the sympathetic trunk was not examined. Lymphocytic infiltrates with perivascular distribution were not found anywhere in the nervous system. Electron microscopic examinations of the left distal sural nerve showed profound changes with a remarkable reduction in both myelinated and unmyelinated fibres, which decreased to 12%, and 4500/mm²/unit respectively. The size/frequency histogram of myelinated fibres showed a reduction in both large and small fibres. The histogram of axons devoid of myelin showed a monomodal curve with a peak situated at about 1.2 μm. Numerous budded Schwann cell bands were found (figure C), often associated with cells surrounded by additional layers of basement membrane. Myelin sheath irregularities were occasionally encountered. Regenerative alterations such as growth cones, clusters of small myelinated axons, and onion bulb formations were rarely seen.

The patient rapidly developed severe autonomic failure with only mild sensory nerve involvement manifested by dysesthesia and hypalgesia. Orthostatic hypotension and diminished sweating indicated sympathetic failure. Parasympathetic failure was assumed from alternating diarrhoea and constipation, myelin ovoids in teased fibres. The hand grip test and the cold pressure test showed no rise in blood pressure. There was no overshoot in the Valsalva manoeuvre. Serum noradrenaline concentration decreased to 110 pg/ml (normal 145–575 pg/ml) at rest, and failed to respond to tilting. A noradrenaline infusion test (0.01–0.04 μg/kg/min) showed an excessive increase in blood pressure, from 90/58 to 120/78 mm Hg. The R-R interval variation was 4.55% at rest (normal 3%–6%). During ocular pressure test the patient had a normal bradycardic response. The instillation of 1.25% adrenaline into the conjunctival sac of the eye produced 37.5% dilatation of the pupil (normal <25%). Five per cent cocaine and 5% tyramine produced 12.5% and 28.6% dilatation respectively (normal; >30%). Addition of 2.5% methacholine resulted in a 12.5% reduction in pupillary size (normal <25%). Sympathetic skin responses were not evoked. Amezinium methylsulphonate, an indirect sympathomimetic agent, was effective on orthostatic hypotension and coughing attacks. In April 1992, the patient fractured both legs in a traffic accident and was admitted to the Department of Orthopedics in Hiroshima University Hospital. On admission, he still complained of dizziness on standing, defective sweating, urinary bladder symptoms, and impotence. No sensory symptoms and signs were found. Nerve conduction studies were normal. The leg fractures were difficult to heal, and he underwent orthopaedic surgery several times. Although nerve conduction studies again disclosed no abnormality, he developed severe pneumonia and died of respiratory failure at the age of 25 in 1994.
of acute idiopathic autonomic neuropathy have been verified by necropsy.3 Fagius et al. and Tohgi et al. found a marked loss of myelinated nerve fibres in the dorsal column, dorsal root, and peripheral nerve. Disappearance of nerve cell bodies replaced by clusters of satellite cells in the dorsal root ganglia was found in the patient of Fagius et al. Stoll et al. also found symmetric degeneration of the dorsal columns with severe ganglionitis of both the sensory and autonomic ganglia. However, their patients showed a marked sensory disturbance with no evoked sensory nerve action potentials, as well as motor nerve involvement of a greater or lesser degree. Therefore, these cases could be classified as acute autonomic and sensory neuropathy or acute autonomic and sensory and motor neuropathy. Also, the patient of Fagius et al. had an associated malignant tumour in the testis that recurred during the course of pan-dysautonomia. Neuropathological examination disclosed CNS involvement manifested by degeneration in the preganglionic autonomic nervous system in the case of Tohgi et al. and a mild chronic encephalopathy with perivascular lymphocytic infiltrates in the patient of Stoll et al. The present case could be the first that showed sensory ganglionopathy associated with acute pandysautonomia.

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menstrual bleeding is a sudden fall in circulating levels of progesterone and oestra-
diol. Both sex steroids have numerous regulatory effects on the immune system,
including an influence on T cell populations, and the production of cytokines.

Inflammatory cytokines, or so called Th1 cytokines, such as INF-γ, tumour necrosis factor-α (TNF-α), and interleukins 1 and 2 (IL-1 and IL-2), seem to play a key part in the generation of exacerbations in multiple sclerosis. Pathways through which sex ster-
oids influence the immune system are complex and incompletely understood. Oes-
trogens may inhibit the release of Th1 cytokines, such as IL-1 and TNF-α, whereas progesterone may enhance the release of Th2 cytokines, which inhibit the production and activity of the Th1 cytokines. Thus the abrupt withdrawal of progesterone and oestradiol in the premenstrual phase may shift the balance in favour of the production of inflammatory Th1 cytokines. Also, other hormones, such as inhibin, may contribute to this effect. The circulating concentration of inhibin, a hormone which decreases FSH-production, also sharply declines just before the menstruation. Changes in concentra-
tions of circulating sex hormones during the menstrual cycle were also found to influence disease activity in other autoimmune diseases, including rheumatoid arthritis, systemic lupus erythematosus, and autoim-
mune thyroid disease.

An important question that needs to be investigated is whether the premenstrual period is an independent risk factor for excava-
tions in the whole female multiple sclerosis population. This should be exam-
ined by a large scale prospective study. Understanding the roles of sex hormones in the immune sys-
tem and cytokine network that may regulate disease activity in multiple sclerosis may pro-
vide clues for the development of new thera-
peutic strategies.

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6 Owens T, Stram S. The immunology of multi-
8 Pacifici R, Eustrogen, cytokines, and pathogen-
9 Pecinari M-P, Giudizi M-G, Biagiotti R, et al. Progestrone favors the development of human T helper 2 cells producing Th2-type cytokines and promotes both IL-4 production and mem-

CORRESPONDENCE

Autonomic effects of selegiline: possible cardiovascular toxicity in Parkinson’s disease

(1) We read with interest the article by Church-
yard et al showing that selegiline in combina-
tion with levodopa was associated with significant impairment of the normal reflex responses controlling blood pressure to head up tilt and standing. It was suggested by the authors that this could be one explanation of the finding of increased mortality in the com-
bined levodopa/selegiline arm of the Parkin-
son’s Disease Research Group of the United Kingdom trial. We are currently conducting a study investigating the cardiovascular
reflexes in patients recruited from a commu-
nity disease register for Parkinson’s disease, diagnosis being based on identical clinical diagnostic criteria to the reported study. Patients were excluded from the study if they were known to have diseases associated with impaired autonomic function or if they were currently being treated with drugs other than those for Parkinson’s disease. We have identified 27 such patients, five receiving selegiline and levodopa and 22 receiving levodopa. With similar techniques and equip-
ment as the authors we have measured ortho-
static blood pressure at 1 minute, Valsalva ratio, and heart rate on standing (30:15 ratio). Age, sex, duration of disease, Webster scale, and daily levodopa dose did not differ significantly between the group of patients on levodopa alone and on levodopa and se-
gleline combined (table). There was no significant difference in the results of autonomic function testing between the two groups with analysis of variance (ANOVA) and t tests. Both groups of patients showed falls in blood pressure on standing and this did not seem to be associated with the group on levodopa plus selegiline compared with patients on levodopa alone. This finding is surprising given the much lower dose of levodopa prescribed in our study compared with that of Churchyard et al. However, our failure to show significant hypotensive inter-
action between selegiline and levodopa may have resulted from the lower dose of levodopa prescribed in our study. We also have not actually looked at blood pressure changes during 45° head up tilt. As yet we have not been able to retest patients in whom selegiline has been withdrawn to see if any significant changes become apparent, and the sample sizes reported by Churchyard et al and our own study, we think that both sets of results should be interpreted with caution. In elderly patients with Parkinson’s disease even mod-
est doses of levodopa seem to be associated with orthostatic hypotension. It seems un-
likely that the additional hypotensive effect of selegiline could be the sole explanation of the apparent increased mortality with levodopa and selegiline compared with levodopa alone.

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2 Lees AJ, on behalf of the Parkinson’s Disease Research Group of the UK. Comparison of therapeutic effects and mortality data of levodopa and levodopa with se-

(2) We have read with great interest the article by Churchyard et al. that appeared in the Journal. There are several issues that we comment on.

The study design is not scientifically sound: the trial is not randomised, the number of patients in the two groups is unequal, and half of the patients were selected from an earlier study. According to the authors the two groups were matched for age, duration, and severity of the disease, and the dose of levodopa. Due to the study design the patients could not, however, be matched according to the autonomic functions, al-
though there were no significant differences in the occurrence of clinical postural dizzi-
ness. The change in the systolic blood pressure after standing was, however, signifi-
cantly lower in the selegiline group (group II) after the withdrawal than in the group receiv-
ing only levodopa (group I). Also one patient in group I had a clear hypertensive reaction (systolic blood pressure>200 mm Hg) while standing. This suggests that the autonomic function in group II even without selegiline was more compromised than in the group I, thus showing a selection bias.

It is not, however, a new finding that orthostatic hypotension could occur when

Table 1 Mean (SEM) median indices for patients taking levodopa only or levodopa and selegiline

<table>
<thead>
<tr>
<th>Levodopa (n=22)</th>
<th>Selegiline (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (y)</strong></td>
<td>71.7 (1.7) 72</td>
</tr>
<tr>
<td>6.6 (0.9) 5.5</td>
<td>10.4 (1.9) 5.0</td>
</tr>
<tr>
<td><strong>Duration (y)</strong></td>
<td>13.4 (1.4) 15</td>
</tr>
<tr>
<td>10 (1.4) 10</td>
<td>10 (1.4) 10</td>
</tr>
<tr>
<td><strong>Webster scale</strong></td>
<td>12.2 (1.4) 10</td>
</tr>
<tr>
<td>10 (1.4) 10</td>
<td>10 (1.4) 10</td>
</tr>
<tr>
<td><strong>Daily levodopa dose (mg) (mean duration 7 y)</strong></td>
<td>343 (43) 350</td>
</tr>
<tr>
<td>269 (254) 400</td>
<td>269 (254) 400</td>
</tr>
<tr>
<td><strong>Supine systolic BP</strong></td>
<td>158.8 (5.3) 158</td>
</tr>
<tr>
<td>143.6 (7.6) 145</td>
<td></td>
</tr>
<tr>
<td><strong>Standing systolic BP</strong></td>
<td>147.7 (5.9) 143</td>
</tr>
<tr>
<td>133.6 (10.8) 143</td>
<td></td>
</tr>
<tr>
<td><strong>% Change in BP</strong></td>
<td>17.6 (6.1) 8.4</td>
</tr>
<tr>
<td>7.5 (3.1) 6.5</td>
<td></td>
</tr>
<tr>
<td><strong>30:15 Ratio</strong></td>
<td>1.03 (0.01) 0.02</td>
</tr>
<tr>
<td>1.02 (0.02) 1.06</td>
<td></td>
</tr>
<tr>
<td><strong>Valsalva ratio</strong></td>
<td>1.10 (0.03) 1.15</td>
</tr>
<tr>
<td>1.2 (0.01) 1.19</td>
<td></td>
</tr>
</tbody>
</table>
selegiline and levodopa are given together. Orthostatic hypotension is often found in late stage Parkinson's disease due to autonomic disturbances. All dopaminergic drugs such as levodopa or dopamine agonists have been shown to cause orthostatic hypotension. In a recent double blind study Turkka et al. prospectively followed up patients in a double blind study measuring autonomic function with a similar method to Churchyard et al. for several months. They found that with time selegiline was significantly more orthostatic hypotension assessed with the tilt test in the selegiline plus levodopa group than placebo plus levodopa group. However, only two out of 27 patients in the selegiline group fulfilled the criteria of orthostatic hypotension. The mode of action of orthostatic hypotension with dopaminergic drugs is not clear. Selegiline is known to potentiate the therapeutic effect of levodopa but also has adverse effects if the dose of levodopa is not reduced sufficiently. The authors claim that selegiline would impair the noradrenaline and heart rate responses to tilt although no significant changes were detected between the groups. The authors make hasty conclusions that selegiline would be cardiotoxic with no scientific verification. If a drug causes orthostatic hypotension it does not mean that the drug would be cardiotoxic! Furthermore, the authors showed that the clinical condition of the patients deteriorated considerably after withdrawal of selegiline. As the disability was considerably worse after the withdrawal than during selegiline treatment, the effect of adequate dopaminergic medication on cardiovascular responses remains unknown. It is possible that adding a sufficient amount of dopaminergic medication to group II after withdrawal of selegiline would cause similar orthostatic hypotension to that found when selegiline was combined with levodopa. Indeed, Kaufmann et al. analysed patients with Parkinson's disease with orthostatic hypotension and found no significant difference between patients treated with levodopa, dopamine agonist, or the combination of selegiline and levodopa. Finally, the authors suggest that their findings would be related to the metabolites of selegiline. The authors did not take into account the amphetamine metabolites are of levoform. Furthermore, d-methamphetamine or d-amphetamine often cause increases of blood pressure, not hypotension. Similarly, there is a dose proportional increase of blood pressure in rats caused by d-p-hydroxy amphetamine and d-p-hydroxy-norephedrine. The authors imply that selegiline would cause withdrawal effects in humans and refer to an experimental study on rats (cited by Churchyard et al.). The authors also suggest that selegiline loses its selectivity during treatment. A postmortem study showed, however, that there was no increase of monoamine oxidase-A inhibition along with long term selegiline treatment. 

References

The authors' reply:
Heinonen and Myllyla have raised several issues regarding our article which appeared in J Neurol Neurosurg Psychiatry. As they note, the study, which examined autonomic function in those on long term treatment (mean>5 years), was of necessity not randomised. We chose selection bias was minimised by recruitment of all outpatients on levodopa and selegiline or levodopa without selegiline within a given time and regardless of the presence or absence of symptoms suggestive of autonomic dysfunction. That there was no bias towards more severely affected cases being placed on selegiline is strongly suggested by the excellent match between the two groups for age, duration and severity of disease, and the dose of levodopa and the greater frequency of symptomatic postural dizziness in those on levodopa alone. Moreover, as noted by Heinonen and Myllyla, the combination of selegiline and levodopa was associated with a higher incidence of postural hypotension than levodopa and placebo in a prospective, randomised double blind study. Heinonen and Myllyla note that depression change in systolic blood pressure, but not the absolute levels, was lower in those previously on selegiline and levodopa three months after withdrawal of selegiline and also in those originally on levodopa alone. However, both the standing systolic blood pressure and the percentage drop were greater than when patients were taking selegiline and levodopa. That is, the hypotensive effects of standing had improved with levodopa and stopping selegiline even though the average daily dose of levodopa had been increased (not significant) and seven (44%) patients required addition of the potentially hypotensive ergoline pergolide. This suggests that the orthostatic hypotensive effect was specific for selegiline and levodopa rather than a non-specific consequence of dopaminergic treatment itself. Therefore, we think that our finding that selegiline and levodopa cause a greater drop in standing systolic blood pressure than levodopa alone is robust and represents an unwanted and potentially dangerous drug interaction. Coyle, et al examined standing systolic blood pressure, 30:15 ratio and 30:15 ratio in 22 patients on levodopa alone and five on selegiline and levodopa. They found that standing precipitated a small and asymptomatic fall in systolic blood pressure that was similar in both groups and by contrast with our finding that levodopa and selegiline caused a greater drop in standing systolic blood pressure than levodopa alone, however, the number of those on selegiline and levodopa was small and, as Coyle et al note, the daily dose of levodopa was lower. Moreover, although both groups were apparently matched, the mean age of those on levodopa alone was seven years more than those on the two drugs and the SEM of age of those taking selegiline and levodopa was 10%, implying a much greater age range in this group and so raising the possibility that orthostatic hypotension in those on levodopa alone as a result of ageing might have exerted a confounding influence on their data. Coyle et al reasonably caution that autonomic function has been examined in only a few published cases. Collectively, we and Turkka et al have studied 43 patients on levodopa and selegiline with both groups finding that the combination of drugs was associated with greater cardiovascular disorientation than levodopa alone. In a separate study of 20 patients on selegiline (unpublished data) we have again found a similar impairment of cardiovascular reflexes which occurs as a result of long term levodopa treatment. Thus, we think that our findings indicate that the combination of selegiline and levodopa impairs cardiovascular control in at least some and perhaps even a majority of patients with moderately advanced or severe Parkinson's disease.

We agree with Heinonen and Myllyla that the causes of orthostatic hypotension induced by selegiline and levodopa are unknown. We considered two potential causes: an amphetamine effect or increase in inhibition of monoamine oxidase-type A which might be expected to increase plasma concentrations of the false transmitter tyramine, which also causes orthostatic hypotension. Selegiline may lose some of its selectivity for monoamine oxidase type B at high doses or with chronic treatment at<10 mg/day. Riederer et al found that >65% of monoamine oxidase type activity is inhibited by treatment with selegiline at 5–10mg/day in the brains of seven patients with Parkinson's disease and noted that the degree of inhibition of monoamine oxidase type B was increased with increasing duration of treatment. Selegiline comprises the l-isomer of deprenyl and is thought to be largely metabolised to l-amphetamine and l-metamphetamine which have less potent cardiovascular toxicity than the d-isomers. Although amphetamines cause supine hypertension, they have also caused orthostatic hypotension by impairing sympathetic function in humans. To our knowledge cerebral and plasma concentrations of the l-isomers and d-isomers of amphetamine have not been measured in those on long term selegiline treatment. Thus the possibility that high cerebral or plasma concentrations of l-amphetamine are sufficient to cause toxic cardiovascular effects as a result of long term treatment with selegiline and levodopa cannot be excluded. In the submitted study of 20 patients on selegiline already referred to we found that the impaired cardiovascular reflexes due to selegiline and levodopa treatment normalised within four to seven days of stopping selegiline. This time course was consistent with either an amphetamine effect
or loss of selectivity for monoamine oxidase type B resulting in excess plasma tyramine. However, in this study selegiline seemed to cause supine hypertension as well as orthostatic hypotension. This combination would be consistent with either an amphetamine or a monoamine effect.

The failure of patients with severe orthostatic hypotension induced by selegiline and levodopa to develop a compensatory tachycardia indicates impairment of cardiovascular reflexes and as such is consistent with significant, albeit reversible, drug toxicity by whatever mechanism.

Andrew Churchyard and Andrew Lees


Idiopathic generalised epilepsy in adults manifest by phantom absences, generalised tonic-clonic seizures, and frequent absence status


Panayiotopoulos et al. reply:

We thank Bleck for vividly illustrating the challenging diagnostic and management problems of these patients that were among the main purposes of our report. His patient, like ours, had infrequent generalised tonic clonic seizures with onset in the late teens and frequent episodes of absence status that was misdiagnosed as complex partial status epilepticus. Also, he probably had phantom absences during interictal generalised 3–5 Hz spike and slow wave discharges but this needs documentation with breath counting or other means of testing for mild impairment of cognition. Similarly to our cases, he was also erroneously treated with phenytoin, carbamazepine, and barbiturates for many years and seizures stopped only when appropriate medication of divalproex was prescribed. He was fortunate not to receive vigabatrin, which exacerbates absence and absence status.

The only difference from our cases is that Bleck’s patient had prolonged, 8 minute, severe absence seizures provoked by hyperventilation after withdrawal of all antiseizure medication. Although briefer, this was similar to the absence status in our patients; this severe electroclinical state was documented only during spontaneous absence status, not during hyperventilation. However, in all patients over-breathing increased the generalised 3–4 Hz spike or polyspike and slow wave discharges that were often associated with mild impairment of cognition, shown with errors of breath counting. Hyperventilation was the only means of inducing generalised 3–4 Hz spike and slow wave discharges in some of the patients whose resting EEG could be normal. This is in accordance with the provoking effect of hyperventilation on absence status of the idiopathic generalised epilepsies.

C P Panayiotopoulos, M Koutroumanidis, S Giannakodimos, A Agathonikou
variably under the eponymous label of Pick's disease. Yet in some instances, the editors do not take the generalist's side. Surely, it is unreasonable to recommend special neurohistological techniques like Cajal's gold chloride, the silver impregnation of Bielschowsky and Cross, and Holzer's method, when the information which these preparations provide can be obtained with the immunoperoxidase technique which is in everyday use in the general histopathology laboratory. Antibodies against H\&E-peptide, paired helical filament-related tau epitopes, ubiquitin, glial fibrillary acidic protein, and neurofilament protein are commercially available, and the technique is standard, of reproducible quality, and may be automated. Diffuse and neuritic forms of the senile plaque, neurofibrillary (tangle) degeneration, Pick bodies and Pick cells, cortical L Lewy bodies, and Pick cell-like inclusions of motor neuron disease, and astrocitic gliosis are all easily demonstrated with this panel of antibodies. There is merit in recommending the combined Luxol fast blue and cresyl violet preparation (which stains myelin sheaths blue and neuronal perikarya purple, when properly done) because it offers considerable help with anatomical localisation of individual nuclei and fibre tracts in sections of the brain stem. However, plaques of demyelination are just as easily diagnosed on haematoxylin and eosin stained sections, so that the pathologist who is confident of his results can dispense with traditional myelin stains too.

I am disappointed with the index. Look up ubiquitin and none of the page numbers to which you are referred will tell you about its role in myelin sheaths, neurological disorders, or tau pathology. Look up tau and you will be referred to pages about neurofibrillary tangles but not to the sections on Pick bodies or the tangle-like inclusions of corticobasal degeneration. There are many examples.

The reader is also let down with some of the illustrations. It is gratifying to find a substantial neuropathology textbook selling for significantly less than £100 but a book which is intended to assist someone peering down a microscope at coloured histological preparations should have many more colour photographs. Surely, modern publishing technology can produce colour illustrations and still keep to moderate prices. Also there are several errors. Two examples will make the point: the two photographs in figure 3.12 (a) and (b) are wrongly positioned in relation to the legend, and the photographs in figure 5.10 are clearly from luxol fast blue preparations (indeed it says so in the legend) but the stain/magnification label says H\&E.

One other niggle is the tendency, in a few chapters, for the authors to overrefer to the texts. As the style of referencing is that of authors and year of publication, rather than numerical superscript, overreferencing can make a chapter unpleasant to read and impossible to scan for particular information (such as a key word from the index). David Mann's chapter on Down's syndrome is a particular example of the way in which references pepper the text like an obstacle course. The remarks in the last four paragraphs do not diminish significantly my admiration for this book. I concur with the view of Sir Bernard Tomlinson who remarks, in the Forward, that "the principal authors have, through their own clear accounts, their perceptive insight into pathologists' needs, ...produced a book which will be a most welcome addition, and perhaps a treasure, in many laboratories, clinical libraries and personal collections". I am very pleased to have it and I recommend its purchase.

JOHN XUEREB


"A detailed neurological examination is . . . a test of concentration and cooperation (even) in those in good health . . . . It may be necessary to conduct the examination in more than one session". These are not quotations from Michael Donaghy's attractive book but from a book on clinical methods published in 1968. Comparison of this with Donaghy's book provides a clear demonstration of how clinical neurology, not just neuroscience, has advanced in the intervening 30 years. Generations of medical graduates have been discouraged about neurology because of the overwhelming (and often overbearing) way in which it was taught. Donaghy's book is representative of a more realistic way of teaching neurological clinical methods which hopefully will produce a new generation of clinicians practising neurology as a practical science. In particular the neurological examination is portrayed as a set of techniques to be applied as appropriate to the clinical problem at hand, rather than an arcane (and mentally taxing) ritual played out with the mind in neutral.

After an initial chapter discussing important parts of the neurological history a basic neurological examination is well described and illustrated. Here the only obvious omission is the valuable test of asking patients to outstretch their arms with supinated hands and closed eyes, a very sensitive screen for significant neurological deficit in the upper limbs, widely used by neurologists in practice. Subsequent chapters pursue more detailed examination techniques in the context of specific clinical problems. This approach works well and is complemented by the later chapters reviewing common neurological syndromes. Management is touched on, including telling patients about incurable disease, but assessment of disability, as opposed to deficit, is not much considered.

The aim of the book is to provide students with "a working knowledge of common clinical problems in neurology, and teach a simple, quick, and reliable neurological examination". This is what medical students require to cope with the neurology they will meet as junior hospital doctors and on which they can build if they decide to become physicians, general practitioners, or even neurologists. In my view the author succeeds in his aims and is to be congratulated on producing a well illustrated and laid out paper back introduction to neurological clinical methods. Students in my university will be particularly amused to see the photographs of Donaghy testing the muscular strength of a member of the Oxford University Boat Club!

CHRIS ALLEN


Oosterhuis is a well known figure in the world of myasthenia gravis, has published extensively on the subject, and clearly has accumulated the depth of experience on the subject that only comes with time. However, this book is not simply a review of the subject but a very personal account of the years he has spent managing 800 patients with the disease in his native Holland. It is a delightful read from the historical aspects, which are so important to understand the therapeutic options and relative benefits in contemporary medicine to the explanation of differential diagnosis. Also he covers in succinct detail the epidemiology of myasthenia and reviews the diagnostic criteria and tests, as well as the treatments now available for this condition which is the archetypal immunologically mediated neurological disease. The book is extremely well illustrated with historical and clinical photographs and diagrammatic representations of disease course with relation to different serological and clinical indices. If there was any criticism to be levelled at this book it would be that the frequency of spelling mistakes and typos can be a little irritating, but then I am sure my Dutch would be worse. I would recommend anyone who has a specific interest in myasthenia or indeed those who are likely to come across the disease in clinical practice to acquire this book, they will not regret it and it will continue to be a relevant clinical guide for many years.

NEIL ROBERTSON