Reviews in Medicine

Neurology

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Introduction

The past few years have seen a significant improvement in our ability to diagnose and treat neurological diseases. New imaging techniques such as computed tomographic (CT) scanning and magnetic resonance imaging (MRI) have had a major impact on the practice of neurology. Whilst techniques such as positron emission tomography (PET) are mainly research orientated at present, they may soon find wider clinical application. New electrophysiological examinations such as magnetic brain stimulation have found use in the investigation of central motor conduction pathways. The application of the techniques of molecular biology to the study of neurological disease is having a profound effect on our understanding of the mechanisms underlying these diseases. The clinical application of this knowledge is being seen in genetic counselling and the diagnosis of neurodegenerative disorders.

The past few years have also seen major advances in the treatment of such diseases as epilepsy, Parkinson's disease, Guillain-Barré syndrome and migraine. Considerable work is now being directed to effective treatment of disorders such as Alzheimer's disease and multiple sclerosis. In this review, we have sought to provide an update on selected topics chosen to cover a wide spectrum of neurological practice. They have been written to emphasize recent advances in our understanding of the mechanisms of these diseases as well as in their management.

Neurological emergencies

Third generation cephalosporins in treatment of meningitis

In a comprehensive review of recent advances in the pathophysiology and treatment of bacterial meningitis,

Tunkel *et al.*¹ point out that the mortality has not changed significantly over the last 30 years but the prognosis for Gram-negative meningitis has been markedly improved by the introduction of third generation cephalosporins.

In adults and older children the commonest causative organisms are *Neisseria meningitidis* and *Streptococcus pneumoniae* and the treatment of choice in the UK is intravenous benzyl penicillin, with chloramphenicol as a second line agent. In children aged 4 months to 6 years the most likely organism is *Haemophilus influenzae* type b which may be resistant to ampicillin. Initial treatment in this age group has been chloramphenicol and ampicillin until sensitivities are known, but Peltona *et al.*² found that the third generation cephalosporins cefotaxime and ceftriaxone were as effective as ampicillin and possibly better than chloramphenicol in a randomized comparison of these four drugs in the treatment of bacterial meningitis in 197 children aged 3 months to 15 years. They found that ceftriaxone sterilized the cerebrospinal fluid more rapidly than the others and discuss the advantages and disadvantages of each agent rather than expressing any firm preference.

Schaad *et al.*³ conducted a randomized, prospective study comparing ceftriaxone (100 mg/kg/day as a single daily dose) with cefuroxime (240 mg/kg/day in four divided daily doses) for the treatment of bacterial meningitis in 106 children aged 6 weeks to 16 years. *H. influenzae* was the commonest infecting organism and *N. meningitidis* the next most frequent. Both drugs were clearly effective but results were better with ceftriaxone. Cerebrospinal fluid cultures were still positive at 24 hours in 6 out of 52 patients treated with cefuroxime compared with one out of 52 in the ceftriaxone group, and moderate to profound hearing loss was found in 9 of the cefuroxime treated patients and 2 of the ceftriaxone group at 8 and 10 weeks after discharge. Moderate to severe sensorineural deafness is thought by some to be due to bacterial invasion of the cochlea. It occurs in about 10% of children treated with ampicillin or chloramphenicol and is

no less common following cefuroxime. If this complication can be reduced by ceftriaxone its place in treating this serious infection can be recommended.

Encephalitis

Herpes simplex encephalitis is uncommon, affecting 2 to 4 per million of the adult population per year, but it should be considered in encephalopathic patients particularly if there is accompanying fever, behavioural changes, focal disturbances or seizures. The mortality untreated is around 70% and survivors are often severely impaired, but in patients treated early with acyclovir nearly 40% recover with no or little residual deficit. This subject was reviewed recently by Whitley.⁴

Laboratory confirmation may be difficult and waiting for a demonstrable rise in antibody titres is of little practical help in the acute situation. Rowley *et al.*,⁵ in a preliminary report, detected herpes simplex virus DNA in cerebrospinal fluid (CSF) by using the polymerase chain reaction, in all 4 patients with biopsy proven herpes simplex encephalitis and in none of their 6 control patients with other neurological diseases. This method amplifies very small amounts of DNA, not otherwise detectable, and the results are available within 2 to 3 days. It is likely to be much more reliable than CSF culture, which is rarely informative, and is less invasive than brain biopsy, particularly as CSF is required anyway in the emergency investigation of these patients to exclude other conditions.

Subarachnoid haemorrhage and stroke

Thunderclap headache

Patients with proven subarachnoid haemorrhage often report recent symptoms suggesting a previous haemorrhage – the ‘warning bleed’ – and in most cases either the patient or the doctor has not appreciated the significance of the symptoms at the time. Conversely, it is not uncommon for patients to present with sudden severe headache where appropriate investigation reveals no evidence of subarachnoid haemorrhage. Harling *et al.*⁶ reported a small but useful prospective study of 49 patients presenting with symptoms suggesting subarachnoid haemorrhage. Thirty-five had haemorrhage confirmed by CSF examination, CT brain scan or both. Eight of the 14 patients with both normal CSF and CT scan had angiography and this was negative in every case. In all 14 patients follow-up for 18 to 30 months revealed no subsequent subarachnoid haemorrhage or serious disease. Even in retrospect, it was not possible to identify the patients who had bled on clinical grounds alone, so investigation is important, but

the authors conclude that angiography is not necessary if both CSF and CT brain scan are normal. Patients who delay presentation so that these investigations cannot be done within 2 weeks of the headache may need angiography.

Nimodipine in subarachnoid haemorrhage

The value of nimodipine in improving the outcome in patients with subarachnoid haemorrhage has been confirmed by Pickard *et al.*⁷ in a randomized, double blind comparison of nimodipine, 60 mg four hourly, orally, for 21 days, against placebo. Treatment was commenced within 96 hours of the ictus. Cerebral infarction occurred in 61 out of 278 (22%) patients given nimodipine, compared with 92 out of 276 (33%) patients given placebo. Poor outcome, including death, vegetative state, or severe residual disability at 3 months, occurred in 55 patients (20%) treated with nimodipine and 91 (33%) on placebo and the death rate was lower in the nimodipine treated group (43 compared with 60).

Nimodipine is a calcium-channel blocker which readily crosses the blood–brain barrier and has a vasodilator effect on cerebral vessels, but little effect on the peripheral vasculature. It was thought that it would reduce vasospasm which is often seen on angiograms following subarachnoid haemorrhage. It is interesting that in this study there was no apparent reduction in vasospasm, angiographically, in patients on nimodipine, and the incidence of rebleeding was slightly lower in the nimodipine group. It seems likely that nimodipine provides some benefit directly by blocking calcium entry into neuronal cells.

Nimodipine in acute stroke

Gelmers *et al.*⁸ reported benefit from nimodipine in acute ischaemic stroke in a prospective controlled trial of 186 patients in whom treatment was started within 24 hours of onset, but a more recent, larger, placebo-controlled, double blind trial of oral nimodipine, 120 mg/day for 21 days, has provided no support for the administration of this agent following acute stroke.⁹ Treatment was allocated randomly and commenced within 48 hours of onset in 1215 patients over the age of 40 who were hemiparetic, conscious and able to swallow, and had been functionally independent beforehand. There was no difference between the nimodipine and placebo treated groups in terms of survival and degree of independence at 7 days, 21 days and 24 weeks in the trial as a whole and no difference between the groups in 441 patients commencing treatment within 24 hours.

The results of clinical trials correlate with experimental studies¹⁰ which suggest that nimodipine

minimizes ischaemic damage if given before or within minutes of the onset of ischaemia, but once an infarct has become established little benefit can be expected.

Surgery for primary intracerebral haemorrhage

The value of surgical treatment for primary intracerebral haemorrhage generally has not been considered helpful, but improvements in imaging techniques, intensive care and surgical methods prompted a reassessment of this topic by Fujitsu *et al.*¹¹ They report a retrospective study comparing medical treatment and microsurgical evacuation of hypertensive putaminal haemorrhage in 180 patients admitted within 3 hours of the ictus. All 69 patients with haemorrhages greater than 2 cm in largest diameter admitted to the Yokohama City University Hospital were treated surgically. The 20 patients with haemorrhages smaller than 2 cm and all 91 patients with larger haemorrhages admitted to two affiliated hospitals were treated medically.

Patients were graded at 6 hours or immediately preoperatively according to a modified Glasgow coma scale into fulminant, rapidly progressive, slowly progressive, or non-progressive groups. Only in the rapidly progressively deteriorating patients, under the age of 65, but with no signs of tentorial herniation, was any benefit from surgery evident. All these patients had large haematomas (> 5 cm in diameter). Of the 18 'rapidly progressive' patients treated conservatively, by 6 months, 13 were dead or 'totally disabled' and 5 were partially disabled, i.e. partially self-sufficient. Of the 24 surgically treated patients 7 were dead or 'totally disabled' 15 were partially disabled, one was minimally disabled, and one was well and capable of full employment at 6 months and improvement in the surgically treated group was apparent in the first 7 days. In the study as a whole, all patients over the age of 65 had died or were totally disabled at 6 months.

Bearing in mind the limitations of a retrospective study, the selection criteria and possible differences in care at the different institutions, it is possible that surgery may be of some benefit if undertaken early enough in some patients under 65 years with large haemorrhages who are deteriorating rapidly but do not have tentorial herniation. This study lends no support to the routine evacuation of primary intracerebral haematomas.

The aetiologies and prognosis of non-traumatic intracerebral haematomas are discussed in depth by Weisberg *et al.*¹² who review 358 cases categorized according to site of haemorrhage. The commonest sites were putamen (100 patients), thalamus (50 patients), pons (40 patients) and cerebellum (29 patients) and hypertension was the major risk factor. They also discuss 98 patients

with lobar haemorrhages where hypertension was less common. They found that at each site the prognosis was better in non-hypertensive patients or in hypertensive patients with evidence of chronic vascular disease than in hypertensive patients without evidence of chronic vascular disease.

Acute spinal cord compression

Acute spinal cord compression requires urgent recognition and appropriate referral if permanent paraplegia with loss of sphincter control is to be avoided. In their retrospective review of 76 consecutive patients, Maurice-Williams and Richardson¹³ found that avoidable delays in referral to neurosurgical units were common and only 45% of patients reached the referring hospital within 14 days of their first visit to a doctor, and in 33% it took longer than 14 days from the first hospital admission to reach a neurosurgical unit. At first consultation 68% were able to walk unaided but only 10% were able to do so on arrival at the neurosurgical centre.

The commonest cause of acute spinal cord compression is an extradural metastatic lesion and Kim *et al.*¹⁴ in a prospective study of 59 patients with extradural spinal cord compression due to malignant disease, found that of all factors analysed, only pretreatment motor function correlated with functional prognosis after treatment. Similarly, Sorensen *et al.*¹⁵ in a retrospective analysis of 345 cases treated by emergency decompression and/or radiotherapy, concluded that the main factor determining short term outcome was the degree of disability at the time of treatment.

A particularly treacherous, though fortunately rare, cause of spinal cord compression is spinal epidural abscess which has been the subject of two recent reports. Hlavin *et al.*¹⁶ carried out a retrospective analysis of 40 patients with this condition treated in their unit between 1980 and 1989. In 16 patients, categorized as chronic, symptoms had been present for more than 2 weeks. Thirty out of 33 patients, in whom an adequate history could be obtained, complained of back pain. Fever, sweats and rigors were present in three quarters of the series, 13 had a radicular sensory disturbance, 14 noted weakness, and 9 had sphincter dysfunction. The rate of neurological progression varied from hours to weeks; 14 patients deteriorated while in hospital and 9 of those were already on appropriate antibiotics. Of the 39 patients treated surgically, 9 died, 2 remained paralysed despite surgery within 12 hours of onset of paralysis, 10 had some residual neurological deficit and 18 were normal neurologically. The organism responsible was *Staphylococcus aureus* in 24 out of 37 in whom identification was established and 13 patients were diabetic.

In another report¹⁷ of 29 patients, findings were

similar in that 10 were diabetic, and the infecting organism was *S. aureus* in 13, streptococci in 5, and Gram-negative aerobes in 5. The outcome was a little better: 2 died, 6 had mild to moderate disability; and the neurological outcome in 21 was good. The authors emphasize the importance of thinking of this condition in a febrile patient with a painful spinal syndrome.

Migraine

Classical migraine is a recurring syndrome of stereotyped attacks, in which an aura of focal neurological symptoms, lasting less than one hour, is followed by headache, usually unilateral, accompanied by nausea and/or vomiting, which resolves within 72 hours. Common migraine is a similar recurring syndrome without the aura.

Pathophysiology

The vasogenic hypothesis proposed by Graham and Wolff in 1938, that the aura is caused by focal ischaemia due to vasoconstriction and the headache is due to dilatation of extracranial vessels, has been repeatedly challenged in favour of a primary neurogenic mechanism. The migraine aura extends to contiguous parts of the cerebral cortex and does not seem to be restricted by arterial boundaries. It has been estimated to spread across the cortex at a rate of 2 to 3 mm/minute, a rate which intriguingly approximates to the rate of progress of the 'spreading depression of Leao'. Spreading depression is a wave of reduced neuronal activity which can be induced by a variety of insults to the cerebral cortex of experimental lissencephalic animals.

Studies of cerebral blood flow

Over the last decade, estimations of regional cerebral blood flow (rCBF) using radioactive xenon (^{133}Xe) have become more reliable. It is evident that a migraine attack is associated with reduction in cerebral blood flow followed by hyperperfusion. The oligoemia does appear to spread across the cortex at a rate of 2 to 3 mm/minute and is not constrained by the borders of main arterial territories. These observations, however, have not reestablished the vascular hypothesis, because the observed oligoemia precedes and outlasts the focal neurological features and persists well into the headache phase of classical migraine. Furthermore, Andersen *et al.*¹⁸ using ^{133}Xe inhalation and single photon emission tomography (SPECT) analysis in spontaneously occurring classical migraine attacks, have shown that hyperperfusion persists for some hours after the headache has subsided.

Skyhoj-Olsen and Lassen¹⁹ investigated 11 patients using intra-carotid ^{133}Xe injection during attacks of classical migraine. They found that rCBF was focally decreased to around 20 ml/100 g/min (normal 54 ml/100 g/min), which is probably low enough to produce an ischaemic effect. They point out, however, that, although the territory of hypoperfusion appeared to spread, this effect could be produced by a gradual decrease in flow in a fixed area, because of the scattering effect of nearby brain tissue on the radiation emitted (Compton effect). These observations, therefore, are compatible with, but not specific for, a primary vascular mechanism.

Kobari *et al.*²⁰ utilized a sophisticated method of measuring local cerebral bloodflow (LCBF) by combining the high resolution of CT brain scanning with ^{133}Xe inhalation in migraine sufferers. Six patients with common migraine and 4 with classical migraine had normal LCBF when free from headache. LCBF was increased, however, during the headache phase in cerebral cortex and subcortical grey matter, most markedly in the thalamus, but also in basal ganglia and white matter of both hemispheres, in the 6 patients with common migraine and 6 patients with classical migraine. Furthermore, the increase in LCBF was symmetrical and the findings in patients with common migraine were similar to those with classical migraine. These findings are not consistent with either a spreading oligoemia or spreading cortical depression as the primary cause, but suggest a neurogenic or chemically mediated cause for the vasomotor changes. The absence of differences between results in common and classical migraine patients supports a common aetiology, and the authors suggest that the lack of asymmetry between the right and left hemispheres supports the view originally proposed by Wolff that the headache is likely to be due to dilatation of extracranial vessels.

Magnetoencephalography

The question of whether the observed changes in cerebral blood flow are primary or secondary to a primary neurogenic mechanism, remains unresolved, but the new non-invasive techniques of magnetoencephalography (MEG), for recording magnetic signals from the brain, has recently been used to try to clarify the pathophysiology of migraine.

Barkley *et al.*²¹ have detected three types of signal from migraine sufferers which they have not found in controls. The first type – large amplitude waves – was detected in 4 out of 9 migraine patients during attacks and 5 out of 12 migraine sufferers between attacks, but was not found in any of the 12 headache-control subjects during non-migrainous headaches nor in any of the 12 normal control

subjects. The second feature was the observation of 'long-duration decrements in spontaneous cortical activity', in 6 out of 9 migraine sufferers during attacks but in none of the headache-controls. There is evidence from animal studies that this phenomenon may be due to spreading cortical depression. The decrements in spontaneous cortical activity were not seen between attacks except in one case after a failed attempt to induce an attack in a patient prone to exercise-induced migraine. The third observation was of long duration, large amplitude field changes in three migraine patients and in none of 6 control studies. This is the first report of MEG studies in migraine attacks and clearly requires independent confirmation, but it may be the first demonstration of spreading depression in migraine.

Advances in treatment

Sumatriptan

The effectiveness of the 5HT agonist ergotamine in the treatment of a migraine attack is well known, but there are many unwanted side effects of this drug, such as nausea and vomiting, as well as the more serious dangers of peripheral vasoconstriction. Sumatriptan (previously GR 43175) is a highly selective 5HT 1D agonist,^{22,23} which may be valuable in the treatment of a migraine attack and may have fewer side effects than ergotamine because of its greater selectivity.

Perrin *et al.*²⁴ report that clinical studies with intravenous sumatriptan in a dose of 64 µg/kg body weight, given to 31 patients during the headache phase of an attack of classical migraine or common migraine, was effective in 27 cases. In a small double blind study, 14 out of 15 patients responded to sumatriptan within 20 minutes, compared with 2 out of 15 responding to placebo. The same authors also report the successful use of a dispersible oral preparation of 70 mg or 140 mg in an open study of 45 patients. By two hours, 14 patients were completely free of headache, and marked improvement occurred in all but 3 of the rest. Oral treatment of a migraine attack is often ineffective because of the failure of intestinal absorption, particularly in the presence of nausea or vomiting, but absorption of oral sumatriptan seems adequate and plasma levels of sumatriptan taken during the attack were similar to those found when the drug was taken outside an attack.

The same group²⁵ reported results from a multicentre trial of sumatriptan administered subcutaneously to 111 patients during 125 migraine attacks. Six out of 18 patients had responded to 1 mg and 21 out of 22 patients had responded to 4 mg after 30 minutes.

Preliminary results with sumatriptan, therefore,

appear promising. It is well tolerated, and no serious adverse reactions have been reported. It seems to relieve headache, nausea and vomiting and to be effective if taken even at a late stage of a migraine attack which, if confirmed, would be an advantage over alternative therapies.

Flunarizine

Flunarizine is a class 4 calcium channel blocker which appears to be helpful in treating migraine. Previous reports (see review by Andersson and Vinge²⁶) have been supported by recent studies in confirming the efficacy of flunarizine in prophylaxis and in treating the acute attack.

Ludin²⁷ found that, in a double blind, multicentre study of 71 adult patients, both propranolol (40 mg thrice daily) and flunarizine (10 mg once daily) were similarly effective in reducing the frequency of migraine attacks in about half of the patients over a 4 month period, compared with the preceding month, during which placebo was administered in a single blind manner.

Soyka *et al.*²⁸ reported a response in 23 out of 31 patients given 20 mg of flunarizine intravenously, compared with 8 out of 29 patients given placebo in a double blind trial, and Pfaffenrath *et al.*,²⁹ also in a double blind study, observed a response in 19 out of 32 patients within one hour of receiving 20 mg flunarizine compared with 10 out of 33 receiving placebo. Serious adverse effects were not observed in either of these trials.

This calcium channel blocker looks promising and might prove to be valuable in preventing cerebral infarction, which is a rare complication of a migraine attack.

Multiple sclerosis

The cause of multiple sclerosis (MS) remains unknown although intensive research efforts are providing valuable insights into the possible mechanism(s) that underlie this disorder. It seems most likely that an environmental exposure (e.g. virus) in a genetically susceptible individual leads to an abnormality of immune regulation.

Evidence for an environmental influence in the aetiology of MS has come from epidemiological data. A recent study has demonstrated a geographic variation within Australia, with high southern and low northern prevalence as well as a genetic resistance amongst aborigines.³⁰ A genetic predisposition is suggested by the association of certain HLA types with MS – linkage with DR2 and DQW1 in particular. Twin studies have also shown a higher concordance rate in identical than non-identical twins, supporting a genetic influence in the aetiology of MS.

The basis for the diagnosis of MS remains clinical and requires the demonstration of neurological deficits related to white matter lesions separate in time and anatomical distribution. Optic neuritis is a common mode of presentation of MS. The development of clinically definite MS is estimated to occur in 75% of patients who present with optic neuritis.³¹ This risk increased in patients who were HLA-DR3 positive and further enhanced in those who were both HLA-DR3 and DR2 positive.

Visual evoked potentials are very useful in identifying lesions of the optic nerve even in patients who give no previous history of visual deficit. Brainstem and somatosensory evoked potentials can also be helpful in identifying lesions. Central motor conduction times have been used to identify defects in motor tracts but rarely add significant information to a detailed clinical examination. Lumbar puncture with CSF examination for oligoclonal bands is a useful adjunct to evoked potentials in a patient thought to be suffering from MS. Oligoclonal bands are immunoglobulins synthesized locally with the CNS to as yet unidentified antigens. These immunoglobulins are present in CSF but not in serum, and are found in 90% of patients with clinically definite MS, and approximately 40% of patients with isolated optic neuritis. Oligoclonal bands are not specific for MS and are found in other inflammatory or infective diseases affecting the CNS.

The application of magnetic resonance imaging (MRI) to the study of MS has produced significant advances in our understanding of this disease. It must be emphasized that MRI is not a 'diagnostic test' for MS. The results obtained from imaging must be interpreted in the context of the patient's clinical history and examination. The lesions seen on MRI in MS can be mimicked by several other diseases. Ten per cent of normal adults over the age of 50 years have multiple small abnormal areas (presumably ischaemic) on MRI. With this in mind, 60% of patients with optic neuritis have cranial lesions compatible with MS. Fifty-six per cent of acute and 82% of chronic spinal syndromes have abnormal MRIs consistent with MS. Thompson *et al.*³² found no relationship between the extent of lesions as demonstrated by MRI and the patient's disability. MRI scanning is not therefore useful in predicting clinical disability in individual patients.

The treatment of MS remains a difficult area. Although the temptation for therapeutic nihilism should be avoided, therapeutic intervention requires carefully balanced judgement. Steroids remain the most popular and effective means of controlling exacerbations of MS. Steroid courses should be limited to those relapses that are disabling. Intravenous methyl prednisolone has become the most favoured method of delivery either as

500 mg for 5 days or 1 g alternate days for 3 doses.

Preventing the progression of MS has been the object of a multitude of trials and treatments. Azathioprine and cyclophosphamide have each been used as immunosuppressants in MS.^{33,34} The minimal beneficial effect of azathioprine is outweighed by its side effects. The initial report on the use of cyclophosphamide is encouraging; results of a formal double blind clinical trial are awaited with interest. The use of cyclosporin A in MS has also been shown to have some benefits, but again these seem to be outweighed by toxicity. If cyclosporin A is used, benefit does not appear for 15–18 months and so its use is not appropriate for rapidly progressive MS.³⁵ Plasmapheresis, total lymphoid irradiation, transfer factor and interferon α are other treatments attempted but which have not shown any great promise.

Following a report of the benefit of amantidine in MS,³⁶ three studies have now shown that amantidine improves the fatigue associated with MS in just over half the patients treated.³⁷ Amantidine administration was associated with an increase in β -endorphin- β -lipotropin, higher levels of which were observed in responders.³⁸ Ataxia in MS may improve with carbamazepine.³⁹ Pain is common in MS, dysaesthetic pain being the most frequent. Behavioural therapy, anticonvulsants or tricyclic antidepressants may be of some benefit.

Epilepsy

Epilepsy is one of the most common neurological disorders that present to the medical profession. Incidence rates are 20–70/100,000 per year and point prevalence rates 4–10/1000.⁴⁰ Five per cent of the population suffer an epileptic seizure at some time in their life.

The main classification of epilepsy is localization-related, i.e. into partial or generalized seizures. Partial seizures may be simple (without altered consciousness) or complex (with altered consciousness), either of which may evolve to generalized seizures. Generalized seizures may include absence attacks, tonic, clonic, or tonic-clonic seizures and myoclonus. Complex partial and secondary generalized seizures are the most common, accounting for more than half of cases. Tonic-clonic generalized seizures account for about one third of cases. No specific cause for epilepsy is found in almost three quarters of patients. Cerebrovascular accidents, tumours (primary or secondary) and alcoholism account for most of the identified causes (see ref.⁴⁰).

The diagnosis of epilepsy remains clinical and is often very dependent on accurate witness accounts. The patient's description of an aura, especially involving gustatory or olfactory hallucinations, is

often helpful in establishing the diagnosis of temporal lobe epilepsy. If no witness account of tonic-clonic movements is available, complaints of muscle aches, pains and bruises often suggest involuntary movements have occurred. Post-ictal confusion, drowsiness and headache are also important pointers to the diagnosis. In general, it is always best not to diagnose epilepsy if doubt remains, and to simply await the evolution of events. The role of the EEG after the first seizure is still debated. Most feel this investigation will at least provide a valuable 'baseline' if not support the diagnosis, whereas others would await further seizures before performing an EEG. A single routine EEG is estimated to show epileptiform abnormalities in about half of patients with epilepsy.

Similar debate centres on the use of CT brain scans in patients presenting with epilepsy. Some neurologists perform CT scans on all newly diagnosed epileptics over the age of 20 years. Others consider CT scans are only indicated if the history suggests focal epilepsy, if there are abnormal physical signs or if there is a focal abnormality on EEG. A further case for scanning can be made for those patients unresponsive to anticonvulsants. Abnormal CT scans are found in 20% of patients with first seizures – most of the abnormalities are atrophic.⁴¹

Data on recurrence of seizures after a single episode are variable and are influenced by several factors including the population base, diagnostic criteria, timing of entry into trial and study base. Most studies have shown a recurrence rate of 70–80% after the first seizure, most within weeks or months of the first. However, many patients (~40%) will have prolonged remission from recurrent seizures.

There is some suggestion that early treatment with anticonvulsants can improve the prognosis and increase remission rates. At present, it is standard practice to begin treatment only when the diagnosis is certain and the patient has had two or more seizures. However, in view of the high risk of a second seizure within the first 3 months or so of the first, some neurologists are now prescribing anticonvulsants for a period of 6 months after the first documented seizure. This strategy is clearly intended to reduce recurrence rate. Continuation of treatment is then dependent on whether the patient relapses.

Once the decision to begin treatment has been made, the choice of which anticonvulsant is to be used must be made. Absence attacks in childhood and adolescence are best treated with ethosuximide, which may be supplemented with sodium valproate if necessary. Absence attacks in adulthood are best treated with sodium valproate. Carbamazepine or phenytoin are useful in gener-

alized tonic-clonic and partial seizures. The use, side effects and interactions of the commonly used anticonvulsants have recently been excellently reviewed.⁴² Vigabatrin has recently been introduced as add-on therapy for seizures that have not responded to first line drugs. Vigabatrin is a structural analogue of gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter inactivated by GABA transaminase. Vigabatrin is an irreversible inhibitor of this enzyme and so increases GABA concentrations in the brain. Two to three grams of vigabatrin daily have been shown to improve seizure control in about half of patients. The drug is well tolerated but can be associated with drowsiness, fatigue and, rarely, confusion. Psychotic reactions may occur in patients with pre-existing psychiatric disorders. The drug is excreted unchanged and plasma levels are no guide to efficacy.

Surgery is likely to play an increasingly important role in the treatment of intractable epilepsy.⁴³ The selection of patients suitable for surgery is crucial and depends upon clinical data suggesting partial attacks, neuropsychological assessment and demonstration of an abnormality by CT, MRI or positron emission tomography and neurophysiology. The temporal lobe is resected most frequently in those found suitable for surgery. The mortality (0.5%) and substantial morbidity (5%) rates are low in experienced centres. More than half of patients operated on can be expected to have their seizures relieved completely.

Muscle disease

Muscular dystrophies

X-linked Duchenne muscular dystrophy (DMD) has been the focus of much attention since the complete cloning of the DMD complementary DNA (cDNA).⁴⁴ The cDNA is 14 kb long and encodes a 3685 amino acid protein Mr 400 kDa called dystrophin. Dystrophin has been localized to the sarcolemmal region of muscle fibres by immunocytochemistry. This localization of the defective gene product is consistent with the 'membrane theory' of the disease. It has been suggested that dystrophin is a binding molecule that anchors the cytoskeleton to the plasma membrane. Abnormal function of such a binding protein would predispose muscle fibres to disintegration and necrosis.

The sites of deletion within the DMD gene can vary although most tend to occur within two regions of the gene. However, patients with identical deletions but markedly different clinical phenotypes have been described.⁴⁵ Becker muscular dystrophy (BMD) is a milder form of DMD but is determined by the same gene. It is possible

that the difference in clinical severity between DMD and BMD depends on whether the gene deletion disrupts (DMD) or maintains (BMD) the open reading frame for protein translation.

Whatever the position of the deletion within the DMD gene, it is clear that all DMD patients have greatly reduced amounts of dystrophin in their muscle. Immunocytochemical staining with dystrophin antibodies, the analysis of dystrophin by protein separation and immunoblotting and the use of genomic DNA probes which recognize restriction fragment length polymorphisms within the DMD gene have all proved invaluable in the diagnosis of DMD patients and carriers.

Two new approaches to the treatment of DMD have resulted from the recent advances in our understanding of the molecular mechanism underlying this disease. The first is based on the observation that injected myoblasts are capable of fusing with host myoblasts with expression of the donor genes in the resulting hybrid multinucleated cell. A study using myoblast transplants in the mouse muscular dystrophy model resulted in expression of dystrophin in up to 40% of muscle fibres examined. The second approach involves the introduction of the intact or modified dystrophin gene into affecting cells. This latter approach is at present only theoretical.

Mitochondrial myopathies

The mitochondrial myopathies are a heterogeneous group of disorders most frequently due to defects of the mitochondrial respiratory (electron transport) chain. Patients may present at any age from the neonatal period to late adulthood. Involvement may be confined to the ocular muscles with ophthalmoplegia and ptosis, or widespread with an encephalomyopathy often dominated by features of CNS disease such as dementia, ataxia, seizures, stroke-like episodes, deafness and retinal pigmentation. The proteins that comprise the respiratory chain are the products of both the nuclear and mitochondrial genomes. Mitochondrial DNA is maternally inherited and so any disease resulting from a defect of a mitochondrially encoded protein should be passed from the mother to all offspring but with subsequent transmission through the female line alone. Such maternal inheritance has been observed in certain families with mitochondrial myopathy; however, most cases appear sporadic. Deficiencies of specific nuclear encoded respiratory chain polypeptide have been observed in some patients, whilst deletions of mitochondrial DNA have been observed in about one third of cases. Point mutations of mitochondrial DNA have been associated with the myoclonic epilepsy with ragged red fibres (MERRF) syndrome⁴⁶ and with Leber's hereditary optic neuropathy.⁴⁷

Parkinson's disease

The last two years have seen important advances in clinical, pathological, therapeutic and aetiological aspects of Parkinson's disease (PD).

Clinical

PD is characterized clinically by bradykinesia, rigidity and tremor. Onset is asymmetrical but usually becomes symmetrical as the disease progresses. Dementia is now recognized to be more common in PD patients and its appearance is correlated to the severity of PD symptoms and signs.⁴⁸

There are geographic variations in the prevalence of PD: 59 per 100,000 in Nigeria compared to 341 and 352 per 100,000 in American blacks and whites respectively. This geographical variation together with other epidemiological data suggesting clustering of PD around wood mills and among well-water drinkers supports the proposition that environmental factors play some part in the development of PD. The recent description of a kindred with autosomal dominant PD⁴⁹ together with the reappraisal of the twin data on PD, suggest that there may be a significant hereditary element to the development of this disease.

Pathology

The presence of Lewy bodies in surviving nigral neurones is regarded as the morphological hallmark of PD. The Lewy body is an intracytoplasmic, eosinophilic round inclusion, 5–25 µm in diameter and is composed of aggregated filament with a high ubiquitin content. The relevance of the Lewy body to the pathogenesis of idiopathic PD has been discussed in an excellent review by Gibb and Lees.⁵⁰ The Lewy body is not specific to PD and is found in elderly individuals with no evidence of PD during lifetime, and also in neurodegenerative diseases such as olivopontocerebellar atrophy as well as in anterior horn cells of patients with motor neurone disease.

The discovery of nigral Lewy bodies in approximately 10% of elderly control brains lead to the suggestion that these patients had pre-clinical PD, dying before the development of clinical features. A pre-clinical period seems likely as PD is probably the end result of a long period of neuronal fallout and dopamine depletion. However, the proposition that this Lewy body positive group does indeed represent pre-clinical PD awaits further biochemical and pharmacological confirmation.

Therapy

L-Dopa together with a dopa decarboxylase inhibitor remain the mainstay of the symptomatic

treatment of PD. Recent advances have been made in the method of delivery of L-dopa with the introduction of slow release preparations. These still have to be given 4 times a day and often have to be supplemented with short acting standard L-dopa preparations at the beginning of the day. Nevertheless, the slow release tablets can lead to better control of motor fluctuations in PD, reducing 'off' periods in particular.

The use of continuous subcutaneous infusions of the dopamine agonist apomorphine has led to a substantial improvement of fluctuations in some patients. The infusion requires an insulin type pump and the injection site has to be changed regularly so many PD patients find this system difficult to cope with. One alternative is the 'Penject' system of apomorphine delivery used during 'off' periods to supplement standard L-dopa treatment. Such use of apomorphine requires the administration of domperidone to prevent nausea and vomiting. Recent attention has also been focused on the use of low dose L-dopa in combination with direct dopamine agonists such as lysuride or bromocriptine. There is increasing evidence that such combinations may decrease the incidence of dyskinesias and response fluctuations associated with long term L-dopa monotherapy.⁵¹ The use of adrenal autografts and human fetal nigral grafts in the treatment of PD are still under evaluation. The original success with implanting adrenal gland tissue into the head of the caudate has not been replicated at other centres. The risks of this operation in terms of mortality and morbidity are high and the benefits limited or non-existent. Fetal nigral grafts are injected stereotactically and so the risk of this procedure is much lower.

One of the most exciting advances in the treatment of PD came with the results of two studies which showed that 10 mg/day of the mono-amine oxidase-B inhibitor selegiline was able to delay the requirement for L-dopa in newly diagnosed PD patients by approximately one year.^{52,53} This result suggests a protective effect against nigral neuronal degeneration and thus represents the first attempt at disease modification in the treatment of PD. It is now common practice to begin all newly diagnosed PD patients on this drug.

Aetiology

The discovery that the neurotoxin MPTP is capable of inducing Parkinsonism in man and other primates was a major advance in our understanding of the possible mechanisms underlying idiopathic PD. Recent work has shown that the specificity of MPTP for the dopaminergic neurones of the substantia nigra is the result of selective uptake and conversion pathways. MPP⁺, the active metabolite of MPTP, induces nigral cell

death through its specific inhibition of NADH CoQ reductase (complex I) the first protein of the mitochondrial respiratory chain. The discovery of complex I inhibition in the substantia nigra of patients with PD provided a remarkable link between the idiopathic disease and the animal model. This biochemical defect is confined to the substantia nigra in PD and is not present in multiple system atrophy, another degenerative disease affecting the substantia nigra.

The re-evaluation of a possible genetic contribution to PD and the mitochondrial link to the MPTP model suggests that idiopathic PD may be the result of an interplay between hereditary and environmental factors.

The chronic fatigue syndrome: neurological aspects

Despite the recent interest in the chronic fatigue syndrome which has attracted considerable attention both in medical circles and elsewhere — including practitioners of 'alternative medicine', the lay press and self-help associations — this is by no means a new complaint. Nevertheless, substantial problems still exist as to its nature and nosological status. The renewed interest that has developed over the past three decades or so stems from the outbreak of a paralytic disorder at the Royal Free Hospital in 1955⁵⁴ although similar outbreaks had occurred before. Subsequently the emphasis shifted more to sporadic cases in which the symptomatology has been dominated by subjective fatigue. The symptom complex seen in most current patients bears considerably greater resemblances to 'neurasthenia' or 'nervous exhaustion' as recognized in the latter part of the last century⁵⁵ than to that of the Royal Free epidemic. It is important to appreciate the heterogeneity of the syndrome.

Clinical manifestations and terminology

1. Acute epidemics

In the outbreak of 'encephalomyelitis' at the Royal Free Hospital in 1955⁵⁴ the patients were described as usually beginning with constitutional symptoms, including malaise, headache, and pains in the neck, back and limbs. Enlargement of posterior cervical lymph glands was noted in some individuals. These symptoms were succeeded by widespread muscle weakness without wasting or reflex depression, accompanied by tremulous or jerky voluntary muscle contraction and prolonged painful muscle spasms. Paraesthesiae and sensory loss were reported but were less consistent than the motor features. These symptoms were accompanied by considerable emotionality, including prolonged

periods of uncontrollable weeping.

Recovery from the acute illness was protracted and relapses often occurred. It was dominated by extreme fatigability, often produced by relatively minor exertion, such as being subjected to neurological examination. Affected individuals continued to complain of muscle aches and pains, often aggravated or precipitated by exertion, and the jerky pattern of muscle contraction tended to persist.

The majority of those affected were female, predominantly nursing staff. Haematological and biochemical screening tests were negative and the cerebrospinal fluid was consistently normal. Electromyography was believed to show characteristic changes which will be considered later. It was proposed that the disorder represented an encephalomyelitis, although no viral agent was detected. The term 'benign myalgic encephalomyelitis' was introduced to designate the syndrome, later abbreviated to 'myalgic encephalomyelitis' or 'ME'.

Other acute outbreaks have occurred, both antedating and following the Royal Free epidemic. The clinical picture was similar and muscle weakness was again the predominant symptom. In some, the manifestations were considered to resemble poliomyelitis, as in Icelandic or 'Akureyri disease',⁵⁶⁻⁵⁸ whereas others were designated epidemic neuromyasthenia.⁵⁹⁻⁶¹

2. Sporadic cases

As already stated, the majority of patients now seen are sporadic and arise in the community. Although the term myalgic encephalomyelitis is often used for such cases, the label 'chronic fatigue syndrome' is more satisfactory. This emphasizes the dominant symptom and makes no unsubstantiated aetiological attributions. The same criticism applies to the designation 'postviral fatigue syndrome'. The sense of fatigue is assumed to be muscular. Ramsay,⁶² one of those most closely involved with the original Royal Free outbreak, has stated that 'This phenomenon of muscle fatigability is the dominant and most persistent feature of the disease and in my opinion a diagnosis should not be made without it'. Behan and Behan⁶³ have stated that the chief organ affected is skeletal muscle. The 'muscular fatigue' is frequently accompanied by myalgia that tends to develop with a latent interval after physical activity. The symptom complex usually also includes exhaustion on mental effort.^{64,65} The sense of fatigue is therefore not purely muscular.

The chronic fatigue syndrome can be considered as comprising a triad of manifestations, fatigue, muscular and mental, constituting the first compo-

nent. The second component comprises emotional changes. Mild depression, accompanied by anxiety, hypochondriasis and 'intense introspection' are listed as the most consistent psychiatric features,⁶³ but disturbances in sleep patterns and appetite also occur. The third component comprises a wide variety of somatic symptoms, referred particularly to the cardiovascular and gastrointestinal systems. Mild anemia is also often reported.

It is generally agreed that physical signs indicative of neurological disorder are absent and that, if present, their explanation should be sought in other directions. In recent years, cases seen by the author (PKT) in which a presumptive diagnosis of the chronic fatigue syndrome had been made have included instances of hypothyroidism, myasthenia gravis, the Lambert-Eaton myasthenic syndrome and multiple sclerosis. Metabolic myopathies may also give rise to confusion. Particular attention towards seeking such disorders should be given if the psychiatric components described above are lacking.

The variability of symptomatology between patients labelled as having the chronic fatigue syndrome poses considerable problems for case definition, although progress towards a consensus agreement is being made.^{66,67} Part of the problem stems from difficulty in interpreting the descriptions given by the patients to describe their symptoms. Fatigue may be reported as 'weakness' or 'tiredness' and, as pointed out elsewhere,⁶⁸ the distinction between unpleasant fatigue and pain is not easy. In the study reported by Wessely and Powell⁶⁹ on patients with fatigue from a variety of causes, it did not prove possible to distinguish between the various synonyms used by patients to describe fatigue.

Neurophysiological investigations

1. The epidemic disorder

Electromyographic studies on patients during the Royal Free outbreak identified a pattern of abnormality characterized by 'grouped motor unit activity' during voluntary contraction. This equated with the jerky muscle contraction observed clinically and which was subsequently recognized to be typical of simulated weakness with poorly sustained intermittent muscle contraction.⁷⁰ Personal (PKT) electromyographic observations on cases from the original epidemic have shown low and intermittent motor unit firing rates on maximal volition and simultaneous activation of agonist and antagonist muscles,⁷¹ again typical of simulated weakness. The findings are similar to those obtained in patients with 'pseudomyasthenia'⁷² or the 'asthenic syndrome'.⁷³

2. Sporadic cases

More extensive investigations have been undertaken into the pathophysiology of the complaint of muscle fatigue in sporadic examples of the chronic fatigue syndrome. Muscle fatigue can be defined as a failure to maintain a required force or output of power during sustained or repeated muscle contraction. Fatigue is subdivisible into peripheral and central types.^{74,75} Peripheral fatigue results from disturbances at or distal to the neuromuscular junction. Central fatigue implies a failure of neural drive reflected in an inability to maintain motor unit firing frequency. This could result from a defect in motor axons or from a decrement in the activation of anterior horn cells from supraspinal levels, including reduced motivation. A helpful subdivision can also be made into subjective and objective fatigue. Objective fatigue is a physiologically demonstrable failure in the maintenance of muscle force, seen after intense anaerobic exercise or prolonged aerobic exercise. With lesser degrees of force output, it is observable in a variety of neurological disorders including some metabolic myopathies, myasthenia and multiple sclerosis.⁷⁶ Subjective fatigue involves a reduction in voluntary effort secondary to the occurrence of uncomfortable sensations following exercise.

Isometric muscle force production in quadriceps was measured in patients with the chronic fatigue syndrome by Stokes *et al.*⁷⁵ All the males generated and maintained normal force levels. About half the females failed to do so but when electrical stimulation of the muscle was interpolated, this yielded normal force. This finding indicated submaximal effort. Stokes *et al.* also studied muscle fatigability in adductor pollicis from repetitive contraction produced by electrical stimulation of the ulnar nerve. No abnormality was detected in the patients. Lloyd *et al.*⁷⁷ studied endurance as assessed from measurements of repeated maximal isometric contractions of the elbow flexors. Patients with the postinfectious fatigue syndrome showed little abnormality as compared with healthy controls.

Jamal and Hansen⁷⁸ reported increased jitter on single fibre electromyographic recordings in about 75% of a series of 40 patients with the chronic fatigue syndrome. This result is difficult to interpret as it has not been replicated by others⁷⁹ (N.M.F. Murray, personal communication).

Other investigations

Muscle biopsies have revealed only minor and inconsistent structural abnormalities⁶³ and extensive biochemical studies by Byrne and Trounce⁸⁰ have shown no evidence of an abnormality in mitochondrial or glycolytic enzymes. Serum creatine kinase activity is consistently normal. A

patient with persistent fatigue and myalgia after chicken pox was reported by Arnold *et al.*⁸¹ to develop early and abnormally severe intracellular acidosis as measured by ³¹P nuclear magnetic resonance spectroscopy during exercise. It was suggested that the patient's sense of fatigue could have been the result of lactic acid accumulation from excessive glycolytic activity. The muscle biopsy showed type II fibre preponderance which could have contributed to the result, which cannot be accepted without careful controls for the effects of disuse.⁸² Furthermore, this finding is not present in all patients with the chronic fatigue syndrome and also has been observed in schizophrenia.^{83,84}

The conclusion to be derived from the physiological studies on muscle performance in patients with the chronic fatigue syndrome is therefore that there is no good evidence of muscle dysfunction. The findings indicate that the fatigue is central in type.

What is the chronic fatigue syndrome?

All the evidence indicates that this is not a unitary disorder. There can be little doubt that the acute epidemics, such as the one that occurred at the Royal Free Hospital, represent mass illness behaviour.^{70,85} Within these outbreaks, however, identifiable neurological disorders may be concealed, including postinfectious encephalomyelitis.⁷¹

In a series of 47 patients with sporadic chronic fatigue syndrome seen at a specialist neurological hospital, Wessely and Powell⁶⁹ found that 72% had evidence of a psychiatric disorder using diagnostic criteria modified to exclude fatigue. No less than 47% showed major depression and in 15% there was somatization disorder. In only 1 of the 47 patients was conversion disorder present. There is a considerable overlap in the symptomatology of depression and the chronic fatigue syndrome. Complaints of 'decreased energy' and fatigue are almost universal in depressed patients, as are nonspecific symptoms of somatic dysfunction. Fatigue occurs in the majority of patients with somatization disorder.⁸⁶ In addition, post-exercise myalgia is a frequent complaint in depressed patients.⁶⁹ It is also experienced by individuals who are physically unfit and who overexert themselves. It is then related to eccentric muscle contraction (when a muscle lengthens during work), this being potentially damaging to muscle fibres.^{87,88}

In the series of patients with the chronic fatigue syndrome studied by Wessely and Powell,⁶⁹ no psychiatric disorder was identifiable in 28%. The explanation of the complaint of fatigue in these patients is uncertain, but it must be recognized that depression may manifest itself with a complaint of fatigue before other features appear.

This brief review of the neurological aspects has

not addressed the possible role of viral infection as a trigger mechanism, or persistent viral infection as a cause of the chronic fatigue syndrome. Substantial epidemiological problems exist in relation to the studies that have been undertaken, which have been reviewed recently by Wessely and Thomas.⁶⁸

Conclusions

The available evidence indicates that the chronic fatigue syndrome is heterogeneous. There can be little doubt that for the sporadic cases that are now encountered, the major explanation is depression. Such patients are often characterized by a violent refusal to accept a psychiatric explanation. The sociological reasons for this have been discussed by Wessely and Thomas.⁶⁸ In doing so, patients often do themselves a disservice as they may deny themselves appropriate treatment. It is also essential for the physician to be aware of this aspect so that psychiatric disorder does not go unrecognized.

The chronic fatigue syndrome is not a manifestation of encephalomyelitis. The carry-over from the supposed cause of the Royal Free epidemic is unfortunate and is encapsulated in the use of the label 'ME' which is favoured both by the lay press and by patients. Yet despite the failure to demonstrate any inflammatory disorder affecting the central nervous system, reports still attribute complaints such as mental fatigability and anomia to encephalitic manifestations.^{64,65}

It is evident that fatigue in this syndrome is of the subjective type. Little is known about the underlying neural mechanisms. The identification of the relevant pathways and the neurotransmitters that are involved could in the future lead to improved treatment for this troublesome and highly unpleasant symptom.

Diabetic neuropathy: a metabolic, vascular or degenerative disorder?

Satisfactory therapy for diabetic neuropathy will depend upon establishing its cause. It is possible to prevent the deterioration of neuropathy once it has appeared either by continuous subcutaneous insulin infusion⁶⁹ or by pancreatic transplantation⁹⁰ but neither of these forms of treatment is applicable for the majority of patients. Accepting that adequate control is not achieved in a high proportion of patients by conventional therapy, knowledge as to the particular consequences of the diabetic state that result in neuropathy could lead to the adoption of measures that specifically protect the peripheral nerves even in the face of glycaemic control that is less than ideal. The causation of peripheral nerve damage is therefore currently the central question relating to diabetic neuropathy.

A problem that immediately arises is the wide range of manifestations that are encountered in diabetic neuropathy. The commonest clinical syndrome is a chronic distal symmetric sensory polyneuropathy, often with accompanying autonomic disturbances of varying severity.⁹¹ An acute painful neuropathy may also occur.⁹² Apart from such symmetric polyneuropathies, patients with diabetes may develop focal and multifocal neuropathies, including cranial, trunk and limb mononeuropathies.⁹³ Diabetic subjects are also more susceptible to compression and entrapment neuropathies. Finally, lower limb motor neuropathies occur (diabetic amyotrophy), often, but not always, mainly proximal in distribution, sometimes with asymmetric and at others with relatively symmetric involvement.⁹⁴ Mixed syndromes are not infrequent.

Metabolic hypotheses

The salient metabolic abnormality in diabetic nerve is the accumulation of sorbitol. This is the result of increased flux through the polyol pathway in which glucose is converted to sorbitol by an aldose reductase and sorbitol to fructose by a polyol dehydrogenase. A proposal as to the way in which this might lead to neuropathy was developed largely from observations on experimental diabetes in rats. The accumulation of sorbitol was linked to a depressed intraneural concentration of the cyclic hexitol, *myo*-inositol and this, via reduced synthesis of phosphoinositides, to diminished intraneural sodium-potassium adenosine triphosphatase (Na^+K^+ -ATPase) activity.⁹⁵ The reduced Na^+K^+ -ATPase activity was believed to have a variety of effects, such as the impairment of nerve conduction velocity, altered axonal transport and defective amino acid uptake into sensory and autonomic ganglion cells, that ultimately resulted in neuropathy. It proved possible to prevent the reduction in nerve conduction velocity either by the administration of aldose reductase inhibitors that reduced the accumulation of sorbitol, or by giving dietary *myo*-inositol supplementation. This was so, despite persisting hyperglycaemia. Both these measures restored nerve Na^+K^+ -ATPase activity.

This appeared to be an attractive formulation but a number of lines of evidence now make it unlikely that the hypothesis accounts for diabetic neuropathy. Further animal studies have revealed a poor correlation between nerve *myo*-inositol concentrations and Na^+K^+ -ATPase activity. Firstly, as distinct from nerve trunks, in sensory ganglia Na^+K^+ -ATPase activity is not correlated with *myo*-inositol concentrations in streptozotocin-induced diabetes in rats.⁹⁶ Moreover, in galactose-induced neuropathy in rats where flux in the polyol pathway is also increased, leading to accumulation

of galactitol instead of sorbitol in nerve, nerve *myo*-inositol concentrations are reduced but Na^+ - K^+ -ATPase activity is *increased*.^{97,98} The most cogent piece of evidence is that in nerve biopsies from human patients with diabetic neuropathy, although sorbitol concentrations are increased, those for *myo*-inositol are not reduced.⁹⁹

Nevertheless, sorbitol accumulation is still a contender for the causation of nerve damage. The severity of nerve fibre loss is directly correlated with the amount of sorbitol accumulation.⁹⁹ Moreover, there is some evidence that aldose reductase inhibition leads to increased regenerative sprouting in patients with diabetic neuropathy when assessed in serial nerve biopsies.¹⁰⁰ But if sorbitol accumulation is the culprit, its mechanism of action has still to be elucidated in man.

Vascular hypothesis

Early views as to the causation of diabetic neuropathy implicated large vessel disease^{101,102} but this is no longer entertained. Fagerberg¹⁰³ noted the occurrence of thickening of the walls of the small neural vessels by PAS-positive material, later shown to be reduplicated basal lamina. The view was therefore advanced that diabetic neuropathy is related to microangiopathy. This view, which had fallen into disfavour because of a poor correlation between neuropathy and the vascular changes,^{104,105} has recently been strongly revived by a number of laboratories. It seems probable that many of the focal nerve lesions that occur in diabetic subjects are related to ischaemia, but the pathological verification for this is still limited and rests mainly on postmortem observations on patients with acute third cranial nerve lesions.¹⁰⁶ What is now suggested is that the totality of diabetic neuropathy may have a vascular basis.

Observations on streptozotocin-induced diabetic rats have documented reduced neural blood flow and reduced intraneural oxygen tension.¹⁰⁷ The reduction in nerve conduction velocity can partially be prevented by maintaining the animals in hyperbaric oxygen.¹⁰⁸ Yet the relevance of observations in the diabetic rat model to human neuropathy is still uncertain. Rats do not develop the degenerative changes in nerve seen in man.

It was reported that the numbers of 'closed' capillaries in nerve biopsies was greater in patients with diabetic neuropathy than in controls and that their number was correlated with the severity of neuropathy.¹⁰⁹ This observation has not been confirmed by others.^{110,111} The causal role of the thickening of the walls of endoneurial capillaries has been questioned. Vessel wall thickening may be observed in other neuropathies such as in hereditary motor and sensory neuropathy¹¹¹ and the reduplication of the basal lamina could therefore

be a secondary event, perhaps related to capillary wall hyperplasia. The persistence of the basal laminal material in diabetes could be the consequence of abnormal collagen cross-linkage produced by non-enzymatic glycation.¹¹²

The pattern of nerve fibre loss in nerve biopsies from patients with diabetic neuropathy has been found to be patchy, which was taken to support an ischaemic basis.¹¹³ Yet a similar patchy pattern of nerve fibre loss is seen in hereditary motor and sensory neuropathy, a disorder in which a vascular causation has not been entertained.¹¹⁴ The explanation for this is still uncertain. Sugimura and Dyck,¹¹⁵ Dyck *et al.*¹¹⁶ and Johnson *et al.*¹¹⁷ have found multifocal fibre loss in lower limb nerves in autopsied cases that suggested ischaemia. On the other hand, these patients were elderly and concurrent vascular disease would not have been unexpected.

Direct measurements of intraneural oxygen tension in patients with diabetic neuropathy have revealed reduced values in comparison with control subjects.¹¹⁸ This conclusion cannot yet be accepted without reservation as the age of the control subjects was significantly less than that of the diabetic patients. It is important that this study be repeated with age-matched controls.

Thus, although an impressive body of evidence favouring a vascular cause for diabetic neuropathy has been assembled, none of it is yet conclusive.

Diabetic polyneuropathy as a degenerative neurological disorder

Degenerative disorders constitute a major component of the spectrum of neurological disease. In these conditions there is a progressive disturbance related to loss of neurones, as in motor neurone disease, to a 'dying-back' distal axonopathy, as in Friedreich's ataxia, or to demyelination. Such disorders are often characterized by the fact that particular sets of neurones are affected and they are thus referred to as system atrophies. They clearly represent an aetiologically heterogeneous group, but the common theme is a failure to maintain cellular integrity or a failure of the processes involved in the maintenance of cell structure, as in the distal axonopathies. In earlier times, the occurrence of these events led to the use of the term 'abiotrophy'.

For diabetic polyneuropathy it is perhaps surprising that the precise pattern of pathological change is still not fully established. But there are many features that suggest a system degeneration. There is a predominant involvement of sensory and autonomic neurones with relative sparing of motor function. It is possible that the pathology will prove to be a central-peripheral distal axonopathy.¹¹⁹ A distally-accentuated degeneration of axons in the

peripheral nerves has been shown.^{120,121} Although degeneration is known to occur in the posterior columns of the spinal cord,^{104,105} it is not yet known whether this shows a rostral accentuation. The elucidation of the pattern of change that occurs is vital to the understanding of diabetic neuropathy.

In neurones, virtually all protein synthesis occurs in the cell bodies. Structural proteins, enzymes, etc., are then translocated down the axons to the periphery in the antegrade transport systems. There is no major disturbance of fast axonal transport, at least in experimental diabetes. Slow component a, in which the structural proteins are transported, is mildly impaired in streptozotocin-diabetic rats¹²² but, as already stated, this is not accompanied by a degenerative neuropathy. In this model, retrograde transport is also affected.¹²³ Whether a more profound disturbance in slow axonal transport occurs in human diabetic neuropathy is unknown, but it seems unlikely as axonal atrophy is not observed.

Insulin, apart from its action on glucose homeostasis, has important effects on protein metabolism. These could conceivably be involved in the degenerative changes that occur in diabetic neuropathy. The uptake of amino acids into dorsal root ganglia is known to be reduced in streptozotocin-diabetic rats¹²⁴ and is accompanied by reduced protein synthesis. Peripheral nerve, like the central nervous system, is not dependent on insulin for acute metabolic exchanges. Nevertheless, peripheral nerve, including the sensory ganglia, possesses insulin receptors,^{125,126} as does the central nervous system. Their function is obscure, but they could be involved in longer term neurotrophic effects in nervous tissue. If this is so, a disturbance of their function could underlie the degenerative neuronal changes that characterize diabetic neuropathy. These, so far, are speculative concepts, but they deserve further exploration.

A further possibility is related to nerve growth factor (NGF). Sympathetic and sensory neurones require NGF both for their development and for their maintenance in adult life. Endogenous levels of NGF have recently been shown to be altered in streptozotocin diabetic rats.¹²⁷ It was suggested that this may be implicated in some of the functional deficits that occur in the peripheral nervous system in diabetes.

Conclusion

The variegated clinical picture presented by the diabetic neuropathies¹²⁸ strongly suggests the operation of multiple causal factors. Thus it is probably a mistake to search for a single explanation but instead to think in terms of a variety of disturbances of varying importance in different individuals.

Neuroimaging

Introduction

In the field of clinical neuroimaging, the development of magnetic resonance (MR) scanning undoubtedly represents the greatest technical advance of recent years. Computerized X-ray tomographic scanning (CT) has changed very little in technical terms but its wider availability in district general hospitals has altered and in most respects improved the diagnostic process for patients with neurological and neurosurgical disorders. Vascular imaging has advanced and diversified with the development of digital subtraction technology and more widespread application of ultrasonography, although the precise clinical role of these techniques remains rather poorly defined. Sophisticated functional imaging and measurement by means of emission tomography continues to make a major contribution in the research field, with relatively little in the way of practical application in everyday clinical neurology. These various techniques will be reviewed and discussed in more detail.

Magnetic resonance scanning

As an imaging technique in brain and spinal cord MR is superior to CT in almost every respect, both for showing normal anatomical structure and pathological tissue. For many cerebral lesions, however, MR will simply show the same abnormality rather more clearly than CT, and there are relatively few common clinical disorders for which the indication for MR scanning can be regarded as absolute. Nevertheless, the development of less expensive and cumbersome magnetic scanners and the increasing requirement for cost effective investigation, preferably avoiding invasive inpatient procedures, will eventually lead to greater availability and use of MR scanning for routine clinical use.¹²⁹ The option of buying time on a mobile MR unit is particularly attractive in this respect.

The investigation of suspected demyelinating disease is a prime example for which CT scanning is rarely helpful and MR often diagnostic. Lesions are usually most obvious in the peri-ventricular white matter of the cerebral hemispheres but plaques can also be shown in the cerebellum, brainstem, spinal cord and optic nerves, structures which only very rarely appear abnormal on CT scans. The appearances are not pathognomonic of MS, however: like the finding of oligoclonal immunoglobulins in the CSF, multifocal white matter lesions may also be seen in various other conditions which include sarcoidosis, systemic lupus erythematosus, cerebral vasculitis, postviral encephalomyelitis and HIV-related disease. Uncertainty may also arise in middle aged and elderly

subjects, in whom areas of high signal around the ventricles are often present in the absence of any symptoms of disease, probably reflecting age-related vascular changes. The use and limitations of MR imaging in the diagnosis of multiple sclerosis is well reviewed in a study by Appel and colleagues.¹³⁰

Because of the limitations imposed on X-ray CT by bone artefact arising from the skull base and the use of only the transaxial imaging plane, MR scanning is also vastly superior for demonstrating structural lesions in the posterior fossa, particularly within the brainstem and at the cervico-medullary junction. Anatomical abnormalities at the foramen magnum and cervical syringomyelia are particularly well shown by this technique.

Imaging of the spinal cord in general is an area in which MR may eventually replace the existing standard procedure, which is myelography with or without CT scanning.¹³¹ This is particularly true when inflammatory or other intrinsic spinal cord pathology is suspected and visualization of the nerve roots is not a priority. For cervical and lumbar radicular lesions, myelography with CT probably remains the investigation of choice because neither MR nor plain CT of the spine shows the nerve roots clearly within their intrathecal course, particularly in the lumbar region.¹³¹ Intramedullary vascular lesions are likely to be well shown by MR scanning but extramedullary (dural) arteriovenous malformations may be missed by this technique; these lesions are still most appropriately pursued by myelography as a preliminary screening procedure, followed by spinal angiography if the diagnosis remains likely.

In the field of cerebrovascular disease, MRI has greater sensitivity than CT for detection of subtle vascular lesions, particularly small lacunar infarcts and the more confluent subcortical lesions that result from diffuse small vessel disease. So sensitive is the technique, however, that distinction between clinically significant subcortical vascular lesions and apparently benign age-related changes may be difficult. This lack of specificity becomes a problem in the very age group most likely to be affected by vascular disease of the brain. Magnetic resonance is clearly superior to CT for the demonstration of infarcts and very small haemorrhagic lesions in the brainstem, but in most other respects it has relatively few advantages for the routine investigation of cerebrovascular disorders.

Various functional applications of MR are being developed and these are likely to become clinically important in the future. For example, modification of the imposed magnetic field by means of gradient pulses can produce a subtraction angiographic image of the brain or, with different sequences, information about regional tissue blood flow. Quantitative blood flow measurements are still some way off but noninvasive MR angiography

seems more likely to become clinically applicable, and this would represent a major advance, particularly for the diagnosis and follow-up of cerebral aneurysms.

X-ray CT scanning

Apart from shortening of scanning times and some improvements in image quality, relatively few advances have been made in X-ray CT technology in the last 10 years. Functional applications of CT such as cerebral blood flow measurement with stable xenon are expensive and time consuming without having any of the versatility of emission tomography.

Wider availability of CT in district general hospitals allows more patients to be scanned, which is usually to their advantage. It also saves unnecessary travelling to regional centres for many ill patients with stroke, head injury and undiagnosed encephalopathy, although limited funding of district units in the present economic climate often precludes out-of-hours emergency work. When 24 hour scanning does become possible, it is critical for the safe management of neurological emergencies that the availability of neurodiological expertise should have developed in parallel with that of the scanning facilities. Another occasional source of difficulty is the use of more readily available CT scanning as a substitute for careful neurological assessment of the patient.

The addition of CT scanning during myelography in selected cases has undoubtedly improved diagnostic precision, although performance of this combined procedure may sometimes present logistical difficulties in a busy X-ray department with limited scanning time. Plain CT scanning for spinal disease is a rapidly expanding use of the technique, albeit with some limitations. In the cervical region it is rarely helpful without intrathecal contrast administration and concurrent myelography, but disc lesions in the lumbosacral region are often well shown without the need for spinal contrast injection. Laterally placed disc lesions causing compression of nerves roots beyond their intrathecal course may be missed by myelography alone and shown better by CT. The reverse is also true: prolapsed discs causing distortion of the theca and displacement of roots within it may be poorly shown by CT alone and only clearly visible on myelography.^{131,132} Any paraspinal soft tissue component of a malignant or inflammatory lesion is best shown by CT but again intrathecal contrast and conventional myelographic views may also be necessary to demonstrate the degree of spinal cord or cauda equina compression.

Vascular imaging: angiography and ultrasonography

Development of tomographic brain imaging — both CT and MR — has substantially reduced the requirement for intracranial angiography. The main indications for this procedure are now subarachnoid haemorrhage, delineation of arteriovenous malformations when surgery is contemplated, preoperative assessment of potentially vascular tumours and the diagnosis of rare conditions such as cortical thrombophlebitis, cerebral vasculitis and other unusual angiopathies.

The arrival of intravenous digital subtraction angiography (DSA) and vascular ultrasonography have reduced the risks and also the cost of cervical vascular imaging, which can now be carried out as an outpatient procedure. However, the relative merits of these two techniques and the clinical indications for performing them remain the subject of much debate and a rather confusing body of literature.¹³³ As a broad generalization, carotid ultrasound is probably superior for looking at plaque morphology and for providing some functional information — flow velocity for example — whereas good quality DSA gives a clearer anatomical picture of the type that most vascular surgeons like to see before considering endarterectomy. There is, however, a general trend towards more conservative management of carotid artery disease and this has somewhat reduced the clinical demand for imaging of the extracranial vessels in the last few years. Only the results of the European and North American endarterectomy trials can show whether or not this trend is justified.

Although labour-intensive and strictly operator dependent, carotid ultrasound is particularly useful as a research technique: being noninvasive and serially repeatable, it offers the best chance of following the natural history of carotid atherosclerotic disease in patients not being subjected to surgical treatment. Examination of large intracranial arteries by means of transcranial Doppler has also remained predominantly a research technique up to now, and the possible clinical applications suggested by some authors are not generally agreed upon.

Emission tomography

The principles of tomographic detection and reconstruction can be applied to the distribution of radioisotopes within the brain or cerebral vascular compartment to produce emission, rather than transmission, tomographic images. Depending on the isotope and its handling within the tissues, these functional images can display regional blood flow, blood volume, metabolic consumption of oxygen or glucose, cerebral pH, or the distribution of

neurotransmitter storage sites or receptor density within the brain. The distinctive twin photon radiation produced by positron-emitting isotopes enables their concentration in the brain to be measured in absolute units, since it is also possible to measure tomographically and correct for the attenuating effect of the tissues. Positron emission tomography (PET) is therefore a quantitative technique, the images being merely a convenient means of displaying the data. Apart from the cost of the tomographic camera itself, one disadvantage of PET is the very short half-life of most of the biologically useful positron emitting isotopes, which therefore require a cyclotron for their production in or near the scanning unit. Single photon emission tomography (SPECT) cannot be truly quantitative but it does represent a less expensive and elaborate form of functional imaging.

The greatest initial impact of PET was in the study of cerebrovascular disease, dementia and epilepsy. Quite apart from the considerable contribution on the research side, in these areas PET has produced information of some diagnostic and practical value to clinicians. Its possible role in the management of cerebral tumours is less clearly established.¹³⁴ In recent years there has been further progress in the delineation of distinctive regional patterns of disturbance in various dementia syndromes, and also in the field of movement disorders.¹³⁵ Characteristic patterns of subcortical and cortical metabolic activity, striatal DOPA uptake and dopamine D2 receptor binding sites have been described in idiopathic Parkinson's disease, the less common parkinsonian syndromes and in Huntington's disease.¹³⁵ The considerable interest in applying PET to identification of individuals with Huntington's disease in the presymptomatic stage has been overshadowed to a large extent by developments in DNA technology in the last 5 years.

Emission tomography remains predominantly a powerful and expensive clinical research tool. Whether there are any definite applications for the technique in everyday clinical neurology is still rather questionable. As one might expect, the concept of a clinical PET centre is more highly developed in the United States and there is some difference of opinion about the clinical role of PET on each side of the Atlantic.^{134,135} These two reviews by Brooks¹³⁵ and Kuhl¹³⁴ are a good starting point for further reading about PET and its applications.

Dementia

Introduction

Deterioration of intellect in the middle aged and elderly is not only a common clinical problem but also a major public health issue, made all the more

acute by the combined pressures of an ageing population and the increasingly competitive funding of community health care. The difficult challenge of managing young people with dementia has been brought sharply to our attention by the AIDS epidemic. Much progress has been made in the last 20 years, both in the clinical assessment and classification of dementia syndromes and in our knowledge of their underlying neurochemistry, pathology and molecular biology. The pathophysiological basis of dementia resulting from vascular disease has been the subject of more critical analysis and periodic review. The wider availability of CT scanning and the emergence of magnetic resonance imaging have gone some way towards improving the precision of clinical diagnosis, particularly the distinction between degenerative and multi-infarct disease. Nevertheless, more than one pathology may often coexist in the same patient and autopsy studies continue to reveal a higher than expected incidence of clinical misdiagnosis in patients with dementia. In certain specific instances, prognostic information and genetic counselling can be immensely helpful to patients and their families. Regrettably, however, the considerable mass of information accumulated from recent research has so far produced little of immediate practical or therapeutic value to patients with dementing disorders.

Alzheimer's disease

The major clinical features of Alzheimer's disease – memory loss, dysphasia, dyspraxia and visuospatial disturbance – reflect the predominantly cortical nature of the disease, in contrast to so-called subcortical dementias (see below). In the early stages the clinical syndrome may be remarkably focal, consisting for example of dysphasia with little or no evidence of more global dementia. Depressive symptoms are common and often responsive to treatment.¹³⁶ Disintegration of personality and behaviour later add to the already distressing consequences of the cognitive deficits. With progressive loss of insight, the impact of the disease shifts away from the patient to some extent and increasingly onto the carers, a point which has important implications in the management of the disorder.¹³⁷

In most cases, there are few physical neurological signs, although the presence of extrapyramidal features has been increasingly recognized in patients with otherwise typical features of Alzheimer's disease. This clinical point remains the subject of some debate,¹³⁸ to which has been added recently the wider acceptance of dementia as a feature of Parkinson's disease. The combination of classical parkinsonism and dementia may result either from coexistent Alzheimer-type pathology in

an otherwise typical parkinsonian patient or from widespread involvement of the cerebral cortex by diffuse Lewy body disease.¹³⁹

Epidemiological evidence suggests that, particularly amongst patients developing symptoms at an early age, Alzheimer's disease is often acquired by autosomal dominant inheritance, whereas patients presenting later in life are more likely to have the sporadic form of the disorder. The familial Alzheimer gene has been located to the proximal long arm of chromosome 21. This was of interest in relation to the frequent occurrence of Alzheimer pathology at a relatively early age in patients with Down's syndrome, but the site of the genetic defect on chromosome 21 has been shown to be distinct in the two disorders. A specific β amyloid protein found in the central core of senile plaques and in cerebral blood vessels of patients with Alzheimer's disease is also coded (via a precursor protein) from chromosome 21. However, there is new clear evidence that the gene sites for this β amyloid and familial Alzheimer's disease are not identical either, and the precise nature of the genetic defect in Alzheimer's disease has yet to be identified.¹⁴⁰

The discovery of MPTP-induced parkinsonism has revived interest in environmental neurotoxins, but none so far has been convincingly linked with Alzheimer's disease. The high aluminium content of neurofibrillary tangles and the fact that similar (but not identical) tangles are found in the brains of patients with dialysis-related dementia has led to much speculation about aluminium as a possible aetiological agent. However, its presence in high concentration in the lesions of Alzheimer's disease could equally well be a secondary consequence of some other primary pathophysiological mechanism. Certain clinical and pathological similarities between Alzheimer's disease and the transmissible spongiform encephalopathies raise the possibility of a slow virus or prion as the causative agent. Although this is conceivable, the generally late age of onset in Alzheimer's would be rather difficult to account for on this basis. The topical question of prion disease and spongiform encephalopathy has recently been reviewed.¹⁴¹

No treatment has so far been shown to improve the cognitive impairment in patients with Alzheimer's disease. The discovery of a pronounced loss of central cholinergic neurones led to the hope that there might be effective pharmacological treatment, analogous to the use of dopaminergic agents in Parkinson's disease. This was the basis for the use of tetrahydroamino acridine (THA), a centrally-acting anticholinesterase inhibitor, for which dramatic claims were made in some of the preliminary trials. However, subsequent studies have not so far borne out the impression that this agent has a useful therapeutic effect.^{136,142} Earlier trials with physostigmine and other centrally-acting cho-

linergic agents have been equally disappointing and these drugs have a high incidence of unacceptable side effects.¹³⁶ Low doses of selegeline (Deprenyl) have been said to reduce anxiety, depression and agitation in some patients, implying that deficiency of central dopaminergic neurotransmission may contribute to some of the behavioural disturbances of Alzheimer's disease.¹³⁶ It was inherently unlikely that all the manifestations of this disorder could be attributed to failure of a single neurotransmitter system and there is now evidence to implicate other monoamines, amino acid transmitters and neuropeptides in the pathophysiology of the disease.¹⁴³ The prospects for effective pharmacological modification of symptoms therefore remain poor at the present time. Management of patients with this devastating disease still depends largely upon the provision of practical and emotional support for the family with the help of a team of appropriate therapists and community workers.^{137,144}

Non-Alzheimer degenerative dementias

Progressive focal syndromes with cerebral atrophy confined to the frontal or temporal lobes have often been lumped together in the past under a diagnostic label of Pick's disease. In recent years it has become clear that patients in this clinical category do not always have the characteristic pathological changes of Pick's disease, namely localized cortical neuronal loss with the presence of argyrophilic inclusions (Pick bodies) in the neural perikaryon. A group of patients with a frontal lobe syndrome and pathological features apparently distinct from either Alzheimer's or Pick's disease has been described by Neary and others under the heading of 'dementia of frontal lobe type'.^{145,146} A small number of such patients have later gone on to develop features of motor neurone disease. The results of neuropsychological assessment, functional tomography and pathological examination do follow a consistent pattern in many of these patients but there is still some uncertainty about the existence of this disorder as a distinct nosological entity.¹⁴⁶

A more localized unilateral disorder characterized by progressive dysphasia has also been recognized, in which the pathology is largely confined to the sylvian region in the dominant hemisphere. Again there is some debate as to whether this is a localized form of Alzheimer's disease or Pick's disease, or a completely separate entity.¹⁴⁶ Another focal syndrome of 'posterior cortical atrophy' has been described on the basis of clinical and radiological features. These patients presented with severe dyslexia, dysgraphia, dyscalculia, transcortical dysphasia, visual agnosia and disorientation, whilst memory and personality were relatively well preserved. The small number of

reported pathological studies have shown features suggestive of localized Alzheimer's disease in some patients but not others.¹⁴⁶

As indicated above, the combination of progressive generalized dementia of cortical type with apparently classical, dopa-responsive parkinsonism may be associated neuropathologically with the presence of widespread Lewy bodies in the cerebral cortex as well as in the nigrostriatal system.^{139,145} Nevertheless, the Lewy body should not necessarily be regarded as a diagnostic marker for a single disease: like the Pick body, it is no more than a cellular inclusion made up of degraded intracellular proteins. The finding of diffuse Lewy bodies is not always accompanied by parkinsonism¹³⁹ and the clinical features associated with this pathology are quite variable, sometimes including other movement disorders and pyramidal signs as well as dementia and parkinsonism.¹⁴⁷

The concept of subcortical dementia

It has been suggested that in patients with dementia resulting from certain disorders which include subcortical pathology – particularly Huntington's disease, progressive supranuclear palsy and classical Parkinson's disease without cortical Lewy bodies – there is a characteristic pattern of neuropsychological disturbance which is distinct from that of predominantly cortical disorders. Communicating hydrocephalus and diffuse periventricular vascular disease might also be included in the 'subcortical' group of dementing disorders. In contrast to the dysphasia, dyspraxia, agnosia and marked amnesia of Alzheimer's disease, the main features of subcortical dementia are said to be a general slowness of thought (bradyphrenia) and impaired ability to retrieve and manipulate acquired knowledge rather than frank amnesia.^{148,145} The subcortical disorders certainly have in common a disruption of many aspects of motor function, the gait and stance being most obviously affected, and the presence of generalized psychomotor retardation is likely to affect test performance in certain predictable ways. However, not all investigators have been able to support the concept of a clear cut qualitative difference between dementia of cortical and subcortical disease.¹⁴⁹

Huntington's disease

The discovery of a DNA marker closely linked to the locus for Huntington's disease on chromosome 4 has been one of the most important applications of molecular genetics in the field of neurological disease. Much further progress has been made since the original publication in 1983¹⁵⁰ and a number of centres are now offering a predictive testing service based on the analysis of blood samples from

individuals at risk and their relatives, ideally using material from three generations rather than two. This is clearly a major advance but there are still many limitations to the reliability of such testing, and also some difficult ethical problems to be faced by those providing the service.¹⁵¹

Dementia due to vascular disease

Vascular dementia has probably been overdiagnosed in the past. In a recent autopsy study only 6 of 65 demented patients were found to have only vascular disease as the likely cause for their symptoms, while 38 had only Alzheimer pathology and 10 had a mixed picture.¹⁵² Only 1 of 4 patients with a confident clinical diagnosis of vascular dementia had isolated cerebrovascular disease at autopsy, the other 3 having Alzheimer's disease as well. Misdiagnosis in the other direction was infrequent.

The traditional concept of chronic progressive 'cerebral arteriosclerosis' was replaced in the early 1970s by the pronouncement that multiple discrete infarcts were the cause of vascular dementia. Multi-infarct disease could then be classified most simply into two broad categories: bilateral cortical lesions resulting from thromboembolism – usually from the heart, rarely from the neck vessels – or multiple subcortical infarcts of lacunar-type, typically in patients with hypertensive small vessel disease. In a separate, rather ill-fitting category,

was the more diffuse type of subcortical small vessel disease that had been described originally in 1894 by Binswanger. This was something of an oversimplification, since dementia due to vascular disease can result from several pathophysiological mechanisms in a wide variety of clinical settings (see Table I). This classification includes some rare causes of vascular dementia but it does emphasize the range of investigations that may be necessary, particularly in younger patients with unexplained dementia of possible vascular origin. Another important point is that in most of these disorders, including the more common ones, the underlying mechanism may be amenable to therapeutic intervention. Hypertension is by far the commonest treatable factor, contributing particularly to local and diffuse small vessel disease as well as carotid atheroma and cardiac abnormalities. Cerebral vasculitis is rare but probably underdiagnosed as a cause of patchy small vessel disease in patients of all ages.

Some important pathophysiological aspects of vascular dementia are discussed in a recent review by Brown and Hachinski,¹⁵³ including particularly the revival of interest in haemodynamic factors in patients with diffuse subcortical vascular disease. To some extent this line of thought represents a return towards the additional and previously rejected concept of progressive cerebral arterial insufficiency.

Table I Causes of vascular dementia

Type and site of cerebral ischaemic lesion	Underlying vascular disorder
Multiple discrete embolic infarcts (mainly cortical)	Cardiac emboli (Bilateral carotid atheroma) (Fat or air embolism)
Multiple subcortical lacunar infarcts	Subcortical small vessel disease, often hypertensive
Diffuse subcortical ischaemic lesions	Confluent, symmetrical small vessel disease in periventricular white matter ('Binswanger disease')
Bilateral paramedian thalamic infarction	Distal basilar occlusion or embolism Focal small vessel disease
Watershed ('borderzone') infarcts of haemodynamic origin (cortical and subcortical)	Severe bilateral occlusive carotid disease. Cardiac arrest and other major hypotensive insults
Diffuse or multifocal lesions due to rare occlusive angiopathies	Cerebral angiitis of any cause. Amyloid (congoophilic) angiopathy. Hereditary multi-infarct dementia.
Bilateral venous hemispheric infarction (cortical and subcortical)	Cortical thrombophlebitis. Sagittal sinus thrombosis.
Systemic causes of multiple cerebral vascular occlusions	SLE, PAN, TTP Antiphospholipid syndrome, Sickle cell disease, Lymphomatous angiopathies

SLE – systemic lupus erythematosus; PAN polyarteritis nodosa; TTP – thrombotic thrombocytopenic purpura.

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