Problems in neuroscience research

To anyone undertaking laboratory or clinical research in the neurosciences a recent publication by the Wellcome Trust,¹ the world’s largest biomedical charity, is of great interest. Although specifically aimed at reviewing the quality of neuroscience research in the United Kingdom, an important goal was to identify the problems of neuroscientists, which are certainly typical of those encountered in neuroscience research communities across the globe.

Although everyone is aware of the tremendous financial burden imposed on society by neurological and psychiatric disease, the report usefully quantifies this cost. For example, in the United Kingdom these diseases accounted for 8% of all NHS costs in 1994, representing an estimated cost of £3.4 billion, undoubtedly an underestimate. In the United States the annual economic cost of Alzheimer’s disease, depression, and stroke alone has been estimated to be US$174 billion. Not only is this burden, resulting from neurological and psychiatric disorders, set to increase in developed countries where there is steadily increasing longevity, it will also increase in the developing countries, where the shift in the age distribution of the population due to the progressive eradication of communicable diseases will lead to a greater proportion of the disease burden being associated with neurological and related disorders.

Has the response to this increasing burden of neurological and psychiatric disease in terms of research funding been appropriate? In the United Kingdom the main research funding sources are the Medical Research Council (£56.9 million in 1996–97), the Wellcome Trust (about £60 million in 1998), and to a much smaller extent but no less important, many other neurological charitable organisations. In the United States President George Bush heralded in the “Decade of the Brain” in 1990, which led to an NIH-wide real increase in spending of 22% between 1991 and 1995. Even as the decade comes to an end the 1998 budgets for the NIH show an additional and separate US$37 million allocated for research into brain disorders. The European Union launched their own “Decade of the Brain” initiative in 1992. However, although this initiative may have led to increased spending on brain research in the 4th Framework Programme (1994–8) and the current 5th Framework Programme, the neuroscience slice of the biomedical research cake is modest in comparison with the United States. The largest player in the field, however, is of course the pharmaceutical industry, which, it has been estimated, invested $37.3 billion in 1996 for research and development for cures or preventive therapies for neurological and psychiatric disorders.

What then are the main issues confronting neuroscience research today worldwide, according to the sample of neuroscientists surveyed for the report? Interestingly, one might have expected lack of funding to be considered the main issue, but it was second to a perceived lack of career development for young scientists. This mainly related to the young non-clinical neuroscientists, yet it surely also applies to the research training of neurologists and psychiatrists. The third commonest issue identified was the management load of the best researchers. All these problems are of course endemic to working within the United Kingdom university research system, rather than being specific to neuroscience research, but they probably extend beyond the United Kingdom.

The report also summarises the outcome of a workshop meeting to discuss the future of neuroscience research where the main points were:

- The need for multidisciplinary research throughout neuroscience and for funding mechanisms to encourage multidisciplinary research programmes
- The next incremental advance would be to study a further level of organisational complexity within a researcher’s experimental system
- The application of newly developed genetic technologies to neuroscience research
- The need for high quality infrastructural support.

To return to the research training of clinicians in neurology and psychiatry, this differs from one country to the next, and even in the United Kingdom there is no consistency across medical specialties. Currently most junior doctors planning a career in neurology will undertake a period (2–3 years) of either clinical or laboratory based research after their senior house officer posts in general medicine, and before they have even been appointed to a neurology specialist training post. In psychiatry, research is undertaken, often in association with a taught MSc course, during their specialist training. Both models have their advocates, but undoubtedly we are not maximising opportunities to promote the development of high calibre clinician scientists. To complete an MD/PhD and then follow it with 4–5 years of solid clinical neurology training is hardly ideal, leading as it does to a severance from research at a critical time for any trainee wishing to develop an academic career. Equally, is it really necessary for all trainees to undertake such a concentrated, inappropriately timed, period of research when most will become busy clinical neurologists in district general hospitals?

In the United States research training usually takes place after specialty training, during the subspecialty fellowship
Neurology of Whipple’s disease

In 1907, George Hoyt Whipple, then an instructor in pathology at Johns Hopkins University, published a case report of a 36 year old physician who had been domiciled in Constantinople. He developed recurring arthropathy, weight loss, and steatorrhea, became worse, and died. At necropsy the intestine and mesenteric lymph glands were infiltrated by mononuclear and polymuclear giant cells and deposits of fat and fatty acids. Whipple described the large “foamy” mononuclear cells in the intestinal mucosa which were later shown to contain periodic acid Schiff (PAS) positive material. The aetiology of the condition was not established and he wrote “Gland tissue treated by the Levaditi method shows great numbers of a peculiar rod-shaped organism (?) which does not stain by the aniline dyes . . . ” Whether this is the aetiological factor in this disease cannot be determined from this case”. A prescient observation. He suggested intestinal lipodystrophy as a name for the disease.

**General features**

Whipple’s disease is rare—since its first description less than 1000 cases have been reported in the literature which is certainly an underestimate of all cases. Men are affected much more often than women (over 80%) and the mean age of onset approaches 50 although the age range extends from childhood to senility. Cases which have been reported have originated from Europe and North America in the main. Whether this is a true reflection of its aetiology or relates to technical difficulties in reaching a diagnosis is not clear. The natural habitat of the organism is not known, nor are the mechanisms by which infection takes place. The number of cases described in reports is too low to determine whether there is a racial susceptibility. The most common clinical presentation is a malabsorption syndrome with diarrhoea, abdominal pain, weight loss, generalised wasting, variable fever, and lymphadenopathy. Many cases are associated with longstanding and relapsing arthropathies. The onset is insidious and the symptoms and signs are commonly atypical. The CNS, lungs, heart, eyes, and skin may be involved and the disease may first manifest in these organs. Some present with a pyrexia of unknown origin, lymphadenopathy, and a sarcoidosis-like picture. Perhaps as many as 15% of patients do not have gastrointestinal symptoms throughout their illness and jejunal biopsy may be normal. It is therefore not surprising that in many of these atypical cases the diagnosis may not be made for some time and unfortunately, it may be missed until it is demonstrated at necropsy.

*Tropheryma whippelii*

The aetiology and pathogenesis of Whipple’s disease have remained elusive until recently although a bacterial cause has been postulated since the original description. Attempts to culture the organism over the years have been negatory, yet accumulated circumstantial evidence has led to the identification of a bacillus with unique characteristics as the cause. It has been consistently recognised in affected tissue using electron microscopy,2 lying free or degraded to varying degrees within macrophages. Patients with Whipple’s disease who are treated with antibiotics improve and improvement is accompanied by disappearance of bacilli; recurrence of disease is accompanied by re-emergence of bacteria.3–5 The morphology of the organism has been described.6 It is a weakly gram positive rod shaped bacillus which is not acid fast. It is 1–2 µm in length and has a thick wall, the inner layer of which stains with PAS dyes and it is this characteristic which accounts for the brightly staining PAS positive macrophages which are seen in biopsy material and which contain bacillary debris. It has resisted attempts to be cultured. In 1997 reproduction of the organism in tissue culture was reported by Schoeden et al7 who used interleukin-4 to deactivate macrophages. The difficulties experienced in isolating the organism stimulated the application of molecular genetic techniques to the search and led to the identification of a single 16S rRNA gene sequence from tissue derived from small bowel biopsy of patients with Whipple’s disease.8–11 Using the polymerase chain reaction (PCR), positive results have been obtained from other tissues including the heart,12 vitreous fluid,13 peripheral blood cells,14 15 and pleural effusion cells16 It has proved particularly difficult to identify sequences in brain tissue16 yet a recent report gave a high yield for PCR on CSF.17 Analysis of the 16S rRNA gene sequence found a phylogenetic association with the *Actinomyces* and Whipple’s bacillus is thought to be a novel actinomycete. It has been given the name *Tropheryma whippelii*. Whether the same bacterium causes all forms of Whipple’s disease and its multisystem manifestations remains to be determined.
Neurology of Whipple’s Disease

Pathogenesis
Because it has been so difficult to isolate the organism associated with Whipple’s disease, little is known of its occurrence in nature, the method of its transmission to humans, and the mechanisms of production of disease once infection takes place. Humans are the only known host for the disease. There is no evidence for person to person transmission and it does not seem to occur in clusters. Maiwald et al. have recently detected DNA specific for Whipple’s bacillus in sewage water in Germany and they argue for an environmental source of infection. Because of the gastrointestinal location of the disease it is inferred that infection takes place by ingestion of the organism. From there it probably disseminates through the body via lymphatics and bloodstream and spreads infection to other organs. The brain is a favoured site but the mechanisms by which the organism breaches the blood-brain barrier are not known, neither is the role of host immunity. Whether the clinical manifestations of the disease result from direct bacterial invasion, or from a bacterially provoked inflammatory response, is not clear.

Neuropathology
Precedence in describing changes in the CNS in Whipple’s disease is given to Sieracki and Sieracki et al. who were closely followed by Lampert et al. and Badenoch et al. Since then numerous descriptions of pathological changes in the CNS have appeared and in 1977 Romanul et al. published details of a case in which the disease seemed to be confined to the CNS. It is likely that cases of Whipple’s disease with neurological involvement had been described before but it was not recognised in these cases that the underlying disease was Whipple’s. Also, the significance of neurological symptoms in established cases was not recognised. The gross pathological features of Whipple’s disease in the CNS are generalised cerebral atrophy and small chalky nodules or granulomas up to 2 mm in diameter scattered diffusely in grey matter of the cerebral and cerebellar cortex and in subependymal grey matter around the ventricles and the aqueduct. The changes are focal and one area of the brain may be normal whereas an adjacent area may show florid abnormality. Microscopically, those granulomas have been shown to contain strongly positive PAS staining macrophages surrounded by large reactive astrocytes. With more widespread disease PAS positive cells infiltrate white matter and may burst through into the subarachnoid space and be associated with death of neurons, formation of vacuoles, and demyelination. Debris of bacilli may be found in the PAS positive material. Microfibrils have been described, perhaps caused by emboli: vegetations on the heart valves have been found in a substantial proportion of cases at necropsy. In the areas of the brain with the heaviest PAS positive staining, bacilli and bacillary debris may be seen. Electron microscopic appearances were described in 1969 and corresponded to that of the bacilli seen in intestinal Whipple’s disease. The electron microscopic appearance of the Whipple’s bacillus is considered to be quite specific.

Table

<table>
<thead>
<tr>
<th>CNS Manifestations of Whipple’s Disease</th>
<th>Mental change–dementia</th>
<th>Myoclonus</th>
<th>Hypothalamic damage</th>
<th>OMM and OFMM</th>
<th>Epilepsy</th>
<th>Focal cerebral and cerebellar syndromes</th>
<th>Aseptic meningitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>OMM=oculomasticatory myorhythmia; OFMM=oculofacial-skeletal myorhythmia.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Neurological aspects
Because of the rarity of Whipple’s disease it is difficult to know just how often the CNS is affected. Reviews report figures which vary between 5% to just over 40%. Perhaps in as many as 5% of all cases of Whipple’s disease, the presentation is neurological and the disease remains confined to the nervous system for the most part of the evolution of the disease.

In several of these cases there has been no evidence of clinical involvement of the gastrointestinal system which makes diagnosis particularly problematic. Irrespective of disease elsewhere in the body, the neurological manifestations of Whipple’s disease are now sufficiently well described to enable us to recognise some patterns which point to the diagnosis. Dementia, disturbances of ocular movement, abnormal involuntary movements, particularly myoclonus, and deranged function of the hypothalamus are most often found. Epilepsy, focal cerebral signs, ataxia, and meningitic features may also be present. It is not usual to get involvement of the spinal cord or of muscle or peripheral nerve although myelopathy has been described. Headache is a very common symptom.

There is nothing remarkable about the mental changes which accompany Whipple’s disease (table). They constitute the most often encountered neurological abnormalities in just over half of all cases, and coexist with other CNS syndromes. Depression, cognitive decline, confusion, and behavioural and personality change and memory loss may progress insidiously and in the beginning may be dismissed as changes of ageing or even of the onset of Alzheimer’s disease. Disturbances of ocular movement are the next most common finding. Almost always the ophthalmoplegia is of supranuclear gaze palsy type with involvement of vertical rather than horizontal movement. Pure oculomotor palsies are rare. Internuclear ophthalmoplegia may occur.

Movement disorders are the next most common and may involve ocular movement. Oculomotor and oculofacial-skeletal myorhythmia occur and are said to be pathognomonic for Whipple’s disease—Louis et al. claim that these findings have not been documented in cases other than Whipple’s disease and consider them to be diagnostic findings. Oculomotor myorhythmia is characterised by pendular convergent divergent oscillations of the eyes, synchronous with involuntary rhythmic contraction of the muscles of mastication at a rate of approximately one per second. Oculofacial-skeletal myorhythmia is a more widespread expression of the same disorder with synchronous movements at the same rate of muscles of the extremities and face.

Myoclonus is well recognised and has been described affecting limbs alone, and the facial muscles. Ataxia has been recognised in some cases. The triad of dementia, ophthalmoplegia, and myoclonus occurs in about 10% of cases and is highly suggestive of Whipple’s disease.

Hypothalamic derangement causing sleep disruption and excess, polydipsia, and hyperphagia has been described. It will be recalled that the pathology in Whipple’s disease of the CNS may be patchy throughout the cerebral hemispheres and that microembolism may take place. Consequently signs and symptoms focal to the area of the affected brain may be found, hence dysphasia, seizures, cortical blindness, cranial nerve disturbances including trigeminal neuralgia, brainstem, and cerebellar signs have been recorded.

The eye is also a site of Whipple’s disease. Uveitis, retinitis, vitritis, keratitis, optic neuritis, and papilloedema may be found. The clinical picture may easily mimic sarcoidosis and forms of cerebral vasculitis. According to Louis et al. 80% of the patients in their review had clinical evidence of systemic disease and this...
encompassed migratory arthralgias and polyarthritis, unexplained weight loss, chronic diarrhoea, abdominal pain, steatorrhoea, abdominal distension, pyrexia of unknown origin, lymphadenopathy, night sweats, malaise, and uveitis. Such a constellation of symptomatology invites a wide differential diagnosis. The same authors proposed diagnostic guidelines for establishing definite, and possible, Whipple’s disease of the CNS. It is important to remember that the progression of Whipple’s disease is naturally slow and insidious although rapid deterioration may take place. After a lingering prelude of arthralgia and fatigue, weight loss, fever and gastrointestinal complaints follow to merge into cachexia, malnutrition, and death, the whole evolution taking years.

Investigations

Routine laboratory studies are commonly abnormal in a non-specific way. The erythrocyte sedimentation rate may be raised, anaemia and hypoalbuminaemia from steatorrhoea may occur. Liver function tests may be deranged. Routine examination of CSF also discloses non-specific results—protein may be raised, there may be a pleocytosis, results—protein may be raised, there may be a pleocytosis, rhoea may occur. Liver function tests may be deranged. Routine laboratory studies are commonly abnormal in a wide differential diagnosis. The same authors proposed diagnostic guidelines for establishing definite, and possible, Whipple’s disease of the CNS. It is important to remember that the progression of Whipple’s disease is naturally slow and insidious although rapid deterioration may take place. After a lingering prelude of arthralgia and fatigue, weight loss, fever and gastrointestinal complaints follow to merge into cachexia, malnutrition, and death, the whole evolution taking years.

The application of a PCR assay against *Tropheryma whippelii* has transformed the ease of diagnosis. As reported above, positive results have been obtained from several tissues and from CSF and PCR is more sensitive and specific than other techniques. PCR has been shown to be positive in biopsy normal specimens of duodenum. It is now the diagnostic method of choice although its limitations have not yet been defined.

Brain imaging techniques and electroencephalography show abnormalities which are not diagnostic. The EEG has shown slow wave activity. CT and MR images have been normal, have shown atrophic changes, mass lesions with contrast enhancement, white matter non-space occupying high signal areas, ring enhancing lesions, and hydrocephalus. On clinical grounds and after imaging, it can be appreciated that the differential diagnosis of Whipple’s disease in the CNS encompasses a large slice of neurology. Several forms of encephalopathy and some of the more indolent encephalitides, demyelination, and the range of CNS vasculitides have many features in common with neurological Whipple’s disease. Granulomatous disease including sarcoid and more chronic CNS infections such as tuberculosis, particularly if atypical bacteria are implicated, and AIDS is associated can cause diagnostic confusion. The early stages of cerebral degeneration such as Alzheimer’s disease, and if abnormal movements are present, Creutzfeld-Jacob disease can be similar. Therefore it is necessary for the clinician to retain a high index of suspicion that Whipple’s disease may be the cause of these various syndromes.

Treatment

Antibiotics have been used to treat Whipple’s disease as they have become available. Results have been variable. It is difficult to reverse established neurological defects and there is a tendency for the disease to relapse once antibiotics have been withdrawn and indeed, in some cases, deterioration has taken place while treatment has continued. Neurological complications are likely to be the cause of relapse in the first place. When relapse occurs it is more difficult to treat. Furthermore, neurological relapse often takes place some time after treatment has been stopped. Experience suggests that relapse may occur more often in those patients treated with single drug regimes and with antibiotics which do not penetrate the blood-brain barrier. The combination of trimethoprim-sulfamethoxazole (cotrimoxazole) has been reported to be effective but some treatment failures have occurred with this regime. Not surprisingly, when there is so little concentrated experience of the condition in any one centre, no consensus of opinion has been reached regarding the optimal drug regime for the treatment of Whipple’s disease. Most agree that initial treatment with a combination of parenteral penicillin and streptomycin for at least 14 days is appropriate, thereafter cotrimoxazole orally 3 times a day for at least one and probably for 2 years. Others would recommend following on after penicillin/streptomycin with third generation cephalosporins, and this is my favoured option—ceftriaxone parenterally for at least a month to be followed by 2 years of oral cefixime. Chloramphenicol has been used successfully. Experience with rifamicin and the macrolides is too small to allow conclusions to be drawn. There does not seem to be any place for the use of steroids. Symptomatic treatment is given for concurrent complications. Anticonvulsant drugs are given for seizures: valproate, clonazepam and piracetam have been tried for myoclonus and abnormal movements.

It is important that the patient is closely monitored throughout the duration of treatment. Serial brain imaging can demonstrate improvement or deterioration in existing lesions and detect the appearance of new ones. In the past it was usual to monitor progress by serial small bowel biopsy and to gauge success by demonstrating resolution of the histological changes and eradication of the organism from the specimens. Unfortunately this did not always guarantee a successful outcome—recurrence would take place in at least a third of cases. Also histological changes do not always correlate with clinical improvement or with molecular biological test results. PCR is now recognised to be the best tool for monitoring progress and in cases of neurological Whipple’s disease it is prudent to check the CSF as well as bowel for negative results before discontinuing antibiotic treatment. After cessation of antibiotic treatment further PCR checks of CSF should take place at intervals determined by the clinical progress of the patient and the acumen of the physician.

Relapse after treatment of Whipple’s disease is common and CNS involvement carries the highest relapse rate which may take place some years after antibiotic treatment has ceased. It is said that those cases with ophthalmoplegia and mental change respond best to antibiotic treatment, whereas those with more obvious structural lesions such as granulomas, infarcts, and atrophic change do less well. Long term follow up with repeated PCR tissue analysis is necessary for such cases. At this stage it is not possible to say if repeated CSF analysis is sufficient—probably not.

Whipple’s disease is now established as one of the more esoteric of the infectious diseases that affect the nervous system. Much remains unknown about its pathogenesis and how it interacts with host immune mechanisms. Great strides have been made in recent years but the development of a highly specific diagnostic PCR which seems to be effective when applied to CSF. Treatment is
possible with antibiotics and if the diagnosis is made early enough cure can be effected. It is important that neurologists remain alert to Whipple’s disease as a potential differential diagnosis in a wide range of CNS disorders—encephalopathies, chronic meningitides, cerebral vasculitides and granulomas, incipient demetnias and the range of focal cerebral disturbances associated with solid and cavitating lesions on CT and MRI of the brain (much like AIDS). When there is already evidence of gastrointestinal disturbance the diagnosis is perhaps a little easier but it is important to remember that neurological Whipple’s disease can occur as the presenting manifestation of the disease; hence the very wide differential diagnosis. Perhaps in future a request for “PCR for T. whippellii” will become part of the laboratory screening investigation for many of these conditions.

MILNE ANDERSON

Queen Elizabeth Neuroscience Centre, Edgbaston, Birmingham B15 2TH, UK
email Milne.Anderson@birmingham.ac.uk