REVIEW SERIES

Nosological entities?

Nosology. 1. *A classification, arrangement, or catalogue of diseases; a collection or combination of disease.* 2. *(The branch of medicine that deals with) the systematic naming and classification of diseases.*

(Oxford English Dictionary)

The question mark in the heading of this series is deliberate. The most confidently applied diagnoses used for neurological disease are perhaps those in which a reasonably stereotypical clinical presentation has a known pathological substrate, in turn the consequence of a specific biochemical or enzymatic dysfunction. McArdle's disease springs to mind as one such example, although even there some clinical variability is encountered in the expression of myophosphorylase deficiency.

More uncertainty in diagnosis appears when the disease in question shows a much greater degree of variability in its clinical expression, and where the capacity to confirm the pathological substrate is limited. The differences between primary progressive multiple sclerosis and relapsing-relapsing multiple sclerosis are profound, embracing clinical expression, imaging characteristics, and pathological features. Despite that, the entities remain under the same diagnostic umbrella.

The greatest uncertainty arises when diseases have been described, often eponymously, on the basis of a few cases,

and with restricted access to imaging or to pathological characterisation. Inevitably re-examination of these conditions—for example, Schilder's disease—indicates that the case material is not homogenous and that the use of such titles, implying a uniform pathological mechanism, is best abandoned.

The 13 articles in this series, look at various clinical entities, or diagnoses, the specificity of which remains open to question. In some instances, the whole concept of the entity is perhaps in doubt—for example, the whiplash syndrome. In others, a clinical syndrome—for example, the Tolosa-Hunt syndrome—may in reality represent the end state of heterogeneous pathological states.

The authors of this series have been asked to analyse the concept of the individual syndromes, determining whether they remain of value in neurological practice—indeed, whether the question mark can be sensibly removed, cautiously retained, or the diagnosis, as an entity, abandoned altogether.

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EDITORIAL COMMENTARIES

Visual hallucinations in Parkinson's disease: their nature, frequency, and origins

This issue contains two papers which concern the occurrence of hallucinations in Parkinson's disease. This is a matter of great importance in the management of the disease. Hallucinations and related phenomena are of wider interest because they may provide clues to the brain mechanisms involved in their production.

Almost 65 years have passed since the publication of the now classic work of Wolff and Curran¹: *Nature of delirium and allied states*. Their study reported that "no evidence was found that there was any specific relationship between a particular noxious agent and the form and content of the accompanying psychobiologic disturbances." These findings suggest that a range of events may provoke a reaction in the functioning of the brain but with a common clinical presentation. The occurrence of hallucinations in Parkinson's disease raises similar issues.

Barnes and David (this issue, pp 727–733) present detailed accounts of the phenomenology of hallucinations in Parkinson's disease and relate their occurrence to features of the disease which are associated with a higher risk of the experience—namely, greater age and duration of disease, cognitive impairment, depression of mood, and sleep disturbance.² They draw comparison with the hallucinations experienced by patients with visual impairment and comment on the marked similarity in the form and content of the experiences. They suggest that a common "physiological substrate" may underlie the experience in the two settings.

In the study reported by Holroyd *et al* (this issue, pp 734–738) more than a quarter of a consecutive series of patients with Parkinson's disease were found to have experienced visual hallucinations in the previous week.³ There

was a clear association between the occurrence of visual hallucinations and visual impairment as well as with impaired cognitive function, depression of mood, and severity of disease. It is notable that no association was found between the use, dosage, and duration of administration of levodopa or of other antiparkinsonian drugs. Unsurprisingly, in view of previous reports, few patients showed evidence of a paranoid illness, of which hallucinations might form a part.

Research on Parkinson's disease is influenced by the sample of subjects studied. Because the onset of the disease is usually insidious the identification of patients is difficult and estimation of the duration of illness imprecise.⁴ Barnes and Anthony recognise that their sample is difficult to define and is unlikely to be typical of patients with Parkinson's disease. Holroyd *et al* took consecutive subjects attending a specialised clinic for the first time and their sample has the advantages of an "inception cohort" where patients enter a study by the same route and at roughly the same stage of the disease.

Holroyd *et al* use standardised criteria for the diagnosis of Parkinson's disease and for the exclusion of other illnesses but their criteria for the recognition of hallucinations lack detail. Barnes and Anthony use more rigorous criteria for the identification and categorisation of the phenomena found.

Somewhat paradoxically, as research in Parkinson's disease has progressed, it is the diagnosis of the disease itself

which has become problematic. The central category of idiopathic Parkinson's disease is diminishing as similar but distinct syndromes are separated off.⁴⁻⁶ Furthermore, the boundaries between neurodegenerative diseases are becoming less distinct.⁶ This aspect is not really addressed in either paper but is central to the matter stressed by Barnes and Anthony, and touched upon by Holroyd *et al*, that hallucinations may be a non-specific response to a range of circumstances in conditions which predispose to their occurrence.

Both papers are a welcome addition to the research in this difficult field. Relating psychopathology to brain mechanisms is essential if progress is to be made in this area.

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Anosmia in dementia is associated with Lewy bodies rather than Alzheimer's pathology

In the paper by McShane *et al* (this issue, pp 739-743), the olfactory function of 92 patients with dementia and 94 control subjects, accessed through the Oxford Project to Investigate Memory and Ageing (OPTIMA), was assessed and related to neuropathological findings at necropsy.¹ Patients with Lewy body dementia were more likely to be anosmic than those patients with Alzheimer's disease, whose olfactory function was comparable with that in control subjects. The extent of the anosmia in Lewy body dementia was greater in those patients with higher counts of Lewy bodies, as detected by antiubiquitin immunohistochemistry, and was not influenced by the presence or absence, or degree, of Alzheimer-type pathological changes. Such findings are consistent with previous studies in Parkinson's disease, in which olfactory deficits are well documented.² Lewy bodies may therefore be pathological markers of anosmia, whether these occur in the brain stem or cerebral cortex.

The data presented by McShane *et al* are important because they suggest a simple but sensitive, and perhaps more objective, way of discriminating in life between patients with Lewy body dementia and those with Alzheimer's disease. In so doing, olfactory testing may provide a valuable adjunct to present clinical criteria for Lewy body dementia,³ which depend heavily on the presence of visual hallucinations and fluctuating cognition, symptoms difficult to define and quantify objectively and which can be masked in the presence of severe Alzheimer's disease. Unfortunately, in the study there was only one patient with Lewy body dementia who did not have some degree of Alzheimer-type pathological changes in the brain, so the authors were unable to validate their findings

in a group of patients with Lewy body dementia entirely free from such (potentially) compounding influences.

Perhaps, the main unanswered question raised by this study is why patients with Alzheimer's disease do not become anosmic, given that the same topographic areas of brain are affected by plaques and tangles in Alzheimer's disease as those affected by Lewy bodies (and variable Alzheimer pathology) in Lewy body dementia.⁴ Additive effects in Lewy body dementia are possible. In this disease, it is pyramidal neurons of deeper layers 5 and 6 of the cerebral cortex, particularly those of the cingulate gyrus, which receive a dense dopaminergic innervation and project to the corpus striatum and other subcortical regions, which are mostly affected by Lewy bodies. By contrast, Alzheimer-type changes tend to be more abundant in the upper cortical layers where corticocortical projections are formed, but generally in Lewy body dementia these pathological changes are much less abundant than in Alzheimer's disease itself.⁴ Different, and additional, circuitry within the brain may therefore become disconnected by Lewy body pathology in Lewy body dementia, compared with that primarily targeted by Alzheimer-type pathology in Alzheimer's disease. It is possible that the visual hallucinations, fluctuating cognition, and olfactory impairment of Lewy body dementia are symptoms mediated by changes in function of these layer 5/6 pyramidal neurons, rather than as a result of events taking place at the level of the olfactory bulbs (which were not analysed in this study), a region well known to be severely damaged in Alzheimer's disease.⁵

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Imaging counterparts of cognitive decline in multiple sclerosis

Cognitive impairment occurs in 40% to 60% of those with multiple sclerosis, with devastating effects for some. Subtle abnormalities may already be present in those with clinically isolated syndromes, but impairment tends to be more severe as the disease progresses. Difficulties with memory, information processing, and executive functions are frequent, but other cognitive skills may also be impaired. Standard markers of disease burden (T2 lesion load) do not correlate closely with these deficits, as exemplified by the finding that cognition is equally impaired in those with primary and secondary progressive disease despite very different T2 lesion loads. Searching for better predictors of cognition, Zivadinov *et al.* (this issue, pp 000–000) report that loss of brain parenchyma predicts cognitive decline better than other MRI indices.¹ In their 2 year follow up study of 53 patients with early relapsing remitting multiple sclerosis, although T2 and T1 lesion volumes increased during this period, only the progressive loss of brain volume predicted cognitive decline. The 15 patients (28.3%) who declined cognitively lost an average of 8% of brain parenchyma over the study. Cognitive deterioration was not universal in the early stages of the disease, as exemplified by the fact that over two thirds of their patients remained stable or improved over the 2 year period.

In multiple sclerosis the acute inflammatory process initiates a pathological cascade that results in axonal and myelin loss; this loss determines the extent of clinical disability, including cognitive impairment. Axonal and myelin loss is more marked in new lesions and in the active borders of old ones and it may be episodic rather than progressive.² Finding surrogate markers for this neuropathological process is increasingly important, as disease modifying therapies become available. Newer MRI techniques such as magnetisation transfer, capable of giving information about otherwise normal appearing brain tissue, have been reported to correlate better with cognitive decline than T2 lesion load.³ Fast fluid inversion recovery (fast FLAIR) sequences, which are capable of detecting

juxtacortical lesions likely to disrupt important cognitive networks, also hold some promise. But the detection of brain atrophy, and especially its progression over a short period of time, may be particularly useful as it provides a global measure of pathology in the normal appearing brain tissue. The study of Zivadinov *et al.*¹ suggests that brain atrophy occurs early in the disease, at least in some patients, whereas studies in those with well established disease⁴ point towards an annual rate of cerebral atrophy twice as fast in patients with multiple sclerosis as in age matched controls, and to a closer correlation with physical disability.⁵

The rate progression of brain atrophy was recently used to assess the impact of interferon β -1b in patients with secondary progressive disease.⁶ Rates of progression were similar in the drug and placebo arms of the study suggesting that whatever clinical effects were found were likely to be due to the anti-inflammatory/antioedematous effects of the drug rather than its ability to halt progressive axonal and myelin loss. The use of increasingly complex markers of disease activity in trials of new therapeutic agents will help to determine their efficacy, to select those more likely to benefit, and to decide on the optimum timing for their administration.

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