and others have at last realised that much of refuse may be reused profitably. Recycling may not be a moneyspinner, but it should pay the cost of collection. Waste paper, bottles, cans, plastics, and discarded household appliances can all be conserved and the materials reused. If it is to be effective, however, the collection and sorting of refuse must be organised. This should be the duty of local authorities, yet few have taken up the challenge. Other countries seem far ahead of Britain in providing facilities for the collection of reusable materials.

Uncollected refuse is one problem; another is discarded litter. The sheet of greasy newspaper which wrapped up the fish supper 40 years ago has been replaced by a plastic tray. Most refuse associated with fast food is dropped near the point of sale. The provision of one or more large waste bins by the management outside the shop would help the customers to keep the area tidy. But it is not only lager louts who throw plastic trays and empty cans into the road. Citizens of all types discard wrappers from confectionery, cigarettes, newspapers,

and so on on to the street. The twin remedies are provision of waste containers (regularly emptied) and education. Legislation already exists making the dropping of litter an offence, but these laws are rarely enforced. In Moscow someone who drops a cigarette end on the street is likely to find a policeman prodding his ribs and requiring him to pick it up and put it in the appropriate receptable. In Singapore the offence carries a heavy fine and the police are vigilant. Are such activities too robust for the British?

Mr Richard Branson's anti-litter campaign seems to have failed, and even Mrs Thatcher's foray of collecting litter in the park only provided material for the comedians. Yet this is a serious subject. The solution lies in the hands of local authorities; all those who have lost patience with the squalor around them should complain loudly and repeatedly to their local politicians.

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Diagnosis of multiple sclerosis

Remains essentially clinical though silent lesions can now be identified

A diagnosis of multiple sclerosis at once raises for the patient the spectres of disability and loss of independence and a decline in living standards. Self evidently, the diagnosis should be accurate, but because there is still no specific test for the disease it is often delayed and difficult. In the past decade, however, some techniques have been introduced that facilitate diagnosis and enable an earlier classification to be made with confidence in a greater proportion of patients. The results of the new methods of assessment have been widely confirmed and have incorporated a new set of diagnostic criteria.[1]

The diagnosis of definite multiple sclerosis remains primarily clinical and depends on an appropriate history and showing the presence of at least two separate lesions that have appeared at different times in the white matter of the central nervous system. Other possible causes need to be actively sought and excluded.

The diagnosis is easy when physical examination shows evidence of two or more focal lesions in a patient with a clear history of two or more remitting episodes of neurological disturbance of several weeks' duration. It is more difficult in the patient with a steadily progressive course from onset; here, the illness must have been present for at least six months and it must be shown that one or more new, anatomically distinct lesions have appeared since initial presentation. In such less definite cases and in patients presenting with a history of frequent attacks but having few or no abnormal physical signs the new techniques are particularly helpful. The data they give help in two ways: in identifying clinically silent lesions and in showing immunological abnormalities related to the central nervous system.

Asymptomatic lesions may be identified by several techniques, of which the evoked potential methods[2 3] (visual, auditory, and somatosensory) are the most widely available.[4] Overall, the results are abnormal in about three quarters of patients with clinically definite disease, and in this category they are abnormal in around half of patients who have no abnormal signs related to the pathways being tested. Herein lies their usefulness. Abnormal evoked potentials tend to be less common in the less definite cases, but they are nevertheless useful in diagnosis. In an initial episode of optic neuritis, for example, auditory or somatosensory evoked potentials are abnormal in about a quarter of patients.[4] The visual evoked potential is the most generally useful test because of its sensitivity and the stability of the abnormalities and because patients often present with symptoms originating in the spinal cord or brainstem (for example, paraesthaesia, spastic weakness, vertigo) and the visual pathways are anatomically remote from both. The recently introduced techniques for measuring central motor conduction may also be helpful.[5]

By far the most sensitive method for showing lesions in multiple sclerosis is magnetic resonance imaging. Over 95% of patients with clinically definite multiple sclerosis show irregularly shaped periventricular and discrete focal abnormalities in the white matter of the brain (figure, left).[6 7] For technical reasons spinal cord abnormalities have been less easy to visualise, but this limitation is rapidly being overcome. Abnormalities seen on magnetic resonance imaging correspond to the histological lesions of multiple sclerosis.[6 8]

Three common clinical syndromes that may herald the onset of multiple sclerosis are reversible visual loss, vertigo, and weakness or tingling of the limbs, though all have other causes. In about two thirds of such patients multiple clinically "silent" lesions are visible on magnetic resonance imaging in the brain at presentation.[9-12] Follow up studies have shown that more than half of such patients develop multiple sclerosis within 18 months.[13 14] Occasionally these isolated syndromes may be the only clinical expression of an acute disseminated encephalomyelitis, which though multifocal is nevertheless monophasic.[15] For this reason definite multiple sclerosis must not be diagnosed on the basis of a single scan: clinical or magnetic resonance imaging follow up is always required. Magnetic resonance imaging is especially helpful in excluding spinal cord compression (figure, centre) and cerebellar degeneration in the small but important group of patients whose illness is progressive from the onset (figure, right).[6] Here, as in the detection of the multiple sclerosis lesions themselves, magnetic resonance imaging is superior to x ray computed tomography.
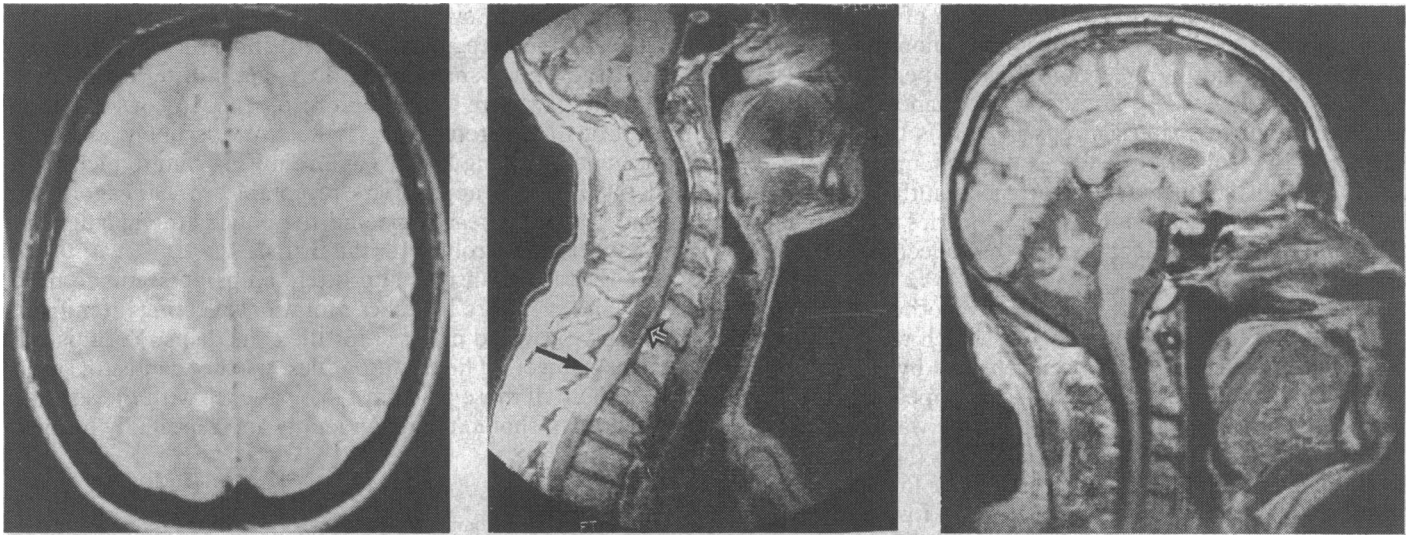
Left: *Magnetic resonance image of brain of patient with clinically definite multiple sclerosis showing multiple periventricular and discrete lesions in central white matter.* Centre: *Magnetic resonance image of cervical spinal cord in patient with nine year history of progressive spastic paraplegia diagnosed as multiple sclerosis. A myelogram four years previously was normal. Filled arrow points to a tumour (astrocytoma grade 2 on biopsy) here enhanced though visible on the unenhanced scan; open arrow points to an associated cyst.* Right: *Magnetic resonance image showing cerebellar and pontine atrophy in patient with familial cerebellar degeneration*

Immunological abnormalities are shown by analysis of proteins in the cerebrospinal fluid. Changes in multiple sclerosis have been known for nearly 70 years, but only in the past decade or so has the characteristic oligoclonal electrophoretic pattern in the cerebrospinal fluid γ globulins—in the absence of such a pattern in the serum proteins—been shown to be present in about nine out of 10 patients with clinically definite disease. This pattern is, however, less common in patients in whom the diagnosis is less definite, and it occurs in only about two in five patients with isolated lesions such as optic neuritis.[16] Although the presence of oligoclonal bands represents an increase in risk for subsequently developing multiple sclerosis,[16-18] their absence in an individual patient does not exclude that possibility, and their presence does not make it inevitable.

The results of all these investigations, then, lack specificity—as do abnormal physical signs. Though they indicate an area of abnormality or a disturbance in the immune response, they cannot identify the nature of the disease process. For example, although a delay in a visual evoked potential with a well preserved wave form is characteristic of multiple sclerosis it may be seen in other conditions such as tumours affecting the optic nerve (probably as a result of pressure induced demyelination[19]) and ischaemic optic neuropathy. Irregular periventricular abnormalities with discrete lesions in the white matter elsewhere are the characteristic findings on magnetic resonance imaging in multiple sclerosis but may occur in cerebral vasculitis,[20] sarcoidosis,[21] and acute disseminated encephalomyelitis.[15] Less extensive abnormalities in the white matter may be seen in a few patients with cerebellar degeneration[6] and in apparently healthy people over the age of 50.[22] Particular care must therefore be exercised in diagnosing multiple sclerosis in older age groups. Oligoclonal bands in the cerebrospinal fluid may be found in a variety of diseases associated with immune reactions in the nervous system, including sarcoidosis, systemic lupus erythematosus, neurosyphilis, Lyme disease, chronic meningitis, and the myelopathy associated with the human T cell lymphotropic virus in patients of Caribbean and Japanese origin.[23-27] Nevertheless, the data that these investigations yield provide information that, when interpreted in the light of the clinical picture, is often diagnostically invaluable.[3 7 28]

The way in which investigative data can be used to supplement the clinical information is laid out in the Poser committee's reports.[1 28] In essence, they allow imaging and evoked potential data to be used as evidence for one of the two necessary lesions that have to be identified in making the diagnosis. The committee introduced a new diagnostic category, that of laboratory supported multiple sclerosis, which is used when the presence of oligoclonal bands is used in reaching a diagnosis. Thus laboratory supported definite multiple sclerosis is diagnosed when oligoclonal bands are present in either patients with a history of two (or more) episodes of neurological disturbance and both clinical and investigative evidence for the second episode or patients with a steadily progressive deficit from onset, provided that the illness has been present for at least six months and sequential discrete lesions can be shown in the central white matter. Laboratory supported probable multiple sclerosis is diagnosed when oligoclonal bands are present together with some but not all of the other required clinical or investigative criteria. Details, with examples of the application of the criteria, are given elsewhere.[1]

There is inevitably an arbitrary element in diagnostic criteria based on the clinical course and frequency of occurrence of certain clinical and investigative features in a disease for which there is no specific diagnostic tests. The need for some flexibility in applying the criteria was recognised by the Poser committee, and the circumstances in which alternative data may be used are given in its reports.[1 29] Crucially, both the clinical and laboratory supported categories require at least one episode of neurological disturbance; this has the implication that a diagnosis of multiple sclerosis is not permissible in the patient without symptoms on purely investigative grounds.

What should be the approach to the individual patient suspected of having multiple sclerosis? When a definite diagnosis can be made on clinical grounds alone investigation is usually unnecessary, although in some patients there may be a case for seeking confirmation by inexpensive and non-invasive methods. In patients in less definite categories evoked potentials should be the first investigation, the particular examinations chosen being those that may show up abnormalities not detected clinically—for example, visual evoked potential and brainstem auditory evoked potential in the patient with a myelopathy. On the other hand, the visual evoked potential usually adds nothing to the assessment of the patient who already has bilateral optic atrophy, and it is wasteful of resources. Lumbar puncture with electrophoresis of cerebrospinal fluid is helpful when other methods fail to

lead to a definite diagnosis, especially in older patients in whom abnormalities found on magnetic resonance imaging may be difficult to interpret.

Facilities for magnetic resonance imaging are still scarce in Britain, and their diagnostic use should be reserved for cases of difficulty. They are particularly useful in patients with a history of multiple episodes of neurological disturbance and signs relevant to only one lesion, in patients with progressive spastic paraplegia in whom there is a need to exclude congential abnormalities and tumours of the foramen magnum, and in those with progressive ataxia in whom cerebellar atrophy without periventricular and discrete abnormalities of the white matter virtually excludes multiple sclerosis.[6]

Finally, there are the questions of when to investigate and what the patient should be told. My guiding principle is to recommend investigation when it is clear to the patient that there is something that needs explanation. So far as the syndromes attributable to a single lesion are concerned, as a definite diagnosis of multiple sclerosis is not at present possible in these cases I usually do not investigate unless there are atypical features or until new symptoms have developed. Some patients, however, are more comfortable with greater knowledge, and it is a matter for judgment as to when they should be investigated.

When to tell the patient the diagnosis is controversial. My policy is to do so without delay when the diagnosis becomes definite, except in the small group of patients who genuinely do not wish to know: careful assessment of the patient's personality and circumstances is a necessary preliminary to reaching such a decision. Some patients in the less definite categories, too, may be helped by discussion of the possibilities. An early follow up appointment should be arranged for frank and full discussion of the questions that arise as the implications of the diagnosis sink in.

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Molecular genetics of colorectal carcinoma

Rapid development in working out the steps of carcinogenesis

It is generally accepted that cancer arises because of changes in the genetic material of cells and that many steps must occur before a patient develops cancer.[1] Analysis of age-incidence curves for various cancers suggests that as many as half a dozen steps may be necessary, and this idea is largely supported by experimental data.[2 3] Such steps probably range from point mutations to gross chromosomal rearrangements, although epigenetic mechanisms may also have an important role.[4 5] These genetic steps have not yet been worked out fully for any tumour, but understanding of the molecular genetics of colorectal carcinoma is currently developing at a rapid pace and causing great excitement.

It was in 1982 that ras oncogenes were shown to be activated in carcinomas and, subsequently, in a high proportion of both adenomas and carcinomas of the colorectum.[6 7] Since mutation of the ras oncogene occurs in premalignant adenomas in sporadic and hereditary[8 9] cases of colorectal carcinoma and has also been reported in "normal" mucosa[10] the mutation is probably an early event. How the product of the gene contributes to carcinogenesis is not yet clear, but it probably acts as a second messenger, passing on messages from external signals—for instance, from growth factors.[11] It seems that once the gene is mutated it remains overactive and may in addition have a destabilising effect on the genome. Importantly, the mutations in ras oncogenes that are seen in colorectal carcinoma may be induced by various mutagens in experimental tumours—thus fulfillng some of a sort of oncological Koch's postulates.[3 11]

More recently it has become clear that recessive genetic changes may be just as important as activation of dominantly acting oncogenes in carcinogenesis. Thus the inheritance of a heterozygous defect in a tumour suppressor gene (or anti-oncogene) may represent a predisposition to cancer.[12] Loss or mutation of the remaining allele might then represent a further step towards cancer. This seems to be what happens in retinoblastoma, the crucial gene for which on chromosome 13, has now been cloned and sequenced.[13]

The genetic locus associated with familial adenomatous polyposis or familial polyposis coli has also now been identified —on chromosome 5.[14 15] This was achieved by linkage with