cytokines at the end of the inflammatory phase would allow recovery mechanisms (for which there is experimental evidence) to restore conduction, despite persistent demyelination.[12]

Studies of large lesions more than two years old by quantitative magnetic resonance imaging have shown that while some are highly cellular (corresponding with the gliotic plaques seen at necropsy) others have a much expanded extracellular space. Other postmortem studies have shown that many chronic lesions have an "open" texture produced by axonal loss.[13] It seems likely that this process makes an important contribution to the emergence of fixed deficit, a hypothesis that is now testable by combining long term serial magnetic resonance imaging with measurement of conduction changes and functional status.

Do all forms of multiple sclerosis behave in the same way? Probably not. The uncommon variant which is steadily progressive from onset (primary progressive multiple sclerosis) shows a number of differences from the relapsing-remitting pattern and from secondary progressive disease. The most striking difference is the rarity of detectable changes in the blood-brain barrier in primary progressive disease.[14] Just what this finding means is not yet clear, but one practical implication is that patients with primary progressive disease should be kept in a separate category in treatment trials.

It is, indeed, in the monitoring of treatment that magnetic resonance imaging is likely to make one of its most useful contributions. Two important reasons for the slow progress towards effective treatment have been the incompleteness of our understanding of the pathogenesis of multiple sclerosis and the lack of an acceptable and reliable way of monitoring disease activity. Just how difficult it has been to assess the disease is underlined by the finding on magnetic resonance imaging that new lesions can be 10 times more common than clinical relapses.[4,14]

Our increased understanding of the pathogenesis of multiple sclerosis is suggesting new therapeutic strategies directed against the inflammatory process—which beyond reasonable doubt is immune mediated. The use of enhanced magnetic resonance imaging will greatly reduce the number of patients needed for preliminary clinical trials and the length of time for which they must be observed.[15] Although it ultimately remains true that therapeutic effectiveness must be judged by clinical measures, what magnetic resonance imaging promises is a means of detecting a reduction in pathological activity, which will be a useful first step in screening putative treatments for use in expensive, large scale, prolonged trials.

Important gaps in our knowledge remain. Though much of the later disability in multiple sclerosis derives from damage to the spinal cord, present techniques are not very good at delineating the extent of the lesions there. It is not yet possible reliably to monitor demyelination directly, but other types of magnetic resonance imaging and proton magnetic resonance spectroscopy (now possible with volumes as small as 1 cm^3, a common size for plaques) promise to overcome these difficulties.

The new understanding of multiple sclerosis is good evidence of the power of the combined experimental and clinical approach. We are now well placed to explore new strategies for controlling the disease in the acute phase. The problem of dealing with the fixed deficit remains, but there are encouraging developments in neurological rehabilitation, including some at the level of basic science—whence real progress is likely to come.[16]

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Multiple sclerosis: therapeutic pessimism

Nothing works long term

Anti-inflammatory, immunosuppressive, immunostimulatory, anti-infective, and dietary treatments have all been tried in multiple sclerosis. So have plasmapheresis, desensitisation, and hyperbaric oxygen.[1,2] None, however, looks like a promising long term treatment. By reducing secondary damage from oedema steroids often provide temporary benefit in acute episodes, such as optic neuritis.

Multiple sclerosis probably results from an infectious process acquired in early life by a genetically susceptible person. Some sort of immunopathological reaction to myelin of the central nervous system seems to be responsible. Whether this is directed against myelin basic protein,[3] proteolipid protein,[4] myelin associated glycoprotein,[5] brain glycolipid,[6] or all of these is unknown. The presumption of an immunopathological process accounts for the many kinds of immunosuppressive treatment that have been tried—for example, cyclophosphamide, azathioprine, antilymphocytic globulin, and total lymphoid irradiation. They have been tried separately, together, and with steroids, but none of these treatments has produced any convincing evidence of long term benefit. Their risks, however, are obvious: patients given properly immunosuppressive doses may acquire

dangerous intercurrent infections and handle them less effectively. The side effects are unpleasant, and there is an increased risk of malignancy.

Plasmapheresis to remove possible harmful agents, including autoantibodies, has been used. On its own and in various combinations with steroids and other immunosuppressive drugs it produced no important benefit.[1] Desensitisation has been tried but is potentially dangerous if myelin basic protein is used as this may itself produce inflammation of the central nervous system. Peptides, which cross react with myelin basic protein and can suppress experimental allergic encephalomyelitis without encephalitogenic properties, have been tried without convincing benefits; similarly with copolymer 1.[1,2] Various anti-infective treatments have been used especially interferon, which has anti-viral properties. As a group interferons may induce sensitivity. Interferon gamma provokes exacerbations; interferon beta may reduce exacerbations but has not yet been shown to reduce long term disability.

Hyperbaric oxygen has been used because it seemed to benefit rodents with experimental allergic encephalomyelitis[7] and patients with fat embolisms of the central nervous system. No convincing evidence exists that this treatment is successful in multiple sclerosis and it too has dangers.

Dietary intervention—for example, a gluten free diet—is of no benefit. Linoleic acid, an important component of myelin, has been used to supplement diets but without appreciable therapeutic effect. The rationale for this was the suggestion that a deficiency of essential fatty acids might result in defective formation of myelin.[2] Suggestions have been made that polyunsaturated fatty acids used prophylactically might be beneficial in patients with multiple sclerosis, especially children. Which children should be targeted for treatment and whether such intervention would be safe are unknown. There is no convincing evidence for malabsorption from the jejunum in multiple sclerosis, and low concentration of linoleic acid are easily restored by mouth. Giving supplements of polyunsaturated fatty acids to patients with multiple sclerosis has been disappointing, and evidence exists that linoleic acid may increase the incidence or accelerate the growth of malignant tumours in laboratory animals.[2]

Given these disappointing findings, what can be done? Supportive treatment; physiotherapy, drugs and occasionally intrathecal phenol for spasticity; drugs and self catherisation for problems with micturition; occupational therapy; physiotherapy to improve walking; and drugs and surgical treatments for tremor all optimise the quality of life. Rest is essential during exacerbations. Neurones stressed by inflammation and oedema should not have to increase their metabolism to do unnecessary work. Even in remission patients who have been paraplegic from transverse myelitis will say that over vigorous exercise is counterproductive, making weakness worse. Activity should not be avoided but should be gauged according to what patients can comfortably manage and enjoy.

'Kicking against the pricks' is not beneficial in this disease, which differs considerably from simple muscular injuries in which the return to full fitness depends on gradually increasing exercise. The central nervous system has little capacity for recovery after damage is complete. During the acute episode passive exercises are useful to retain mobility and reduce spasticity; once the disease is in remission mobility can be increased to a sensible level for the person concerned.

Better treatments await a better understanding of how infection and immunopathological damage combine to produce demyelination. Progress will come from basic research, such as that reporting the prevention of experimental autoimmune encephalomyelitis by using antibodies to adhesion molecules to prevent the entry into the central nervous system of leucocytes that damage myelin.[9] Meanwhile, it is important not to worsen the quality of life of people with multiple sclerosis by prescribing unpleasant treatments that do not work.

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Ductal carcinoma in situ

Trials needed to decide right treatment

Ductal carcinoma in situ of the breast used to be thought a relatively rare condition. Often it was not distinguished from invasive cancer, and it was therefore treated by mastectomy. All this has now changed since the introduction of mammography. The national breast screening project is providing an opportunity for us to learn a great deal more about the clinical behaviour of subtypes of ductal carcinoma in situ and their response to both local and systemic treatments.

The histopathologist diagnoses ductal carcinoma in situ because of malignant cells contained within the ductal basement membrane. The ducts, the terminal duct lobular units, and the lobules may be filled by malignant cells (solid); the lesions may undergo central necrosis (comedo); or they may display a sieve-like appearance (cribriform). They may protrude as papillary projections (papillary or low papillary), or they may cling to the duct wall (clinging type).

Central necrosis may be followed by deposition of calcium—and it is a branching or spicular pattern of intraductal calcification that usually brings the condition to the attention of the screening radiologist. In most cases nothing is