by a dentist with AIDS.^{2,4} The Royal College of Pathologists' report provides details of serological testing of patients who had been operated on by HIV infected surgeons, together with estimates of the theoretical risks of transmission. There have been no known instances of transmission of HIV infection from surgeons to their patients. Health care workers who are infected with HIV should not perform invasive procedures if there is a possibility of their blood being transferred to the patient; readers are referred to recent British⁵ and north American guidelines.⁶

A skilled adviser who can balance the risks from inoculation injury against other risks in occupation and in life in general can be very helpful to a member of staff or a patient exposed to HIV infection. The latest follow up studies continue to confirm the rate of transmission from patients to staff members from a single inoculation injury with HIV positive blood as 0.36% or 1 in 275 (upper limit of 95% confidence interval=0.69%). The risk from mucocutaneous exposures is less than this; no seroconversions have been reported from 921 exposures in prospective studies. Reassuringly, extensive studies have failed to confirm evidence of transmission from patients to staff during general ward care and invasive procedures, including dentistry and orthopaedic surgery, even in areas with a high prevalence of HIV.

The Royal College of Pathologists' report does not help in the difficult decision on whether to recommend zidovudine after exposure. As previously detailed in an editorial in this journal⁷ no data on efficacy are available and there are unlikely to be any in the foreseeable future; the low rate of seroconversion after inoculation injury means that a study of the efficacy of prophylactic zidovudine would require the recruitment of many thousands of people. The authors of the report reiterate advice from the United States stating that, after careful consideration of all data then available, zidovudine "could not

be considered a necessary component of post exposure management."⁸ They then record five instances of apparent failure of prophylaxis with zidovudine, in only one of which the time to administration was less than two hours; they also record details of short term toxicity.

The report advises health districts to consider the arguments for and against the use of zidovudine and develop a local policy on its use. It is all too easy to decide, in the absence of data on efficacy, that zidovudine after exposure is not justified, and this decision is much easier to make where the perceived prevalence of HIV is low. If zidovudine prevented a small proportion of cases of nosocomial transmission, perhaps 10% or less, there would be no question about its use. We have, however, no way of obtaining such data. Currently it seems that most British and north American hospitals are providing access to zidovudine in cases of significant percutaneous exposure to HIV infected blood. Evidence suggests that the rate of acceptance is low, but making the drug unavailable would surely be wrong.

D J JEFFRIES

Professor of Virology,
St Bartholomew's Hospital,
London EC1A 7BE

- 1 Royal College of Pathologists. *HIV infection: hazards of transmission to patients and health care workers during invasive procedures*. London: RCPATH, 1992.
- 2 Centers for Disease Control. Possible transmission of HIV to a patient during an invasive dental procedure. *MMWR* 1990;39:489-93.
- 3 Centers for Disease Control. Possible transmission of HIV to a patient during invasive dental procedures—Florida. *MMWR* 1991;40:21-7.
- 4 Centers for Disease Control. Update: transmission of HIV infection during invasive dental procedures—Florida. *MMWR* 1991;40:378-81.
- 5 UK Health Departments. *AIDS-HIV infected health care workers. Recommendations of the expert advisory group on AIDS*. London: Department of Health, 1991.
- 6 Centers for Disease Control. Recommendations for preventing transmission of human immunodeficiency virus and hepatitis B virus to patients during exposure-prone invasive procedures. *MMWR* 1991;40:1-9.
- 7 Jeffries DJ. Zidovudine after occupational exposure to HIV. *BMJ* 1991;302:1349-51.
- 8 Centers for Disease Control. Public health service statement on management of occupational exposure to human immunodeficiency virus, including considerations regarding zidovudine post exposure. *MMWR* 1990;39:RR-1.

Multiple sclerosis: diagnostic optimism

How magnetic resonance imaging has advanced understanding and research

Great strides have been made in our understanding of multiple sclerosis in the past decade. This new knowledge comes from experimental studies into the mechanism of immune mediated damage in the central nervous system and from magnetic resonance imaging.

The first step was the recognition that abnormalities in the brain in multiple sclerosis are easily identified by magnetic resonance imaging and that the lesions shown by the technique correspond with the plaques within the nervous system.^{1,3} Soon it became clear that there was often a remarkable waxing and waning in size of the areas of abnormality over a matter of weeks.⁴ Moreover, when the enhancing agent gadolinium-diethylenetriaminepenta-acetic acid (Gd-DTPA) was combined with magnetic resonance imaging some lesions became enhanced while others did not.^{5,6}

These observations became understandable after frequent serial scanning in patients and a comparison of the results with the findings in allergic encephalomyelitis in animals and necropsy studies. Enhancement has been shown to correspond with regions of focal increase in permeability of the blood-brain barrier in association with inflammation.^{7,8} Quantitative magnetic resonance methods have been used to study the nature of the "disappearing" element in the lesion and the structure of the residual scar.

The sequence of events is as follows (reviewed in reference

9). The earliest detectable abnormality is an increase in permeability of the blood-brain barrier. This change may precede the development of corresponding symptoms, though evoked potential recordings done at this stage do show impairment of conduction, probably contributed to by demyelination. Oedema follows and may be extensive. The change in the blood-brain barrier gradually reverses and is usually over after a month. The oedema then resolves to leave a smaller residual scar. The process may be repeated in a ring-like form at the edge of large lesions, which then grow centrifugally.

One of the outstanding characteristics of multiple sclerosis is the near complete clinical recovery that occurs after most early attacks despite persisting evidence of demyelination as shown by evoked potentials. Ultimately many patients develop persistent neurological deficits. The mechanism of these events has long been a puzzle. Magnetic resonance imaging is now helping to solve it.

Serial studies of patients with optic neuritis have shown that the acute symptoms and signs (including pain and visual loss) occur during the inflammatory phase and resolve as the permeability in the blood-brain barrier returns to normal. This implies that inflammation as such plays a part in the pathophysiology of the lesion.¹⁰ These effects may possibly be mediated by cytokines, some of which have striking effects on excitable membranes.¹¹ A reduction in the production of

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 cm³, 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

W I McDONALD

Institute of Neurology,
National Hospital,
London WC1N 3BG

- 1 Young IR, Hall AS, Pallis CA, Legg NJ, Bydder GM, Steiner RE. Nuclear magnetic resonance imaging of the brain in multiple sclerosis. *Lancet* 1981;ii:1063-6.
- 2 Stewart WA, Hall LD, Berry K, Paty DW. Correlation between NMR scan and brain slice data in multiple sclerosis. *Lancet* 1984;ii:412.
- 3 Ormerod IEC, Miller DH, McDonald WI, du Boulay EPGH, Rudge P, Kendall BE, *et al*. The role of NMR imaging in the assessment of multiple sclerosis and isolated neurological lesions: a quantitative study. *Brain* 1987;110:1579-616.
- 4 Willoughby EW, Grochowski E, Li DKB, Oger J, Kastrukoff LF, Paty DW. Serial magnetic resonance scanning in multiple sclerosis: a second prospective study in relapsing patients. *Ann Neurol* 1989;25:43-9.
- 5 Grossman RI, Gonzalez-Scarano F, Atlas SW, Galetta S, Silberberg DH. Multiple sclerosis: gadolinium enhancement in MR imaging. *Radiology* 1986;161:721-5.
- 6 Miller DH, Rudge P, Johnson G, Kendall BE, MacManus DG, Moseley IF, *et al*. Serial gadolinium enhanced magnetic resonance imaging in multiple sclerosis. *Brain* 1988;111:927-39.
- 7 Hawkins CP, Munro PMG, MacKenzie F, Kesselring J, Tofts PS, du Boulay EPGH, *et al*. Duration and selectivity of blood-brain barrier breakdown in chronic relapsing experimental allergic encephalomyelitis studied by gadolinium-DTPA and protein markers. *Brain* 1990;113:365-78.
- 8 Katz D, Taubenberger J, Raine C, McFarlin D, McFarland H. Gadolinium-enhancing lesions on magnetic resonance imaging: neuropathological findings. *Ann Neurol* 1990;28:243.
- 9 McDonald WI, Miller DH, Barnes D. The pathological evolution of multiple sclerosis. *Neuropathol Appl Neurobiol* (in press).
- 10 Youl BD, Turano G, Miller DH, Towell AD, MacManus DG, Moore SG, *et al*. The pathophysiology of acute optic neuritis. An association of gadolinium leakage with clinical and electrophysiological deficits. *Brain* 1991;114:2437-50.
- 11 Sawada M, Hara N, Maeno T. Ionic mechanism of the outward current induced by extracellular ejection of interleukin-1 onto identified neurons of Aplysia. *Brain Res* 1991;545:248-56.
- 12 Bostock H, Sears TA. The internodal axon membrane: electrical excitability and continuous conduction in segmental demyelination. *J Physiol (Lond)* 1978;280:273-301.
- 13 Barnes D, Munro PMG, Youl BD, Prineas JW, McDonald WI. The longstanding MS lesion: a quantitative MRI and electron microscopic study. *Brain* 1991;114:1271-80.
- 14 Thompson AJ, Kermode AG, Wicks D, MacManus DG, Kendall BE, Kingsley DPE, *et al*. Major differences in the dynamics of primary and secondary progressive multiple sclerosis. *Ann Neurol* 1991;29:53-62.
- 15 Miller DH, Barkhof F, Berry I, Kappos L, Scotti G, Thompson AJ. Magnetic resonance imaging in monitoring the treatment of multiple sclerosis: concerted action guidelines. *J Neurol Neurosurg Psychiatry* 1991;54:683-8.
- 16 Compston A. Limiting and repairing the damage in multiple sclerosis. *J Neurol Neurosurg Psychiatry* 1991;54:945-8.

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.¹² 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