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 encephalomyelitis⁷ 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 catheterisation 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 inflam-

mation 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

palpable, so when a localisation biopsy is performed this requires close collaboration between the radiologist, the surgeon, and the pathologist to ensure that the correct lesion is completely excised.¹

What, then, should be said to a woman found to have a ductal carcinoma in situ without evidence of invasion? Most of the available evidence comes from uncontrolled studies before mammography was in widespread use. The published series included a variety of types of ductal carcinoma in situ. If a biopsy has shown the presence of ductal carcinoma in situ, and if no further action is taken an infiltrating ductal carcinoma will evolve in the ipsilateral breast in 30-50% of cases.² If a wide excision is performed—with confirmation of clearance—and the microcalcification measures no more than 4 cm an invasive lesion still occurs in about one in 10 cases. Multicentric ductal carcinoma in situ (disease in another quadrant) is found in 20-30% of mastectomy specimens.^{4,5} Spread to the axillary nodes occurs very rarely (1%), usually arising from an area of invasion missed because of a sampling error.^{4,6}

So what does this all mean? Certainly there are some women with the condition who will never develop an infiltrating carcinoma (because of natural involution). This view is supported by necropsy studies of women dying from natural and unnatural causes.⁷ If a single focus of ductal carcinoma in situ can be removed surgically, without undue cosmetic deformity, can the breast be safely conserved? We don't know. Two trials—one organised by the European Organisation for Research into the Treatment of Cancer and one by the national surgical adjuvant breast project—are currently investigating whether radiotherapy reduces the risk of progression to infiltrating carcinoma.⁸ Patients who have histologically verified complete excision are being randomised to no further treatment or to receive 50 Gy to the breast.

A national trial has been set up in Britain to ask an additional question—namely, does tamoxifen inhibit progression of ductal carcinoma in situ to invasive disease, with or without external radiotherapy?⁹ Patients with ductal carcinoma in situ detected on screening that is histologically confirmed to have been completely excised are being randomised to one of four options: firstly, observation; secondly, external radiotherapy (50 Gy); thirdly, tamoxifen 20 mg daily for five years; and, lastly, radiotherapy and tamoxifen.

To carry out subgroup analysis of the different types of ductal carcinoma in situ will require the recruitment of 1000 patients. So far, around 70% of the screening assessment centres have agreed to take part, and over 100 women have been randomised. Accrual has been slower than expected and centres have been urged to ask every suitable patient to consider acceptance or referral. Patients with cancers detected on screening should provide research groups with a valuable natural asset—which should not be squandered by the use of uncontrolled ad hoc treatments leading to results that cannot be analysed.

Are there any features agreed among surgeons? The answer is yes—in the treatment of extensive ductal carcinoma in situ,

for which a total mastectomy is advised with or without immediate reconstruction. Why is ablative surgery the agreed management of a condition that has never been responsible for the death of a patient? In part it is because extensive ductal carcinoma in situ is thought more likely to progress to invasive disease and in part because it is difficult (indeed impossible) for the histopathologist to state that no invasion is present. Nevertheless it is paradoxical that patients with invasive cancers measuring up to 4 cm in diameter can be treated by conservation of the breast and yet ductal carcinoma in situ, a non-fatal condition, is treated by mastectomy.¹⁰

There might be an alternative to mastectomy—systemic treatment in the form of tamoxifen. This is already being used as one of the arms in the British trial of treatment of patients with completely excised ductal carcinoma in situ. There is no direct evidence to support the value of such treatment, but adjuvant tamoxifen has been shown to reduce the rate of contralateral breast cancers,¹¹ some of which are likely to have developed from foci of in situ disease.¹¹

Tamoxifen has also been shown to be an effective alternative to surgery in elderly women with operable breast cancer. Long term regression in primary tumours occurs in up to 30% of patients, and this may represent an inhibition of the growth of both infiltrating and non-infiltrating carcinomas.¹²

A reasonable case can therefore be made for testing the effect of tamoxifen in patients with extensive ductal carcinoma in situ who do not wish to be treated by the standard total mastectomy. In some patients at least tamoxifen may inhibit both extension of the in situ process and its progression to invasive disease. Both the British Association of Surgical Oncology and the European Organisation for Research into the Treatment of Cancer are planning to investigate this possibility by registering patients with incompletely excised ductal carcinoma in situ treated by tamoxifen.

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