The disease may be reactivated, and this may lead to complications such as blindness; but fortunately this is rare. More often activity of the disease seems to decline steadily: relapses are more likely during the initial 18 months of treatment[14] and within one year of withdrawal of steroids.[9 11] There is no reliable method of predicting those most at risk, but arteritic relapses in patients who presented with pure polymyalgia rheumatica are unusual,[12 20] although one study reported a high incidence of complications in polymyalgia rheumatica.[21] We recently found that patients with both polymyalgia rheumatica and giant cell arteritis were more likely to experience relapses than those with polymyalgia rheumatica or giant cell arteritis alone.[14] Men were more likely to experience complications of giant cell arteritis than women in one study,[13] but women needed treatment for longer in another.[12] Temporal artery biopsy does not need help in predicting outcome.[13 14 22]

The risks of continuing treatment with steroids unnecessarily are those of steroid related complications. Between one fifth and a half of patients may experience serious side effects[23 24] unless the initial dose of prednisolone is 10 mg or less and maintenance doses of less than 7·5 mg are used.[8 20 25] High initial doses, cumulative doses, maintenance doses, and increased duration of treatment have all been associated with increased side effects.[12 25] There is still no reliable guide to which patients are most at risk, and studies need to be done to show whether prophylactic treatment to reduce osteoporotic fracture is of value in polymyalgic rheumatica and giant cell arteritis. Azathioprine has been shown to exert a modest steroid sparing effect.[26] Reduction of doses of prednisolone on alternate days once doses of less than 5 mg are reached makes withdrawal easier, and the addition of a non-steroidal agent at this stage may reduce some of the minor muscular symptoms that patients develop as doses of steroids are reduced. Some patients, however, find it impossible to stop taking the final 2-3 mg, and this level of maintenance dose is probably safe.

In summary, patients should be warned to expect treatment for at least two years, while most should be able to stop taking steroids after four to five years. Monitoring for relapse should continue for six months to one year after stopping steroids; thereafter patients should be asked to report back urgently if arteritic symptoms occur. The risk of this happening is small and unpredictable. A few patients may need low dose treatment indefinitely.

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Identification of the cystic fibrosis gene

Practical implications for patients and their families

It is only five years since the discovery of the linkage of the cystic fibrosis gene to the gene coding for the enzyme paraoxonase and the assignment of the linkage group of which cystic fibrosis is a part to chromosome 7.[1 2] So the recent identification of the cystic fibrosis gene itself and its most common mutation represents an extraordinary achievement by all those concerned.[3-5] What are the practical implications of this advance for patients and their families?

The mutation that has been identified is not found in all patients with cystic fibrosis. It occurs in 68% of patients' chromosomes, and neither a complete genomic nor complementary DNA sequence is yet available. This mutation (ΔF508) causes the deletion of an in frame TTT triplet, which corresponds to the predicted loss of a phenylalanine residue in the specified protein. The protein itself has not been purified, although from the genetic sequence it seems to be a member of a family of transmembrane regulatory proteins.

One immediate task is to identify the remaining mutations associated with cystic fibrosis. Current estimates put the number of these additional mutations at about 10-12. At the third North American congress on cystic fibrosis held in October 1989 it was agreed to establish a consortium whereby all laboratories working on the molecular genetics of cystic fibrosis would share new information about sequences and other mutations as soon as it becomes available. The next task—once a full genetic sequence has been established—is to produce models of the disease both by transfecting the abnormal cystic fibrosis gene into epithelial cells in vitro and by constructing transgenic animal models. A third task, which awaits the purification of the protein, is the

characterisation of the biochemical defect—for example, by functional studies in vitro with the protein incorporated into artificial membranes. Finally, it may be possible to correlate specific mutations with the clinical phenotype. Already the haplotypes at loci cosegregating with cystic fibrosis have been associated with the presence or absence of pancreatic insufficiency.[6]

The earliest impact of the new genetic information is likely to be on screening for the heterozygous carrier state. The implications of rapid advances in knowledge for screening in cystic fibrosis have been reviewed recently.[7] While some have suggested that carrier screening should be made available now—even though some 30% of cystic fibrosis chromosomes cannot be detected[8]—others favour waiting until more if not all of the mutations are known.[5,9] Clearly, before large scale population screening is undertaken a realistic assessment needs to be made of the likely demand in order to determine the facilities that will be required and so their cost. Though several studies in cystic fibrosis and other genetic diseases have shown that most people at risk say that they are in favour of screening,[10] the actual take up rate in some studies of patients at risk of Huntington's chorea has been as low as 13-16%.[11] A reasonable compromise, therefore, may be to offer carrier detection only to members of cystic fibrosis families and their partners.

Patients with cystic fibrosis and their families are also anxious to know about the therapeutic implications of the identification of the gene. In theory the abnormally functioning protein could be replaced—by either gene or protein therapy—or its defect restored to normal by drugs. Though techniques exist for gene delivery and human genes can be expressed relatively stably and in a lineage specific fashion in mouse bone marrow cells.[12] The selective introduction and expression of DNA in human epithelial cells seem to require an additional order of complexity. Moreover, as the cystic fibrosis gene product is a member of a family of related transmembrane proteins the selectivity of pharmacological intervention may also prove a problem. The therapeutic impact of the new knowledge may, therefore, not be felt for many years. Though we should continue financial support for these potentially exciting developments, we should not allow all the resources to be diverted at the expense of improving existing lines of treatment.

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Regular Review

Node negative breast cancer

Adjuvant chemotherapy should probably be reserved for patients at high risk of relapse

Patients with breast cancer and negative axillary nodes are not routinely given adjuvant systemic treatment after primary surgery. These patients, whose tumour seems to be confined to the breast, have a good prognosis without such additional treatment. Nevertheless, a clinical alert issued in 1988 by the National Cancer Institute suggested that all patients with breast cancer, regardless of axillary node disease, should now be considered for adjuvant treatment.[1] If widely adopted such a policy would have major implications for the management of patients with breast cancer. It is important, therefore, to review our current understanding of the clinical course of node negative breast cancer and the possible impact on it of adjuvant treatment.

Some 50-60% of all new patients with breast cancer have node negative disease, amounting to over 12 000 patients each year in Britain.[2] The proportion of such patients is likely to rise with the availability of screening programmes, which allow the disease to be detected at an earlier stage. Though most patients with node negative disease have a good prognosis, 20-30% will develop distant metastases and will ultimately die of their disease.[3] Adjuvant treatment might reduce the number of patients whose disease recurs. Before such treatment is offered to all patients, however, several questions should be asked (box).

Prognostic factors

To be of general use a prognostic factor should be easily measurable, give reliable and reproducible results, and allow wide separation of prognostic groups. For patients with node negative breast cancer no one factor satisfies all these criteria. A clear consensus has not emerged on how best to identify patients at high and low risk. The tumour characteristics that have been examined in most detail for prognostic importance include size, histopathological features, oestrogen and progesterone receptor characteristics, measurements of proliferative activity, and tumour ploidy.

The relation of the size of the tumour to relapse free survival and overall survival is well defined for patients with breast cancer and positive nodes but is less certain in patients with node negative disease.[4] The results of two large studies suggest that the prognosis worsens as the size of the tumour increases, but the effect on survival is small.[2,5] The size of the tumour has the advantage of being easy to measure. The same