adrenal suppression. Caution and close observation are required when prescribing inhaled corticosteroids in children. Nevertheless, they remain a major therapeutic advance in management with few serious side effects compared with long term daily oral corticosteroids.

R J STEAD
Senior Registrar in General and Respiratory Medicine

N J COOKE
Consultant General and Respiratory Physician

Department of Respiratory Medicine,
Leeds General Infirmary,
Leeds LS1 3EX

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Predictive testing for Huntington's disease

Progress and problems

In 1983 the first genetic marker for Huntington's disease was found.[1] The discovery not only provided the impetus for advances in many other genetic disorders but also posed important ethical questions about using these markers in predicting a serious and untreatable neurological disease. Five years later how have our thoughts progressed, and how has the work affected the prospects for families with a history of Huntington's disease?

The first point to be emphasised is that the findings have been confirmed widely in Britain[2] and elsewhere.[3] Undoubtedly Huntington's disease is determined by a single genetic locus, an important theoretical and practical point, particularly given that in some other disorders (such as polycystic kidney disease and osteogenesis imperfecta) more than one locus is concerned. Numerous further markers have been studied since the G8 linkage was recognised, several of which are closer to the gene for Huntington's disease than G8.[4-6] Together these markers form a framework for constructing a genetic map of the region of chromosome 4 that contains the gene for Huntington's disease. Physical mapping techniques have also contributed to this map: cell lines derived from patients with Wolf-Hirschhorn syndrome show a variable loss of material from chromosome 4 in this region and can be used to order markers,[7] and pulsed field gel electrophoresis permits the separation and ordering of large DNA fragments in the region. A new approach is radiation mapping, which uses the fragmentation of chromosomes exposed to radiation to order gene markers.[8]

This work has shown that the gene for Huntington's disease is located at the tip of the short arm of chromosome 4, with all the known markers proximal to it and very little DNA between it and the end of the chromosome. Nevertheless, the gene itself has not been identified.

The principal practical consequence from these advances is that predictive testing for Huntington's disease is now a reality, though because of the ethical issues[9,10] clinical applications have been cautious and confined to a few special centres. The initial form of prediction was "exclusion testing" in pregnancy to determine whether a parent had passed on to the fetus either the "at risk" marker type or the type received from the unaffected side of the family.[11] Such testing has the advantage that the parent's own risk is unaltered, whatever the result, but the disadvantage that if Huntington's disease is not excluded the risk for the fetus is raised to 50%, the parent's own risk. None the less, an appreciable number of couples have found this approach acceptable.

Presymptomatic testing for the gene is now under way in several centres in Britain, Canada, and the United States.[12] Given the necessary family structure most subjects can now be given test results that will increase their risk to around 95% or lower it to around 5%. Unfortunately, most individuals do not have the necessary affected relatives in previous generations alive to permit such a definitive prediction, and this, rather than deficiencies in the markers, is the main limitation of predictive testing.[13] The need for DNA isolation and banking of samples from key family members remains as great as when the topic was first discussed five years ago.[14]

No centre should embark on this testing without the most careful consideration of the pitfalls. Foremost is the need for adequate support: not only is the laboratory analysis time consuming but so also are the counselling before the test and the family documentation, which require a multidisciplinary team. A considerable number of people requesting prediction are clinically affected when first seen,[15] a difficult problem for the counsellors, and a further issue is that of prediction for children (notably those for adoption), which we consider cannot be justified at present.[16]

It will be some time before we have adequate information on the outcome of testing—in particular its acceptability and the long term effects on those concerned. Until then the topic is bound to remain controversial, and investigators have a duty to document their activities in detail and to ensure that these are carried out to the highest standards. Once the Huntington's disease gene itself is isolated and its product identified, it will be possible to think in terms of modifying the course of the disorder. When this can be achieved it may

remove some of the problems and inevitable distress from predictive testing for Huntington's disease.

PETER S HARPER
Professor of Medical Genetics

MICHAEL J MORRIS
Research Senior Registrar

Institute of Medical Genetics,
University of Wales College of Medicine,
Cardiff CF4 4XN

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Aetiology of peripheral atherosclerosis

Smoking seems especially important

Patients with intermittent claudication are up to four times more likely than normal people to have coronary artery disease[1 2] and about half will die from a heart attack.[3] Conversely, patients with coronary artery disease have at least a fivefold greater risk of developing intermittent claudication.[4-6] These findings reflect the diffuse nature of atherosclerosis. But why are some people more prone to disease in their peripheral arteries than their coronary arteries?

Vascular surgeons are justified in believing that smoking is almost a prerequisite for developing peripheral arterial disease because over 90% of their patients may give a history of smoking.[7] Studies of intermittent claudication in the community provide a different perspective: the population attributable fraction—that is, the percentage of disease prevalence that may be caused by cigarettes—varies between a fifth and three quarters. Many subjects have apparently never smoked. But smoking does seem to have an independent effect greater than other risk factors[5 6] and to be a more important aetiological variable than in ischaemic heart disease.[6] Most epidemiological studies have shown that raised blood pressure is also likely to be a major risk factor for peripheral arterial disease.[1 2 5 6] The direction of a possible casual association has not, however, been confirmed.

The particularly high incidence of peripheral arterial disease in patients with florid diabetes mellitus is well known, but the extent to which impaired glucose tolerance in the general population is a risk factor is less obvious. A raised casual blood glucose concentration in the Framingham study was more closely related to developing intermittent claudication than heart disease and had an independent effect when other risk factors were taken into account.[9] Conflicting results have, however, been obtained in other population studies.[2 4 5 10] In Oxford, for example, Hughson *et al* found that patients with intermittent claudication did not have a higher fasting blood glucose concentration than controls.[2] Furthermore, in a study in Basle that excluded known diabetes an inverse association was found between the degree of glucose intolerance and the occurrence of disease.[10] These results are important because, unlike those from most other studies,[2 5 9] they are based on a glucose tolerance test. They do, however, have the disadvantage of being derived from cross sectional and not longitudinal data, and more evidence is needed on whether impaired glucose tolerance is a risk factor in the general population.

At least 20 studies have examined the relation between blood cholesterol concentration and peripheral arterial disease, and a consistent picture has not emerged; many studies have found no relation.[8] The role of high density lipoprotein cholesterol has not been widely investigated, but lower mean plasma concentrations have been found in those with disease.[11 12] What is of particular interest is that almost without exception serum triglyceride concentrations have been found to be higher in patients with peripheral arterial disease than in controls. It would be tempting to assume that triglycerides are an important risk factor for atherosclerosis affecting the peripheral arteries and not the coronary arteries, but the independent effect of triglycerides has not been examined adequately in peripheral arterial disease. In line with the findings in coronary arterial disease the association might well disappear when adjusted for other risk factors—especially since triglyceride concentrations are related inversely to concentrations of high density lipoprotein cholesterol.[13]

Any suggestion therefore of a unique risk profile for peripheral atherosclerosis is not supported by the evidence. Smoking seems to be particularly important, but we should be wary that an apparently differential effect of smoking on peripheral arterial disease and coronary arterial disease detected in retrospective studies may simply be a manifestation of a dose response relation in which more smoking is associated with a more severe form of disease. Indeed, claudication tends to occur in older age groups,[4 9] when generalised atherosclerosis is presumably more advanced. On the other hand, people with claudication might represent an attenuated cohort because many of those with severe peripheral atherosclerosis might die from coronary disease at an earlier age. Studies on symptomless subjects in the community may give a clearer picture of the importance of smoking.

Numerous hypotheses have been put forward to explain the atherogenic effects of smoking,[14] but the different anatomical structures and haemodynamics of the peripheral and coronary arteries may explain the differential effects of smoking at these sites. Atherosclerosis occurs most commonly at