a contaminating nuclease be separated from receptor preparations? Cohen has been consistently linked with new advances in the field of growth factors. His pioneering efforts in identifying and purifying EGF and its receptor have led to the discoveries that have set the rest of us in new directions. The new data from his laboratory direct attention to the nuclear effects of EGF and will undoubtedly stimulate discussion and experimentation. However before clamouring to exchange acrylamide for agarose, cell biologists should await further developments. □

Shelley Earp is a member of the Cancer Research Center and Department of Medicine, University of North Carolina, Chapel Hill, North Carolina 27514.

Retinitis pigmentosa

Progress in sight

from Miranda Robertson

THERE is no doubt that molecular genetic technology is leading to an understanding of human genetic disease at a depth and resolution inaccessible to more traditional methods. Because the path to that understanding is often indirect, however, for the time being it presents a problem for clinicians as well as a challenge for research scientists. This is inevitable when the gene defect underlying the disease is unknown, and can be approached only through linked genetic markers. Such is the case in Duchenne muscular dystrophy, for which a marker was first reported two years ago[1], and Huntington's disease, for which a marker was discovered last last year[2]. On page 253 of this issue of *Nature*, Bhattacharya, Wright and their colleagues report an exactly similar marker for the X-linked form of retinitis pigmentosa[3].

As with Duchenne and Huntington's, the retinitis pigmentosa marker is simply an identifiable fragment of DNA that is close enough to the gene to be inherited with it, putting molecular biologists within 'walking' distance of the defective gene itself and offering clinicians the prospect of identifying some symptomless carriers of the gene and, possibly, diagnosing their unborn babies. What are the obstacles confronting the research biologists and the problems facing the clinicians?

Retinitis pigmentosa is the name given to a genetically and phenotypically heterogeneous group of degenerative diseases of the photoreceptor cells of the retina leading, in severe cases, to blindness. The mode of inheritance can be recessive, autosomal dominant or X-linked. The X-linked form, for which Bhattacharya *et al.* now have a marker, is one of the most severe; it accounts for perhaps 30 per cent of all cases and affects about 1 in 20,000 of the population. Because the defective gene is on the X chromosome, of which males have only one, they have no normal gene to compensate for its effects and are severely affected, often in childhood. Females, with two X chromosomes, may have a mild form of the disease or none at all; but they risk transmitting the severe form to their sons. Female carriers of the gene, and the daughters of known carriers, who have no way of knowing whether they themselves are carriers, stand to gain most from the new marker. But it will not help them all, for reasons that follow from the nature of linked markers in general.

The marker in this case is a DNA probe designated L1.28, corresponding to a small fragment of the human X chromosome. What allows this fragment to be used as a marker is its polymorphism — which is to say that it contains minor variations that can be detected by bacterial restriction enzymes (for a slightly fuller explanation of how this works, see ref. 4). L1.28 has two distinguishable variants, A1 and A2. Bhattacharya *et al.* were able to establish the linkage of L1.28 with the retinitis pigmentosa gene on the X chromosome by tracing the inheritance of both the disease and the A1 and A2 variants through five different families.

In the case of close linkage, you would expect the disease to be inherited consistently with one or other of the two variants within a given family; and this is what Bhattacharya *et al.* found. In four families retinitis pigmentosa was consistently inherited with A2; in the other one it was associated with A1. It is just possible that more than one gene on the X chromosome can give rise to retinitis pigmentosa. If so, the linkage will break down in further family studies. So for the time being clinical advice will not be offered on the basis of the L1.28 marker.

But assuming, as seems most likely, that there is only one gene, what are the limitations of L1.28? Most obviously, an affected male relative must be available to establish whether the defective gene is associated with A1 or A2 in the family in question. The second important limitation arises from the fact that both A1 and A2 are present at high frequency in the normal population. Take the case of a young woman whose father has the disease. Since one of her two X chromosomes must be her father's, and his single X chromosome has the defective gene, she will be an obligate carrier and there is an even chance that any son born to her will inherit retinitis pigmentosa. As things stand, she would be offered termination of any pregnancy in which the fetus was male — the entire X chromosome serving as a crude and unreliable marker for the disease. The L1.28 marker makes it possible to distinguish fetuses bearing the normal X chromosome of the mother from those bearing the defective one — but only if the mother is heterozygous for the marker: that is, if she has A1 on one of her X chromosomes and A2 on the other. In that case, if her father's X chromosome bears the A1 variant she can be certain that any male fetus inheriting A1 will also inherit retinitis pigmentosa, and conversely if he inherits A2 he will be normal. But if she is homozygous — that is, she has A1 on both X chromosomes — there is no way of distinguishing a normal male from an affected one before birth. Given the frequency of the two variants in the general population, only 40 per cent of women will be heterozygous.

Similar considerations complicate the case of a woman for whom the family history of retinitis pigmentosa is on her mother's side. Because the symptoms of the disease in women develop late or never, she may not know even whether she is a carrier. If her mother is homozygous for the marker, the marker cannot enable her to find out; though it may, if she herself is heterozygous, enable the disease to be ruled out in some of her unborn sons.

Finally, even for a heterozygote, there is always the slight chance (decreasing with the closeness of the linkage) of misdiagnosis if the defective gene has become separated from the linked marker by genetic recombination. The identification of a second linked marker, on the other side of the gene, would dramatically reduce the probability of mistaken diagnosis; it would also be helpful in the pursuit of the retinitis pigmentosa gene itself.

This, of course, is the longer-term aim of the research: in the end the only entirely reliable genetic probe is the one that identifies the mutant gene. Progress will demand patience and ingenuity. Patience because the distance between L1.28 and the retinitis pigmentosa gene is something on the order of 3 million bases; so to reach the immediate vicinity of the gene will require either a marathon chromosome walk or laborious family studies to find more closely linked markers; and ingenuity to identify the gene once it has been isolated. For retinitis pigmentosa, the best bet may be to compare the genes expressed in normal retinas with those expressed in affected retinas, by means of cDNA libraries from the two tissues.

How soon might a gene probe for X-linked retinitis pigmentosa be available? Should female carriers or suspected carriers wait a year or two before starting families in the hope of reliable prenatal diagnosis? In the case of Duchenne muscular dystrophy, there is still no gene probe two years after the first marker; but optimists expect one this year. □

1. Murray, J.M. *et al. Nature* **300**, 69 (1982).
2. Gusella, J.F. et al. Nature **306**, 234 (1984).
3. Bhattacharya, S.S. *et al. Nature* **309**, 253 (1984).
4. Robertson, M. *Nature* **306**, 222 (1983).

Miranda Robertson is Acting Life Science Editor of Nature.