of evidence is that some 30 per cent of a collection of 40 retinoblastomas, 8 osteosarcomas and 2 undifferentiated tumours arising in retinoblastoma patients showed some structural abnormality in their DNA when fragments generated by restriction enzymes were examined by the p4.7R probe.

The authors do not claim that the evidence is decisive. The failure to detect any alteration in 70 per cent of cases may, as the authors suggest, be explained by the presence of genetic lesions, such as point mutations, that are not detected by the examination of fragments generated by restriction enzymes.

Alternatively, it is possible that the locus detected by the p4.7R probe is not the *Rb* locus itself, but a closely linked locus involved in more complex chromosome rearrangements. This possibility is perhaps made less likely, but is not eliminated, by the fact that in one retinoblastoma and one osteosarcoma, internal deletions were found within the coding region identified by the p4.7R probe. Friend *et al.* contend that this probe should be a powerful diagnostic reagent for distinguishing between the heritable and the sporadic form of retinoblastoma; but it is not immediately clear in what way a probe that yields false negatives in 70 per cent of cases is likely to be particularly useful in clinical diagnosis.

In any case, it should not be long before the identity of the genetic region detected by this probe is firmly established. If this region is the *Rb* locus itself, we can expect soon to receive some sequence information that might provide a clue to the function of the protein that it specifies. Because I adhere to the view that the progressive multiplication of cancer cells is a secondary consequence of their having sustained some genetic alteration that prevents them from completing their normal programme of differentiation, my guess is that the *Rb* locus will be found to specify a protein that is essential for the execution of that programme in the retinal cell.

There is good evidence that homozygosity or hemizygosity of recessive mutations is responsible for tumorigenesis in other malignancies in which predisposition to form the tumour is inherited in a mendelian fashion, for example Wilms' tumour, hepatoblastoma, rhabdomyosarcoma and familial renal carcinoma. But Knudson has argued that there may be a cryptic genetic predisposition in many other tumours, including the common malignancies. In that case, recessive mutations might be responsible for generating a much wider range of malignant tumours than was originally suspected. Certainly the great majority of tumour cells, irrespective of the cell type or the aetiology of the malignancy, and even when the cells bear a well-defined oncogene that is actively transcribed, yield non-malignant hybrids when they are fused with normal diploid fibroblasts[8].

Are there any cellular genes that act to produce tumours in a genetically dominant fashion? They have yet to be found. As several authors have pointed out (see refs 8 and 9) the fact that certain cellular genes when transfected into mouse fibroblast NIH 3T3 cells can induce morphological transformations in these cells and eventually render them tumorigenic, is no evidence that the transfected genes (oncogenes) act in a genetically dominant fashion. The changes that this procedure produces in the genome of the NIH 3T3 cell are very complex and preclude interpretation in formal genetic terms. Where the question has been examined in naturally occurring malignant epithelial tumours[10,11], it has been found that the presence of a mutated oncogene in the tumour is often associated with the absence of its normal allele, a situation very reminiscent of retinoblastoma. In the case of the characteristic translocations involving the c-*myc* oncogene in lymphoid neoplasms, experiments with transgenic mice again indicate that, in addition to the translocation, a second genetic event must occur in the cell before it can generate a malignant tumour[12]. □

Henry Harris is Regius Professor of Medicine and head of the Sir William Dunn School of Pathology, University of Oxford, Oxford OX1 3RE, UK.

First glimpse of the *DMD* gene?

A DECADE ago, molecular analysis of the gene responsible for the X-linked disease Duchenne muscular dystrophy (DMD) seemed an unreal dream. Five years ago, the identification of restriction fragment length polymorphisms genetically linked to the *DMD* gene[1] began to turn the dream into reality. On page 646 of this issue[2], Louis Kunkel, Anthony Monaco and colleagues make further progress with the report of partial characterization of transcripts that probably derive from the *DMD* gene.

Although the results of Monaco *et al.* represent the culmination of a series of brilliant experiments from one laboratory, these experiments would not have been possible without the contribution of many others. Clinicians have provided material from patients (a recent paper[3] acknowledges donations from 25 clinical laboratories); cytogeneticists have defined chromosomal translocations and deletions; somatic cell geneticists have isolated important chromosomes on rodent cell backgrounds; and molecular geneticists have provided a wealth of cloned probes for use as markers in family studies.

These combined efforts resulted in the precise definition of the chromosomal location of the *DMD* gene[3]. As I discussed recently in *News and Views*[4], knowledge of the chromosomal location and the availability of an X chromosome deleted for the *DMD* gene were exploited by Kunkel and colleagues to isolate sequences from the immediate vicinity of the *DMD* locus[5].

A slightly different approach was taken by Ray *et al.*[6] who cloned the sequences present at a chromosomal translocation breakpoint which was associated with *DMD*. The new genetic analysis[3] using both of these sequences suggests that the *DMD* gene is very large, very complex or both. During these studies Monaco *et al.* isolated more than 200 kilobases of DNA from the vicinity of the *DMD* gene. These clones were instrumental for isolating the gene for chronic granulomatonus disease[7] and have now been screened for expressed sequences related to DMD.

Rather than screen valuable messenger RNA with a large number of unique sequence probes Monaco *et al.* first searched for cross-species DNA homology in Southern blots. They argued that any expressed exons would show evolutionary conservation, and found two candidate probes that hybridized to DNA from all mammals tested.

One of these probes, PERT-25, reacts with a 16-kilobase transcript which is present in fetal muscle RNA samples but is not detectable with messenger RNA from cultured human myoblasts or HeLa cells. Short complementary DNA clones, isolated after screening a fetal muscle complementary DNA library with PERT-25, recognize exons distributed more than 110 kilobases of DNA in the *DMD* region. By extrapolation to full-length clones this candidate *DMD* gene may be 1,000–2,000 kilobases long.

As with all scientific advances these results pose many questions which will be difficult to answer. Obtaining the full-length sequence of a mammalian 16-kilobase messenger RNA has only been achieved for one other transcript (apolipoprotein B[8,9]) and the possibility that this candidate *DMD* gene produces multiple transcripts with alternative exon usage will also keep many molecular biologists employed. Finally, obtaining the formal proof that this is the *DMD* gene may be the hardest of all. Nevertheless, the new work is good news to families afflicted with Duchenne muscular dystrophy.

Peter N. Goodfellow

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