group of thymine) of DNA lies in the major groove as well.

Major groove contact is not universal, however. If the the protein in question is not a sequence-specific one, the minor groove can also be its binding site, as reported by Klug and his colleagues in the histone core-DNA structure[8]. Also, proteins involved in transcription, reverse transcription and in the priming of DNA replication have a DNA-RNA hybrid as the binding partner. The hybrid molecule has been shown to assume A-form conformation[9]. Yet in A-conformation only the minor groove is open to proteins, while the major groove is too narrow and deep (2.7Å in width and 13.5Å in depth). Moreover, the two edges of the major groove are laced together by a continuous network of water molecules, making the major groove harder to access. It is then conceivable that the minor groove turns out to be the better binding site for those proteins. Since these DNA-binding proteins are not sequence-specific ones, the less specific minor groove is just good enough.

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The facts on cystic fibrosis testing

SIR—The *News and Views* item[1] on a series of papers[2-5] reporting DNA probes showing linkage to the cystic fibrosis (CF) gene observes "a start has at least been made on the development of the prenatal test for cystic fibrosis". It continues "the new data offer immediate prospects for the prenatal testing of cystic fibrosis". The reader would be entitled to conclude first that no prenatal test for CF currently exists and second that advances in molecular biology have radically altered this situation. Neither conclusion is correct.

Two years ago we reported that measurement of microvillar enzymes in amniotic fluid supernatant could be used as an *in utero* test for CF[6,7]. Our data have been confirmed in many other laboratories and a special issue of the journal *Prenatal Diagnosis*[8] was devoted to this subject. Although the test is not perfect, it has a very adequate detection rate of 95% at 18 weeks of pregnancy and a false positive rate of 5%. In the past two years more than 450 at-risk pregnancies have been prospectively screened by our procedures, and the birth of over 100 children with CF prevented. With the possible exception of Tay–Sachs disease and β-thalassaemia, no other mendelian disorder has been as successfully tackled.

At first sight, it might seem that a restriction fragment length polymorphism (RFLP) tightly linked to the CF gene could improve prenatal testing by moving it from amniotic fluid samples in the second trimester of pregnancy to chorionic villus samples in the first trimester. However, this ignores a cardinal requirement of prenatal testing, namely that some method of confirmation of diagnosis on the abortus be available. This problem has been solved for the second-trimester fetus, first by the observation that most CF fetuses have the macroscopic appearance of meconium ileus[8], and second by protein and enzyme analysis of meconium samples scraped from the fetal ileum[9]. These anatomical and biochemical changes are probably specific to the second trimester and observable only on an intact fetus. If they existed in the first-trimester fetus (which we doubt) they could not be assessed in materials removed by vacuum aspiration, the procedure for termination at this stage of pregnancy.

It is difficult to see how CF-linked RFLPs make reliable prenatal diagnosis 'a reality'. The critical question of the possible genetic heterogeneity of the disease has yet to be addressed. There are suggestions in two of the papers reviewed[3,4] that the CF linkage relationship in the Amish may be different from that in other populations. Even if CF turns out to be a genetically homogeneous entity, much work needs to be done on producing highly informative flanking RFLPs, and on defining the extent of recombination expected with different types of multi-point analysis. But until the CF gene or its protein product is identified, the use of RFLPs on chorionic villus samples will lead to a form of prenatal testing without the benefits of confirmation of diagnosis. It must be emphasized that this is a radical departure from accepted norms of *in utero* testing.

We also have doubts about the value of RFLP-based heterozygote testing in CF. Here the need is for population-wide screening, so that heterozygous couples could be identified before the birth of the first affected child. Programmes of prenatal screening for Tay–Sachs disease and for β-thalassaemia have been effective, largely because heterozygosity tests have been simple, cheap and rapid. The current state of DNA technology is not yet suitable for this type of application.

There has been a tendency recently to exaggerate the immediate clinical benefits of advances in molecular biology. Careful assessment of the potential of RFLP-based diagnosis of genetic disease suggests that its role is likely to be drastically limited by a number of factors such as genetic heterogeneity, the need to have information on whole families rather than individual patients, and expense. Although localization of a mutant gene on a particular chromosome will undoubtedly assist attempts at cloning that gene and identification of its protein product, it must be noted that this is yet to be achieved for any unsolved mendelian disorder, and may well prove more difficult than has been anticipated.

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Long-running experiments

SIR—Your coverage of long-running experiments (*Nature* **318**, 310; 408 (1985)) brings to mind an experiment that although begun in this century will probably not be complete for millennia.

In 1918 Howard and Daniels[1] devised the simple but ingenious idea of sealing nitric oxide in glass tubes, some of which contained potential catalysts. Nitric oxide is thermodynamically unstable ($\Delta G^\circ_{f\,298} = 86.6\ \mathrm{kJ\ mol^{-1}}$) and any decomposition resulting from $2NO \rightarrow N_2 + O_2$ would be followed by $2NO + O_2 \rightarrow 2NO_2$ and the brown nitrogen dioxide produced would be easily detectable. When the tubes were examined 40 years later, decomposition was found neither in tubes containing pure NO nor in tubes containing NO plus catalyst.

The result was no surprise because an extrapolation of their higher temperature work in the presence of a calcium oxide catalyst indicated that 70,000 years would be required for 2% decomposition (the minimum they could detect) at room temperature. Howard and Daniels gave some of their tubes to the Smithsonian Institution, Washington DC, for future examination. In the case of the homogeneous gas phase decomposition of NO at room temperature, even if we assume a detection system sensitive to 100 molecules of NO_2, it would still take $\sim 10^{12}$ years for any decomposition to be noticed.

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