DNA and the doctor

Alan E.H. Emery

The New Genetics and Clinical Practice. By D.J. Weatherall.
Nuffield Provincial Hospitals Trust: 1983. Pp.133. £8.

IF ONLY all scientists could write like this! Professor Weatherall has produced a highly readable, straightforward account of a complex subject. He has avoided cluttering the text with a surfeit of references, no mean achievement when one considers that he is writing about a young discipline in which much is still not clear or is controversial.

The term "new genetics" refers to novel approaches in mapping and determining the fine structure of the human genome using recombinant DNA technology. The clinical application of this technology lies largely in the prevention of genetic disease through the detection of carriers and through prenatal diagnosis. In the more distant future, by isolating and cloning defective genes which are then induced to synthesize their products in the test tube, it will be possible to identify the basic biochemical abnormality concerned where this is not yet known. This approach, of so-called "reverse genetics", could eventually lead to the devising of effective treatments for such disorders. Professor Weatherall's main concern however is with understanding the fine structure of genes, particularly those involved in the haemoglobinopathies, and the avenues this knowledge opens up for prenatal diagnosis.

After an introductory chapter, Weatherall considers the frequency and clinical spectrum of genetic diseases. In round figures genetic disease and congenital malformations account for some 50 per cent of childhood deaths in hospital, and chronic diseases with a significant genetic component occur in about 10 per cent of the adult population. Thus genetic disease produces a considerable burden on the health services. Hopefully developments in recombinant DNA technology will, in various ways, help to reduce this burden in the next few years.

The real value of this little book lies in the masterly way in which the author describes, in relatively simple terms, a complex technology and the insights it has given us into molecular pathology. The single most important development which made the new technology possible was the use of restriction enzymes which cleave DNA at sequence specific sites. Essentially the new technology has allowed certain genes to be isolated, cloned in micro-organisms and their structure determined. In man we now know the detailed structure of, for example, the genes for the haemoglobins, immunoglobulins, insulin and growth hormone. Genes can no longer be considered simply as being discrete and contiguous beads arranged on a string. They are preceded by critical regulatory sequences (RNA polymerase binding sites) and terminated by other sequences; further, almost all eukaryotic genes are interrupted by introns (intervening sequences) which are not transcribed into functional messenger RNA and protein. And between genes are large stretches of DNA with, as yet, no recognizable function — the so-called "selfish DNA".

By generating radioactive DNA sequences for use as probes, it is possible to demonstrate, by hybridization studies, the presence of homologous sequences in DNA extracted from tissues such as leucocytes and amniotic fluid cells. Information currently gained in this way can be applied to prenatal diagnosis in either of two ways. Directly, by demonstrating that a deletion is present, or that there is an altered restriction site within the abnormal gene; alternatively, and of more general application, indirectly, by showing that a mutant gene is in linkage disequilibrium (allele linkage) with a particular set of restriction sites — as in the case of sickle cell anaemia and β-thalassaemia in Sardinia — or by demonstrating within families linkage with a restriction fragment length polymorphism. This latter approach is now a burgeoning area of research, especially with regard to disorders where the nature of the genetic defect is still unknown, such as Duchenne muscular dystrophy and Huntington's chorea.

The subject of gene therapy is dealt with only briefly, but Weatherall is quick to emphasize the problems and his sober account contrasts starkly with the sensationalism which has often accompanied discussions on this emotive subject. Finally, he considers the implications of the new genetics for clinical practice. Quite apart from considerations of cost-effectiveness and ethics associated with population screening and prenatal diagnosis, clinical practice in general is likely to change as the technology inevitably leads to fresh approaches to diagnosis, management and — ultimately — treatment. The medical profession as a whole will have to become informed about the technology, and clinical geneticists in particular will have to become very much involved in what is likely to revolutionize their approach to families with genetic disease over the next few years. For both groups, indeed for anyone with even a passing interest in genetics, Weatherall's book could not be a better starting point. □

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Sorting out the sexes

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The Theory of Sex Allocation.
By Eric L. Charnov.
Princeton University Press: 1982. Pp.355. Hbk $52, £34.50; pbk $17, £11.30.

IT IS one of the pitfalls of modern evolutionary thinking that whilst adaptive explanations spring readily to mind, they are all too often untestable. The study of sex ratios, however, proves a most fruitful testing ground for some of the predictions of evolutionary theory. The idea that the usual 1:1 sex ratio of males to females represents an evolutionary equilibrium resulting from the operation of natural selection is implicit in the work of R.A. Fisher. Sex ratio theory has since been elaborated and, more recently, some of its predictions tested, often using organisms whose sex ratios deviate from 1:1. For example, where local competition for mates occurs, a female-biased sex ratio is predicted, and this is indeed the case in many parasitoid wasps in which mating occurs on, or near, the host from which they have emerged.

But sex ratio is just one aspect of the more fundamental problem concerning the way in which resources are allocated to male and female reproduction. How long, for instance, should a fish which changes sex during the course of its life, spend functioning as a male and how long as a female? How should an hermaphroditic plant divide its resources between production of pollen and ovules? Unlike sex ratio evolution, the broader question of sex allocation has been largely neglected until recently. Now, in *The Theory of Sex Allocation*, Eric Charnov draws on an extensive, though often anecdotal, literature to remedy this failing, exploring sex allocation from an evolutionary viewpoint through theory, observation and experiment.

Charnov's theoretical approach is based on finding the evolutionarily stable allocation between male and female reproductive functions. This simple basis is developed with a minimum of mathematical elaboration. It is then used to explore the conditions under which selection favours the evolution of the three main types of reproduction (dioecy, sequential hermaphroditism and simultaneous hermaphroditism) and the interesting evolutionary questions which each poses. For sequential hermaphroditism such questions concern the sex of an individual at first reproduction, whether it should then change sex and, if so, the age at which this change should occur. Theory predicts