The New Genetics and Clinical Practice

Professor Weatherall was originally asked by the Nuffield Provincial Hospital Trust "... to hazard a guess at the impact that recent developments in molecular biology might have on the care of patients with inherited diseases ...". The result was a monograph which captured at a critical time the imagination of devotees and the genetically uncommitted alike.

Weatherall has now rewritten the monograph and the result is even better. Oxford University Press have done a fine job and the paperback is elegantly produced with particularly clear diagrams (I suspect to be pirated for slides by a generation of lecturers). It does not pretend to be a comprehensive textbook of medical genetics but sticks more or less to the original brief. The subject area is so vast that there are inevitably a few minor errors, for example, in HLA nomenclature and an ambiguity in the theoretical number of base pairs in the human genome. It is a reflection of the rapidity of progress that there is only a brief mention of the mapping of cystic fibrosis and of the use of the Jeffreys probe. The early chapters deal with the frequency and 'load' of genetic disease, how genes work, the tools of the new genetics, and the molecular pathology of single gene disorders. These are valuable sources of facts and lucidly simple descriptions of otherwise dauntingly complex molecular genetics. The excellent chapters on molecular genetics draw heavily, but not exclusively, on the haemoglobin disorders and the section on the molecular genetics and pathology of the immune system is particularly clear.

Professor Weatherall's devotion to the haemoglobinopathies has been entirely vindicated because it is now obvious that they represent clinical genetics in microcosm and they have given us the means to illuminate the entire pathogenic process from gene mutation to disease phenotype. They are also the commonest genetic disorders worldwide and present formidable health and economic problems. While the full spectrum of clinical variability of sickle cell disease is yet to be defined, the natural history of β thalassaemia is well known and may be poignant in the extreme. When available, blood transfusion therapy may allow normal development only to be followed by death from iron overload in the late 'teens. Although painful and expensive treatment is available to eliminate iron, if all affected children received even blood transfusions there would be very little left in the medical budgets of the developing countries. Fortunately a complementary strategy of prevention is possible employing knowledge of the molecular genetics of sickling and of the thalassaemias. The molecular pathology of these disorders is known in great detail and although it has proved to be extremely heterogeneous, this has not prevented the application of methods which allow carriers to be screened and affected fetuses aborted following prenatal diagnosis.

General aspects of the prevention and treatment of genetic disease and of prenatal diagnosis in general are discussed simply and clearly in two chapters on practical applications. In two final chapters Weatherall considers the implications of the new genetics for clinical practice in the future and the ethical issues that might arise. He describes the very real dilemma of research on human embryos which if prohibited entirely would prevent the development of new ways to discover and remove the causes of those many malformations that arise during early embryogenesis. His positive view of gene therapy is commendable and if he appears to advocate mildly more positive genetic counselling than is general in the UK, this is a view that is shared by some clinicians and not a few patients.

Because expensive 'patching up' treatment and prevention are both possible, the haemoglobinopathies and other genetic disorders are excellent examples with which to confront health economists. Should we spend money now for the prevention of future disease and in so doing compromise the limited funds available for the treatment of patients already afflicted? Weatherall is too much the clinician to neglect his patients, but he sees clearly and expounds eloquently the overriding humanity of prevention. If this is at present mainly through the medium of selective termination of pregnancy, the new genetics offers the hope of better things to come by specific treatment with genes or otherwise, and the protection of cohorts of persons genetically susceptible to common diseases like premature vascular disease, diabetes, and cancer. There is no doubt that the progressive and complete exploration of the human gene map will present radically new opportunities for disease prevention.

Governments must invest in genetics but they must also realise that the application of the new genetics is not simply concerned with high technology. It is also a matter of good clinical practice, family medicine, and population education including that of medical students, doctors, and health care professionals generally. By presenting the issues and the
enormous opportunities so clearly. Professor Weatherall has done us all a great service. This book is essential for medical students, doctors in postgraduate training (all of us), research workers, and indeed everyone concerned clinically, scientifically, or economically with medical care in developed and developing countries.

RODNEY HARRIS

The Origin and Evolution of Sex

Sexual reproduction in eukaryotes is thought to have arisen about a thousand million years ago and that in prokaryotes two thousand million years earlier. While the origin of sex is shrouded in speculation, we are better informed on the origin of this book, which began as a workshop on 'Molecular aspects of cellular diversity' at the Marine Biological Laboratory at Woods Hole in 1984. Its aims were summarised by one of the editors as (1) to analyse the molecular basis of sex in bacteria and (2) to lay the foundations for a comparison of sex and sexuality in higher organisms.

With these aims in mind, the book has been subdivided into four sections: (1) Bacterial conjugation: beginning of sexuality in prokaryotes; (2) The DNA of sex in unicellular eukaryotes; (3) Evolutionary patterns in segregation of germ cells; (4) Sex determination and differentiation in vertebrates. Each section concludes with a summary of the discussion written by a discussion leader, whose task cannot have been an easy one. No-one is likely to be surprised that the hoped for evolutionary link between sexual mechanisms in prokaryotes and eukaryotes failed to be identified. Nevertheless, some interesting relationships were suggested.

In a chapter on 'DNA repair and complementation: the major factors in the origin and maintenance of sex', Bernstein et al develop their hypothesis that the necessity to repair genome damage provided the immediate selective force giving rise to one of the fundamental aspects of sexual reproduction, that is, genetic recombination due to breakage and exchange of DNA between homologous chromosomes. This idea is pursued from simple RNA protocells, faced with the problem of coping with damaged information at a low level of gene redundancy, to the evolution of outcrossing diploid organisms. By contrast, Scofield puts forward the view that the prime force leading to sexual reproduction was the challenge from microbial pathogens, which required increased variability in histoincompatibility systems. A third idea, suggested by Margulis et al, is that sex in higher animals is maintained not because of any genetic advantage of mixis, but because of an association of meiosis with morphogenesis. If in most vertebrates sex is inseparable from reproduction, mathematical descriptions of its cost become superfluous.

Eukaryotes also differ from prokaryotes in the possession of Bkm sequences, of which large amounts have been demonstrated on the W chromosomes of some snakes and the Y chromosome of the mouse. This topic is reviewed by Jones. However, there is no mention of the human Y, and the significance of these DNA sequences in relation to sex determination evidently remains to be established.

The section on 'Sex determination and differentiation in vertebrates' contains four chapters, of which the longest is on Drosophila! Of the remaining three, one is a comparative account of sexual differentiation in vertebrates by Segal, while two contributions, by Taketo et al and by McLaren, deal with the development and differentiation of the mammalian gonad. McLaren presents further evidence that the phenotypic sex of germ cells depends on the time of entry into meiosis, which in turn is determined by the tissue environment rather than the chromosome constitution of the germ cells themselves.

Significantly, an involvement of H-Y antigen in gonadal differentiation is no longer regarded as likely. This raises the question of why ambiguous data could bypass the peer review system and convert a hypothesis into apparent fact in both the scientific literature and in textbooks. The present book seems free of dogma and even though it does not deal specifically with human sexual development, it contains ideas that are relevant to the more general aspects of sexual reproduction.

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