LETTERS TO THE EDITOR

X linked α thalassaemia/mental retardation (ATR-X) syndrome

We read with interest the series of reports in the journal on the ATR-X syndrome.¹⁻⁴ The facial features are similar to affected subjects with another X linked MR syndrome in a Canadian family described by us a few years ago.⁵ Cole *et al*² suggested that our family may have the ATR-X syndrome. We studied the three living affected males in the family again. All showed normal haematological indices, no detectable haemoglobin H on electrophoresis, and no cells containing haemoglobin H inclusions using 1% brilliant cresyl blue preparations of peripheral blood smears.

In addition, our patients appear to be less severely retarded than the British families described. The possibilities are that these two disorders may (1) be the result of different mutations, (2) be allelic, or (3) represent an X chromosome contiguous gene syndrome with different sized deletions. In respect to the last hypothesis, high resolution chromosome analysis in our laboratories (Winnipeg and Calgary) and in Houston (courtesy of David H Ledbetter) showed no deletions. Identification of the gene locus and molecular studies will ultimately resolve the issue.

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49,XXXXY syndrome: behavioural and developmental profiles

I read with great interest the recent paper by Lomelino and Reiss,¹ reporting behavioural, psychological, and cognitive profiles of two cases of 49,XXXXY and one of 48,XXXXY/49,XXXXY mosaicism.

In 1964² I reported two cases of severely mentally handicapped patients with XXXXY syndrome, who suffered from similar developmental profiles. Case 1 improved very little in cognition, behaviour, and language

development since 1964 and died from bronchopneumonia at the age of 23 years.

Case 2 is now 44 years of age and intellectually he has improved slightly since 1964. Assessed on the Merrill Palmer Scale, his MA is 5.11 years but he still cannot read or write. His verbal comprehension and expression has shown some improvement. Results of testing on the Reynell Development Language Scales were: raw scores 42, equivalent age 3.03 years. The main characteristics which make him difficult to understand are the very low volume of his voice (he mostly speaks only in a whisper) and his shyness.

However, there are increasing problems with his behaviour. He suffers from temper tantrums, kleptomania, and self-injury, particularly to his hands. He constantly picks a chronic hypostatic ulcer³ on his leg. He is often untruthful and mischievous. The patient has been caught setting fire on many occasions and therefore requires constant supervision.

Sometimes he becomes verbally abusive, swearing and threatening violence, and will resort to throwing things.

Physically he is prone to falls and sustained a fracture of the neck of the right femur and fracture of the left patella, which is adding to his frustrations.

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BOOK REVIEWS

All titles reviewed here are available from the BMJ Bookshop, PO Box 295, London WC1H 9TE. Prices include postage in the UK and for members of the British Forces Overseas, but overseas customers should add 15% to the value of the order for postage and packing. Payment can be made by cheque in sterling drawn on a UK bank, or by credit card (Mastercard, Visa or American Express) stating card number, expiry date, and full name.

The Triumph of the Embryo. Lewis Wolpert. (£14.95.) Oxford: Oxford University Press. 1991.

This book is intended as an introduction to developmental biology for non-specialist readers. The majority of the book is devoted to the mechanisms of embryonic development, but cancer, ageing, and evolution are also covered from a developmental perspective. The reader is taken through the stages of embryonic development by careful discussion of important experiments and well chosen analogies, for example, gastrulation and origami. Professor Wolpert's belief that embryonic development can be described by a series of relatively simple mechanisms, and his sheer enthusiasm for the subject, provide the basis for a clear and comprehensible

account of complex processes, such as limb formation and central nervous system development.

This is an excellent book. It is informative and readable and fulfils its intended purpose (triumphantly). I would recommend it to lay readers wanting a clear and comprehensible account of embryonic development and to any health professional who wanted a gentle introduction to the subject.

E R MAHER

Antenatal Diagnosis of Fetal Abnormalities. Ed J O Drife, D Donnai. (Pp 400; £60.00, DM190.) Berlin: Springer-Verlag. 1991.

An academic paediatrician who recently reviewed advances in genetics commented that the subject had become much too important to be left to geneticists. His realisation only came lately; thus obstetricians should congratulate themselves on being farsighted enough to have established (with perhaps more than a little prompting from a few pioneering geneticists) a multidisciplinary subspecialty which, paradoxically for a subspecialty, has grown to touch upon the lives of nearly everyone in the general population. This, of course, means that workers in the field carry a very heavy burden of responsibility, so it is timely that the Royal College of Obstetricians and Gynaecologists should, in its 23rd study group meeting, examine the state of antenatal diagnosis.

This book contains papers presented at the meeting and edited transcripts of the resulting discussions. Its title is brief but does not mislead into anticipating that its contents will merely be another account of the latest clinical and laboratory techniques, although there are certainly many expert and critical expositions of these. One only has to run through the list of the meeting's participants, noting a philosopher, an economist, a psychologist, a civil servant, and several epidemiologists, to realise that a wide brief is being addressed. The broad sweep of the contribution is reflected in a list of 19 conclusions and recommendations at the end of the book. As well as statements on clinical procedures and laboratory tests, such as ultrasound examination, fetal blood sampling, and maternal serum screening, there are more general statements supporting the organisation of regional genetic centres and fetal medicine centres, calling for improved professional and lay education in genetics and recommending that ethicists should be involved in the introduction of new techniques. Two other recommendations are, firstly, each district general hospital should have a consultant obstetrician with a special interest in and responsibility for the various aspects of prenatal diagnosis and, secondly, that appropriate support, obstetric follow up, and genetic counselling should be available to women who undergo termination of pregnancy for fetal abnormality. I thought there might be a statement on the relative merits of amniocentesis and chorionic villus sampling, given that there is discussion of this at several points in the text, but perhaps the study group did not wish to prejudge the then unpublished MRC trial comparing these procedures.

The book's 25 chapters, which embrace almost the whole subject, are arranged in seven sections and comprise reviews in the

areas of epidemiology of congenital abnormalities and routine screening, DNA analysis, cytogenetic and biochemical disorders, special techniques (two sections, including a review of intrauterine therapy), counselling, economics and ethical issues, and service provision. In the latter section there is a detailed description of the financial and operational basis of the system in the Netherlands (H Galjaard). Here, perhaps, an opportunity was lost to appraise this critically and speculate in the light of the radical changes now threatening our working practice in Britain. In other chapters there are detailed discussions of heterozygote screening for cystic fibrosis, cardiac ultrasound scanning, and the karyotyping of chorionic villi; there are also thoughtful essays on psychological, economic, and ethical aspects of prenatal diagnosis (the latter contains a memorable rebuttal of George Steiner's airing on television of the argument that prenatal diagnosis would have deprived us of Beethoven, in the author's words, Steiner's 'ode to joy'). Finally, there are several reviews which draw attention to new techniques such as preimplantation diagnosis and magnetic resonance imaging.

Given the list of distinguished authors, sustained excellence in content was assured, but for me an additional bonus was the sheer ease with which the book could be read from cover to cover. The editors are to be congratulated on this count, also for getting the book published so promptly and for providing us with edited transcripts of the discussions which followed papers. Many interesting points emerge from these discussions, for example, a scientist wonders how couples can be made anxious by a negative test result, the psychologist argues that the process of prenatal testing causes anxiety in women who do not realise they are at risk (presumably we are dealing with low risks here), and later on in the book a professor claims that in his region it takes four or five weeks to get an amniocentesis result and he spends 20 to 25% of his time on the telephone to patients justifying the delay! Now, if you are itching to discover who these people are or where they work, then you'll just have to read the book. At £60 it is perhaps only painlessly affordable to an obstetrician; perhaps your local one might be persuaded to purchase an extra copy for those who work in the laboratory. The contents of this book certainly qualify as essential, extremely pleasurable reading for everyone whose clinical work is in the field of antenatal diagnosis.

JOHN TOLMIE

The Colonization of the Pacific. Ed Adrian V S Hill, Susan W Serjeantson. (£45.00.) Oxford: Clarendon Press. 1989.

A curious title for a book chosen for review in *Journal of Medical Genetics*? In content, only 23 pages out of the 294 of text touch on topics of clinical relevance (the haemoglobinopathies and thalassaemia) and, apart from malaria in this context, there is barely a mention of any other disease, genetic or otherwise. Yet no justification is necessary, for the book is fascinating as well as informative, and will leave the clinician whose primary concern with DNA is diagnostic very aware of the much wider range of uses to which modern techniques can be put. The sheer physical difficulties of the colonisation of the Pacific

islands, of surviving and making a landfall in primitive canoes after hundreds or thousands of miles of ocean, challenge the imagination. The technical advances of genetics in recent decades, that provide the data used in this book to trace colonisation routes, are parallel if different types of achievement.

Increasing knowledge in the last couple of centuries of the islands and their peoples stimulated enquiries in many disciplines – biology, ethnology, oceanography, oral history – and, in the opening chapter, Bellwood summarily reviews the evidence other than genetic: anthropometry, osteometry, dentition, fossil remains, linguistics, archaeology. Here the only criticism is one of regret at the omission of any mention of the classic work of early investigators, for example, Te Rangi Hiroa; other than to Cook's exploratory and Wilson's missionary voyages at the end of the 18th century and the maverick Heyerdal in 1952, the earliest reference is 1962, by which time the general outlines of the colonisation of the Pacific had become clear. But this chapter is by way of an hors d'œuvre to the main work of appraisal of genetic data. Each of the next six chapters is devoted to a particular set of polymorphisms.

Kirk, with his characteristic thoroughness, reviews the data on red cell antigens, serum protein, and enzyme systems. For the blood groups he deals not only with the widely used polymorphic systems, but also shows the utility of the very rare antigens unique to this region. For the proteins he deals comprehensively with 24 polymorphic systems, draws attention to others for which there are few or no data, and incorporates previously unpublished results.

In chapter 3 on HLA, class I and II antigen distributions in Pacific populations are reviewed in detail for the serologically defined HLA-A, B, C, and DR antigens. Restriction fragment length polymorphisms in class I genes have not yet been explored in Oceania, but those of class II, the RFLPs associated with DR and DQ, are given detailed treatment since they show an unexpected heterogeneity among Pacific populations. The linkage disequilibria among the several loci not only show many haplotypes that are unique in Oceania but give an extra dimension to the definition of population affinities, additional, that is, to those described by gene frequencies alone. The principal surprise is not that the molecular data show greater diversity among groups than serological studies predict, but that such a small segment of the human genome provides such an accurate summary of the history of the colonisation of the Pacific.

The complement components (chapter 4) are less informative, since several are less polymorphic, with fewer available alleles or more extreme frequencies, though again there are alleles unique to the Pacific. There are few data on immunoglobulin allotypes (chapter 5), but then chapter 6 on mitochondrial DNA and chapter 7 on nuclear DNA of the globin gene region clearly show the potential for DNA markers in population studies. They show once again the extreme position of the highlanders of Papua/New Guinea, characterised by low frequencies of single α globin gene deletions, and the striking difference between highland and coastal New Guinea populations. In Melanesia the distribution of high frequencies of $-\alpha$ deletions as well as β thalassaemia shows a clear relationship to malarial endemicity, the two commonest $-\alpha$ deletions being either rare or absent outside Oceania. In Polynesia no hae-

moglobinopathies and no β thalassaemia had been reported, but the DNA analysis of the globin gene clusters shows clear evidence of ancestry from south-east Asia (high frequency of the Ia and the IIa α globin restriction enzyme haplotypes) and with Melanesia (a particular α deletion). On their journeys out from south-east Asia the ancestors of the Polynesians seem to have acquired genes from the Melanesian populations through whom they passed. The Micronesians also show affinities with south-east Asia but less, though unequivocal, genetic evidence of some Melanesian gene flow into Micronesia.

The final chapter draws together the material in the previous chapters. Though each deals with only a small proportion of the human genome, all produce conclusions that are surprisingly but satisfyingly consistent, and provide substantial support for the general interpretation from archaeological and linguistic evidence. The new DNA techniques obviously provide more refined genetic analyses than was previously possible. Apparent phenotypic similarities sometimes mask subtle differences at the DNA level, as shown for the HLA-DR antigens. The non-coding regions of DNA that are less subject to the evolutionary forces of selection provide an additional source of variation. Closely linked markers, sometimes within a gene, permitting analysis of haplotype frequencies and linkage disequilibrium relationships, are indicators of population affinities more useful than most single variants. Yet the more traditional serological techniques make a most important contribution, because larger sample sizes are possible.

This is a book to be recommended. Maintaining the high standards of the series in which it appears (Research Monographs on Human Population Biology), this book is highly professional and informative. It is, moreover, philosophically satisfying as a reminder of what man can be capable of, ourselves today with our sophisticated modern techniques and our earlier forebears without them.

D F ROBERTS

Introduction to Risk Calculation in Genetic Counselling. I D Young. (Pp 158; £12.50.) Oxford: Oxford Medical Publications. 1991.

Many doctors and their colleagues shudder at the thought of genetical statistics and this introduction to the subject should both reassure and educate them. It was designed for those who come across genetic risks, either in a clinical situation or in a laboratory setting. The text is simple, clear, and accurate. Risks for dominant disease are discussed together with the subjects of reduced penetrance, variable expression, and gonadal mosaicism; those for autosomal recessive diseases together with consanguinity; those for X linked diseases with discussion of different mutation rates in the two sexes and gonadal mosaicism. Empirical risks are given when theoretical risks are uncertain. Examples of realistic situations are worked through with figures and lucid calculations, and once the reader has understood the basic argument, a further question is asked to test his/her understanding. Are the risks different if the couple already has two healthy children? How do the risks change if the couple are first cousins instead of second cousins? The