LETTERS TO THE EDITOR

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

We read with interest the series of reports in the journal on the ATR-X syndrome.1,2 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.3 Cole et al4 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) repre- sent an X chromosome contiguous gene syn- drome 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,XXXY 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,XXXY and one of 48,XXXXY/49,XXXXY mosaicism.

In 19644 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 bron- chopneumonia 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 very limited comprehension and expres- sion has shown some improvement. Results of testing on the Reynell Development Lan- guage Scales were: raw scores 42, equivalent age 3-05 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, such as temper tantrums, kleptomania, and self-injury, particular to his hands. He constantly picks a chronic hypostatic ulcer 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 sus- tained 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

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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 discus- sion 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 develop- ment.

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 to any health professional who wanted a gentle introduction to the subject.

E R MAHER


An academic paediatrician who recently reviewed advances in genetics commented that the subject had become much too im- portant to be left to geneticists. His realiza- tion is only partly true, the lay public should understand the issue. Sometimes the recent literature reviewed in this issue, including reports of particular cases where geneticists have been involved, shows that the subject is not only important but vital to understanding the human condition. Geneticists are involved in almost all aspects of clinical medicine and therapy, and in health care today.

The book contains a list of references, but in my opinion it is too short. It would be much better to have a more comprehensive list, as there are many 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 tech- niques. 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 preg- nancy 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 prejudice 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, cytogentic and biochemical disorders, special techniques (two sections, including a review of innovative approaches to genetic 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 both chapters there are detailed discussions of heterozygote screening for cystic fibrosis, cardiac ultrasound scanning, and the karyotyping of choric 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.easiness 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 what these people are or where they work, then you just have to read the book. At £50 it is perhaps only painlessly affordable to an obstetrician; perhaps your local library could 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 anyone whose clinical work is in the field of antenatal diagnosis.

JOHN TOLMIE


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 genetic or otherwise. 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 much wider 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 are discussed 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 the new disciplines of biology, ethnology, oceanography, oral history - and, in the opening chapter, Bellwood summarily reviews the evidence other than genetic: archaeology, 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'oeuvre to the main work of appraisal of genetic data. Each of the next chapters is devoted to a particular set of polymorphisms.

Kirk, with his characteristic thoroughness, reviews the data on red cell antigens, serum proteins, and enzyme systems, for the blood groups he has put together 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 the polymorphic systems, draws attention to others for which there are few or no data, and incorporates previously unpublished results.

In chapter 4 the HLA and 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 II genes have not yet been explored in Oceania, but those of class I, the RFLPs associated with DR and DQ, are given detailed treatment since they show an unexpected heterogeneity among Pacific populations. The linkage disequilibrium 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, added 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 in the ABO and MN 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 genes and large genetic differences. The striking difference between highland and coastal New Guinea populations. In Melanesia the distribution of high frequencies of α deletions as well as that of the ω allele shows a clear relationship to malarial endemicity, the two commonest α deletions being either rare or absent outside Oceania. In Polynesia no haemoglobinopathies 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 frequencies of the La La deletion) and the Gilbert deletion 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 whom and at what time they worked. The Micronesians also show affinities with south-east Asia but less, though unequivocal, genetic evidence of some Melanesian gene influence on them.

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 indicate by Peter Brown's analysis of haplotype frequencies and linkage disequilibrium relationships, are indicators of population affinities more useful than most single variants. Yet the more accurately defined segments of the genome are of most importance, 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


Many doctors and their colleagues shudder at the thought of genetic statistics and this introduction to the subject should both reassure and educate it. 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 results from the Melanesian populations 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 couple already has two healthy children? How do the risks change if the couple are first cousins instead of second cousins? The
Antenatal Diagnosis of Fetal Abnormalities

John Tolmie

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