

to women normally resident in Oxfordshire<sup>7</sup> and (2) spina bifida births and terminations of pregnancy in 1973 to 1987 among women booking for their antenatal care at the John Radcliffe Maternity Hospital, Oxford. Information on the site of the lesion was available from hospital records and necropsy reports on 184 cases of spina bifida in the earlier series and 103 in the later series. The sex ratio was 0.67 (49/73) in cases of spina bifida confined to the lumbar or sacral region and 0.54 (58/107) in those with higher lesions, but this difference was not statistically significant ( $p = 0.18$ , one tail test).

The table summarises the results from the four published studies on the subject, our own data, and two other studies<sup>8,9</sup> of spina bifida where information on fetal sex and spinal location was not included in the original publication but has been provided to us by the authors. Using standard methods to combine the results from all seven studies yielded an overall statistically significant increase in sex ratio among those with low lesions (Mantel-Haenszel,  $p < 0.01$ ). Because there is considerable heterogeneity between the studies in both the overall sex ratio and in the proportion of low lesions, it is not possible to estimate reliably the magnitude of the effect. The between study differences in proportion of low lesions are probably related to the accuracy with which the site of the lesion was determined. If x ray or necropsy examination were used the lesion may be found to be more extensive than on clinical examination. The between study differences in sex ratio are likely to be the result of chance.

Following the original observation of sex differences in the spinal location, explanations have been suggested which relate to the fact that the neural tube is formed by neural folding in a craniocaudal direction followed by canalisation in the sacrum. If female fetuses are less developed at a specific gestational age because on average they are conceived later in the cycle, they may be more susceptible to higher lesions from a gestation specific insult.<sup>10</sup> In the curly tail mouse, female embryos are growth retarded at the time of neurulation<sup>1</sup> and this may, by changing the rate of neural tissue growth, affect neural folding and canalisation in different ways.<sup>5,11</sup>

Whatever the explanation, information on the site of the lesion now needs to be included in epidemiological studies of spina bifida which are aimed at elucidating the aetiology of this disorder.

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Sex ratio (male/female) according to spina bifida location in seven studies.\*

Study	Low lesions	High lesions
London <sup>1,2</sup>	3.00 (15/5)	0.42 (10/24)
Madrid <sup>3</sup>	1.26 (110/87)	0.67 (2/3)
Glasgow <sup>4</sup>	1.67 (10/6)	0.21 (5/24)
Vancouver <sup>5</sup>	0.76 (95/125)	0.86 (37/43)
Cambridge <sup>8†</sup>	0.94 (32/34)	0.55 (18/33)
Grand Rapids <sup>9‡</sup>	0.96 (76/79)	0.66 (21/32)
Present study	0.67 (49/73)	0.54 (58/107)

\* A 'high' lesion is defined as one including the thoracic, cervical, or occipital region; a 'low' lesion is below this.

† When the sensory, rather than cutaneous, level is used they are 1.53 (23/15) for below L3 and 0.57 (27/47) for higher lesions. Five were unclassifiable because of widely asymmetrical levels (G M Hunt, personal communication).

‡ H V Toriello, personal communication.

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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.

**Molecular Genetic Medicine.** Volume 2. Ed T Friedman. (Pp 233; \$55.00.) New York: Academic Press. 1992.

In my (favourable) review of the first volume of this new book series (*J Med Genet* 1992;29:519), I made a plea for more articles about the practical applications of molecular genetic medicine. I was pleased to find that volume 2 adequately answers this need.

There is a great art (which means that a little luck is needed) to choosing appropriate topics for a review series such as this. For instance, the article on the fragile X syndrome (Brown and Jenkins) would have been a damp squib had it appeared in volume 1. Fortunately, the unstable CGG mutation was described just in time: it provides a dramatic finale to a good review of the events leading up to its discovery. Naturally, one would look elsewhere to find out the latest news on genotype/phenotype correlation, but attempts by series such as this to describe the up to the minute situation can easily backfire. This is illustrated by the less successful article 'The impact of molecular biology on the diagnosis and treatment of hemoglobin disorders' (Berg and Schechter). The first half is a standard summary of globin mutations, which can be found elsewhere. The second half launches into locus control regions, globin switching, transcriptional factors, and—confusion. The story will have changed by next year, and those who need to be bang up to date will be better served by following the original publications.

Three of the other five articles will be of particular interest to the geneticist. I was surprised to learn from 'The molecular genetics of Down syndrome' (Holtzman and Epstein) that expression levels of some chromosome 21 genes in this condition are greater than normal by more than the predicted factor of 1.5. Such deregulation of expression dosage may be important in the pathogenesis of the condition. 'Mammalian X chromosome inactivation' (Gartler *et al*) is a scholarly review that summarises basic biological knowledge of the process. The candidate gene for the X inactivation centre (XIST) is not described in detail, a sensible decision as its significance is still unclear. However, of all the articles, I found 'Molecular analysis of mutation in the human gene for HPRT' (Lambert *et al*) the most interesting, probably because of my previous ignorance of the subject. The existence of both positive and negative HPRT selection systems, together with PCR/sequencing technology, make possible the rapid characterisation and comparison of HPRT mutations in both the germline and the soma, currently a unique situation, with important lessons for mutation detection of other genes, oncology, and gerontology. In fact the mutational spectrum in different contexts is generally remarkably uniform, 10 to 15% being gross deletions. A notable exception is that neonatal cord blood T cell mutants comprise 85% deletions: speculatively, this may be related to the massive recombinase mediated somatic gene rearrangements that take place during thymic differentiation of T lymphocytes.

The final two articles 'Hepatitis B virus biology and pathogenesis' (Chisari) and 'Regulatory genes of human immunodeficiency viruses' (Wong-Staal and Haseltine) are no doubt good too. I have to admit that virology became too complicated for me some time ago, and I did not read them in detail.

ANDREW WILKIE

**Genome Analysis: Genes and Phenotypes.** Volume 3. Ed Kay E Davies, Shirley M Tilghman. (Pp 174; \$40.00.) New York: Cold Spring Harbor Laboratory Press. 1992.

*Genes and Phenotypes* presents a rather forbidding title to what is, in fact, a very user

friendly guide, mainly in historical form, to the isolation and preliminary analysis of some very important genes.

In the style of this series each chapter starts with an abstract. The first chapter by Lap-Chee Tsui and Xavier Estivill is entitled 'Identification of disease genes on the basis of chromosomal localization'. The abstract reads as follows:

"Chronic granulomatous disease was the first human disease gene to be identified on the basis of its chromosome localization. Prior knowledge of its biochemical defect made the gene identification relatively easy.

"Duchenne/Becker muscular dystrophy is the largest gene known in the human genome. Deletions are the most common mechanism causing the disease. There is no shortage of landmarks for delimiting the disease locus.

"Retinoblastoma represents a unique genetic system for studying mechanisms of somatic mutations and an excellent model for understanding the role of recessive oncogenes in tumorigenesis.

"Cystic fibrosis shows that it is possible to identify a disease gene solely on the basis of linkage analysis, without any chromosome rearrangements pointing the way.

"Choroideremia provides an extreme example in which only a little can be learned about the basic defect through cloning of the gene.

"Neurofibromatosis type 1 is caused by mutation in a large gene with at least three smaller genes embedded in one of its introns; the gene identification presents an application of human/mouse comparative gene mapping.

"Wilms' tumor demonstrates the difficulty of having too many candidate genes present in a small region of chromosome."

A magnificent attempt at a Complete History Of The (genetic) World In 7½ Chapters. The same chapter ends with some thoughts about the role of competition, triumph, and disaster in medical research.

Another chapter verging on the philosophical, historical, and at times almost hysterical is 'Cloning the mammalian sex-determining gene, TDF' by Peter Goodfellow, J Ross Hawkins, and Andrew H Sinclair. Many interesting lessons can be learnt from this chapter, not least the importance of key clinical material and the sheer hard, and often discouraging, work involved in such a project.

The other chapters have perhaps a less conversational style but are still packed with useful information. 'Molecular genetics of Wilms' tumor' (Jerry Pelletier, David Munroe, David Housman) contains much of importance to geneticists trying to understand the emerging story of the relationship between mutations in the WT gene and nephroblastoma, Beckwith-Wiedemann syndrome, DRASH syndrome, and other developmental anomalies.

Equally important not to miss is the chapter on 'Genetic analysis of multifactorial disease: lessons from type-1 diabetes' by Soumitra Ghosh and John A Todd. The stated aim to provide a concise review of the methodology used in the analysis of complex disease genetics is achieved well with simple mathematical examples which will educate even the less numerate. The genetic analysis of common diseases is an important developing area and this chapter will promote understanding.

The other two chapters cover 'The mouse t complex responder locus' (Linda C Snyder and Lee M Silver) and 'Molecular biology of the W and Steel loci' (Alistair D Reith and Alan Bernstein).

S MALCOLM

**Community Genetics Services in Europe.** A Report on a WHO Survey. B Modell, A M Kuliev, M Wagner. WHO Regional Publications, European Series No 38. (Pp 137.) Copenhagen: WHO Regional Publishers. 1992.

If the 1980s saw the coming of age of molecular genetics, then the 1990s will see the maturation of 'genetics in the community'. This monograph, sponsored by WHO, is an up to date and detailed survey of present community genetic services in Europe, a region which has a population of 850 million. In an introduction, the problems are identified, especially that genetic services have usually developed idiosyncratically and not on a rational or equitable assessment of patient needs. The book emphasises the essential two way relationship between knowledge about the service in the lay community

and the laboratory and clinical services. Other problems are that the genetic services required by specific groups must be appropriate, there needs to be collaboration between primary, secondary, and tertiary health care, there must be public health involvement and careful assessment of the technology, and ongoing evaluation including, among other aspects, ethical issues.

Part 1 covers the basic statistics available and provides an excellent and brief overview of the need for genetic services. The figures for the incidence of genetic diseases are augmented by basic demographic information which includes 30 separate countries. Although recent political changes have caught up with some of those figures (Germany, USSR, or Yugoslavia), there is enough breakdown to make it possible to devise appropriate services in each of the main political regions. Part 2 describes the existing community genetic services with regard to screening for Down's syndrome (based on risk estimation calculated for increased maternal age). There is also the model of screening for autosomal recessives, exemplified by Tay-Sachs disease and haemoglobinopathies in different ethnic groups. The data here are well organised and give a clear indication about what needs to be done. For example, fig 9 analyses the causes of the birth of 193 children with thalassaemia and shows that in 55% of these births the basic reason was patient ignorance and in a further 26% it was based on the obstetrician not arranging testing.

Part 3 moves on to the approaches necessary to provide adequate service delivery, emphasising appropriately the importance of information and education of the public. There is a cost benefit analysis which emphasises not only financial but psychological and other costs.

Part 4 gives an excellent summary of the community genetics services available in Europe and lists 11 recommendations which would be important considerations in any country setting out to improve their genetic services. These recommendations will not be repeated here since I judge that every clinical geneticist will want to read this excellent book. It should also be on the shelf of every Regional Medical and Scientific Officer as well as any other purchaser of genetic services.

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