- 2 Brandi ML, Marx SJ, Aurbach GD, Fitzpatrick LA. Familial multiple endocrine neoplasia type 1: a new look at pathophysiology. *Endocrinol Rev* 1987;8:391-405.
- 3 Shepherd JJ. The natural history of multiple endocrine neoplasia type 1. *Arch Surg* 1991;126:935-52.
- 4 Wilkinson S, Teh BT, Davey KR, McArdle JP, Young M, Shepherd JJ. Cause of death in MEN1. *Arch Surg* 1993;128:683-90.
- 5 Marx SJ, Vinik AI, Santen RJ, Floyd JC, Mills JL, Green J. Multiple endocrine neoplasia type 1: assessment of laboratory tests to screen for the gene in a large kindred. *Medicine* 1986;65:226-41.
- 6 Farid NR, Buehler S, Russell NA, Maroun FB, Allderdice P, Smyth HS. Prolactinomas in familial multiple endocrine neoplasia syndrome type 1: relationship in HLA and carcinoid tumors. *Am J Med* 1980;69:874-80.
- 7 Larsson C, Skogseid B, Oberg K, Nakamura Y, Nordenskjöld M. Multiple endocrine neoplasia type 1 gene maps to chromosome 11 and is lost in insulinoma. *Nature* 1988;332:85-7.
- 8 Larsson C, Shepherd J, Nakamura Y, et al. Predictive testing for multiple endocrine neoplasia type 1 using DNA polymorphisms. *J Clin Invest* 1992;89:1344-8.
- 9 Friedman E, Sakaguchi K, Bale AE, et al. Clonality of parathyroid tumors in familial multiple endocrine neoplasia type 1. *N Engl J Med* 1989;321:213-8.
- 10 Bystrom C, Larsson C, Blomberg C, et al. Localization of the gene for multiple endocrine neoplasia type 1 to a small region within chromosome 11q13 by deletion mapping in tumours. *Proc Natl Acad Sci USA* 1987;87:1968-72.
- 11 Sawicki MP, Wan YY, Johnson C, Berenson J, Gatti R, Passaro E. Loss of heterozygosity on chromosome 11 in sporadic gastrinomas. *Hum Genet* 1992;89:445-9.
- 12 Bale AE, Norton JA, Wong EL, et al. Allelic loss on chromosome 11 in hereditary and sporadic tumors related to familial multiple endocrine neoplasia type 1. *Cancer Res* 1991;51:1154-7.
- 13 Larsson C, Weber G, Kvant E, et al. Isolation and mapping of cosmid clones revealing RFLPs around the MEN1 locus. *Hum Genet* 1992;89:187-93.

BOOK REVIEWS

If you wish to order or require further information regarding the titles reviewed here, please write to or telephone the BMJ Bookshop, PO Box 295, London WC1H 9JR. Tel 071 383 6244. Fax 071 383 6662. Books are supplied post free in the UK and for BFPO addresses. Overseas customers should add 15% 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 price and availability are occasionally subject to revision by the Publishers.)

Advances in Human Genetics. Volume 21. Ed H Harris, K Hirschhorn. (Pp 465; \$89.50.) New York: Plenum Press. 1993.

Each year since 1970 a new volume of *Advances in Human Genetics* has appeared, edited every year by Harry Harris and Kurt Hirschhorn and every year containing five reviews. It must be difficult picking topics which are interesting but not too fast moving for the inevitable slow book production process. Four of the five articles in this volume have suffered to some degree from important advances coming too late to include. Moser's chapter on peroxisomal disorders missed the identification of the gene for X linked adreno-

leucodystrophy. Jennifer Puck (X linked immunodeficiencies) writes that none of the genes, apart from that for chronic granulomatous disease, has been cloned. Goddard and Solomon (Genetic aspects of cancer) discuss oncogenes and tumour suppressor genes but not microsatellite instability. Zannis, Kardassis, and Zanni discuss mutations affecting lipoproteins, but only in connection with heart disease. The fifth chapter is by Grabowski on Gaucher disease. Each author, we are told, was given the opportunity at page proof time to write a short addendum containing the most up to date material, but only Moser took up the offer. The editorial hand was certainly not heavy. Chapters range from under 40 to almost 200 pages, and the style of references varies. Comparing Goddard and Solomon's crisp 50 page summary of Genetic aspects of cancer with Moser's 100 page review of peroxisomal disorders, both read well, but surely they are not aimed at the same audience? One audience wants an outline, the other wants details.

These books of major reviews, two to three years in gestation, are curious beasts. It's heartwarming that people of unquestionable authority are willing to put in so much time and effort for no material reward. The world must be the better for their efforts. But I wonder just how much better it is? How many people on the one hand are ready to spend a day or two digesting the detail but, on the other hand, aren't part of the personal networks by which people active in the field keep themselves informed? I'm reluctant to recommend them to students writing dissertations because most of the benefit to the student is in locating and digesting primary publications. They are good for orienting new postgraduates, with supplemental reading to bring them up to date. They would be good for summarising a field which has reached a milestone: next year would be just right for a major review of Huntington's disease (but this series had one in 1991). Do working scientists read them? Personally I find them too long and too detailed. The much shorter articles in *Annual Reviews of Genetics* are about my limit for general interest topics. *Trends in Genetics*, *Nature News* and *Views* commentaries, and *Cell* minireviews are my main sources for filling in necessary background.

Should you buy *Advances in Human Genetics*? Yes, if it contains a review you particularly want. No, if you just want to keep an adequate reference bookshelf. Looking through the contents of past volumes, if you had them all on your shelf you would not have a summary of the milestone developments in human genetics over the period. For example you would have nothing on physical mapping, on mitochondrial diseases, on microdeletions, on imprinting, on trinucleotide repeats, or, until this year, on retinoblastoma or oncogenes. *Annual Reviews of Genetics* does a better job of covering a wide field at a consistent level. But if you happen to want an encyclopaedic review of lipoproteins – and now that they are involved in Alzheimer's disease as well as heart disease, who doesn't? – then this volume is just the ticket.

ANDREW P READ

Human Gene Mutation. D N Cooper, M Krawczak. (Pp xiv + 402; £49.50.) Oxford: Bios Press. 1993.

Mutation remains both the major intellectual problem in its decipherment and interpre-

tation: it presents the major practical problem of the detection of mutagens and the protection of our future.

When it was assumed that loci were few and alleles few or absent, and that mutation rates were equal at all loci and from all alleles, and equal in man, mouse, and fly, the basis for the birth and death rates of mutations, and their life expectancy, were defined by Haldane, Fisher, Wright, and Muller. These firm theoretical foundations are now known to have a somewhat tenuous relation to reality. The theological concept of the ideal type, the homozygous ideal, based on God's image, continued to permeate concept formation. When variation occurred it was assumed that selection, rather than chance, dominated survival, and Fisher's term linkage equilibrium (now often termed linkage disequilibrium) and E B Ford's term polymorphism were defined in 1930 and 1940 to cover allelic association and common allelic variation respectively.

The realities of blood transfusion and the display of extreme variation by the starch gel showed that reality was other. The concept of neutrality, which abolished both the problem and the possibility of having evolved to discuss it, introduced a fertile mathematical diversion and showed that neutral variants only had to be sufficiently numerous for some to survive, prosper, and even expel their parental alleles.

Now at last there is a book based on raw data, discussed on a sound foundation of words, and aided but not dominated by sufficient and necessary mathematics. Not only are all varieties of mutation discussed, largely around the authors' expertise in blood and how it clots, but extensive appendices provide an anthology of all that is known to ail our species and has been defined at the genomic level. Reading it imposes a pleasant if formidable task on the reviewer. Not only does it excel in clarity but many references, and their discussion, are remarkably recent.

In the treacherous fields of terminology and the word-number interface there are some minor problems worth comment. The diagrams, apparently based on astute use of a spreadsheet package, are very clear, numerous, and well integrated with the text. However, the unnecessary imposition of a third dimension in some does not assist clarity. The computer's expression of chi squared to three places of decimals needs taming. Tuberos sclerosus is now largely split between loci on chromosomes 9 and 16: 11 and 12 have little support, a very recent finding. Harry Harris's operational use of "polymorphism", to cover frequencies exceeding 1%, a reasonable use in the late sixties, is credited to Vogel and Motulsky 20 years later. Ford defined it unambiguously as "the occurrence together in the same locality of two or more discontinuous forms of a species in such proportions that even the rarest of them cannot be maintained merely by mutation". It is now used – or since the word is longer than the neutral term "variant" – misused – so extensively that Ford's useful term, which dominated evolutionary theory for several decades, has died with him, and it is now too late to modify its well established misuse.

Linkage analysis, another casualty of widespread misunderstanding, features as a chapter, and benefits from Clayton's advice. However, the pedigree shown does not need locs as phase is defined and deduction and counting, the appropriate method when phase is clear, are omitted. A few paragraphs on

deduction and counting, a maximum likelihood method, would help introduce this treacherous field. The uncritical use of multipoint methods is discussed and Morton's paper on 'Multipoint mapping and the emperor's clothes' cited.

The authors seem unaware of the contribution of cytogenetics to positional cloning. Notwithstanding numerous contrary claims, while many disorders have had their position found within a few megabases by linkage none has been caught by within-family linkage studies alone. Duchenne was deciphered through a deficiency and the position pinpointed by concordant translocations. Neurofibromatosis was localised by translocations, and assisted by a mouse. Cystic fibrosis, myotonic dystrophy, and Huntington's chorea were caught by allelic association, or between family linkage, which is possible only when old mutations, or highly mutable alleles, are involved. Others were defined by astute recognition of neighbouring candidate loci in man or mice. A human karyotype, annotated by some key loci, is absent from the extensive appendices.

Premutations are discussed, but this useful term is now obscured by the realisation that not only are all alleles potential premutations but some, "hot" alleles, are peculiarly prone to mutation for reasons so clearly described in the text. Identity by descent, mentioned in relation to allelic association, is not the same as inbreeding. Ancestors at any generation level are necessarily rarer than the number of parents in any stable or expanding population and allelic association will then necessarily occur between elderly alleles at neighbouring loci. It is the ratio of ancestral to recent numbers which determines the strength of allelic association.

This is a remarkable book and deserves a wide readership. All possible genetic misprints seem to feature with a detailed description supported by diagrams. It should clarify, and shorten, the voluminous recommendations on radiation safety, which basically amount to "keep below double the background level until we know more", but involve documents whose size and weight limit readership, and whose reasoning is based on older and simpler data. Much of this, such as malformation rates, is of dubious relevance to the problems at issue: until recently recessive disorders, the main problem, were ignored. There is little on mice, but the challenge for a similar book is clear, and the authors were wise to keep to the species on which their extensive expertise is based. It is a big book with hardly a wasted word. To have collected and discussed such massive data, much of it very recent, within 400 pages, is a remarkable achievement for both the authors and publisher. It is almost free from any typographical mutations. The typesetting, done locally near to the publisher, is of unusual clarity as are the extensive tables in appendices. The book is highly recommended: it is a fitting companion to McKusick's book on the phenotype and obligatory reading to anyone involved in mammalian mutation.

J H EDWARDS

McKusick's Heritable Disorders of Connective Tissue. 5th edition. Ed P Beighton. (Pp 748; £96.00). St Louis: Mosby-Year Book. 1993. ISBN 0-8016-6358-X.

Connective Tissue and its Heritable Disorders. Ed P M Royce, B Steinmann. (Pp 709; £185.00). New York: Wiley-Liss. 1993. ISBN 0-4715-88199.

The student of connective tissue disorders has had a lean time of late. Fortunately help is now at hand. After a lengthy period of drought, those with an interest in these conditions can now wallow in the luxury of choosing between two large multiauthor texts published almost simultaneously to plug a gap which has existed for over 20 years. Both of these volumes succeed admirably in providing up to date reference sources with coverage of all the remarkable progress achieved over the last two decades.

There is a striking similarity between these books which extends beyond their titles to size, authorship, format, and style. Surprisingly no author has contributed on an identical topic to each volume, although several distinguished names feature in both. Has there been an element of collusion in these productions? If so no matter. In fact we should be grateful that for each disorder we now have two independent reviews which complement rather than duplicate one another. Individually each of these books is valuable. Taken together they provide a tour de force.

Each text opens with an introductory chapter outlining the basic principles of human inheritance and medical genetics. These are followed by sections on connective tissue structure and function. *Heritable Disorders* opts for brevity with, for example, a single page devoted to elastin, which in contrast is the subject of its own 21 page chapter in *Connective Tissue*. Presumably this differing emphasis on basic biology reflects to some extent the background and interests of the respective editors. Peter Beighton seems to be catering primarily for medical geneticists, whereas Peter Royce and Beat Steinmann clearly have an eye on the basic scientist market also.

The remainder of both volumes is devoted to detailed accounts of individual connective tissue disorders. In maintaining the tradition of previous editions, *Heritable Disorders* is particularly strong on cutis laxa, the mucopolysaccharidoses, skeletal dysplasias, and the Weill-Marchesani syndrome. *Connective Tissue* barely mentions this last disorder but expands its coverage to include conditions with a secondary effect on connective tissue such as epidermolysis bullosa, prolyase deficiency, and the ichthyoses. Generally the clinical contributions in *Heritable Disorders* are more lavishly illustrated and more expansive. For example its chapter on Marfan syndrome extends to 84 pages with 55 illustrations and 528 references, as compared with 31 pages, 11 illustrations, and 276 references in *Connective Tissue*. However, both provide extremely comprehensive reviews and pass with flying colours this reviewer's test of discoursing on the difficulty of confirming or refuting this particular diagnosis in equivocal clinical cases.

In summary, both of these books are excellent. Each provides a scholarly overview of their subject without which no self-respecting departmental library can consider itself complete. *Heritable Disorders* scores highly in terms of cost and production quality with more illustrations, glossier pages, and larger type. This will probably be the first port of call for the practising clinician. *Connective Tissue* offers a more cosmopolitan authorship

with much greater depth in basic biology and science. Essentially "you pay your money and you take your choice". Either way you will not be disappointed.

I D YOUNG

Essential Medical Genetics. 4th edition. J M Connor, M A Ferguson-Smith. (Pp 260; £15.95.) Oxford: Blackwell Scientific Publications. 1993.

This volume lives up to its name. It is concise, and covers the topics with which an undergraduate medical student should have some familiarity. It is useful for preclinical and clinical students, and provides a reasonable core of content. The systematic description of mendelian and polygenic disorders that are likely to be seen, or at least mentioned, in other sections of the clinical course is a great strength. In comparison with some of the competitor volumes, I can recommend this more wholeheartedly to every student. Some other texts are more appropriate for the student who is specifically interested in genetics and the scientific basis of medicine.

This fourth edition has been adequately updated. Already some details require amendment, but that is only to be expected. The only areas that I feel are "essential" and that have not been adequately covered are the closely connected areas of the psychosocial impact of genetics and the ethical issues raised in clinical genetic practice. These areas would be very difficult to cover in a volume of this sort, but I hope that they are attended to in the fifth edition that, I am sure, will deservedly follow before too long.

ANGUS CLARKE

Heredity and Your Family's Health. A Milunsky. (Pp 488; £14.00.) London: The Johns Hopkins University Press. 1993.

As a family doctor with a special interest in medical genetics I read this book for my own education and also for possible inclusion on the patients' library shelf.

The opening chapter has a crusading quality and one assumes that the main readership is intended to be middle class America. Given the importance attached to non-directive genetic counselling, it is interesting to discern a slightly directive style. Dr Milunsky has clearly spent many years picking up the pieces following genetic catastrophes and he feels deeply about helping people to obtain the information to allow them to make the right choices. The issues raised are important and the comprehensive cover inspires one to read on, although some may disagree with the observation that "compassion, patience and love are unusual in most families caring for a child with birth defects".

The reader with at least high school biology will find the chapters on chromosomes detailed and understandable and the simple explanation of mitosis and meiosis is welcome. Here and elsewhere in the book doctors may benefit from technical descriptions of complex areas written for patients. Too often genetic nomenclature leaves even a medical graduate feeling like a stranger in a foreign country.

Problems of intersex are dealt with sens-