Genet. Res., Camb. (1997), **69**, *pp.* 75–78

Book Reviews

Gene Isolation and Mapping Protocols. Edited by JACQUELINE BOULTWOOD. Humana Press 1997. 318 pages. Price $69.50. ISBN 0 89603 382 1.

It is estimated that there are somewhere in the region of 100000 genes in the human genome. To date only sixty or so 'disease' genes have been isolated but the race to isolate and characterize the remainder is well under way due largely to the gathering momentum of the human genome project, which aims to produce a human transcript map by the year 2005. This target seems likely to be achieved, thanks to a broad array of innovative methodologies which allow genes to be isolated and mapped. Methodologies in this rapidly progressing area of genetics are continually undergoing change and adaptation, with fresh ideas and concepts to deal with the new and challenging problems encountered as we travel down this 'genetic information superhighway'. So is there really a niche for yet another book of protocols in the world of the gene hunter? Judged by this book, the answer is probably 'yes'.

Gene Isolation and Mapping Protocols is part of the Methods in Molecular Biology series and aims to provide a 'bench-side' protocol book of 'state-of-the-art techniques' for isolating and mapping disease genes. The book contains 19 chapters, most being method-based with brief theoretical introductions to the techniques in question.

The first chapter is an introduction to gene mapping and its future direction and it serves its purpose well, with useful facts and figures. It is followed by a very well written chapter on linkage analysis, pointing out limitations as well as strengths of current methodology and dealing with complex as well as with simple Mendelian disorders. The middle section of the book is taken up with more technically based chapters on the use of somatic cell hybrids, fluorescence *in situ* hybridization (FISH) and physical mapping – pulse field gel electrophoresis, yeast artificial chromosome (YAC) and cosmid contig construction, the use of dinucleotide polymorphism analyses and expressed sequence tags (EST). All these chapters are very well written and easy to read, highlighting both the strengths and weaknesses of the different approaches.

The next five chapters concentrate on gene isolation using the most powerful current techniques: exon trapping, direct cDNA selection, YAC hybridization to cDNA libraries, differential display and a modification of subtractive hybridization – chemical cross-linking subtraction. Such methods are technically very demanding but these chapters provide easy-to-follow protocols which highlight the absolute requirements for a successful result.

The final section deals with an increasingly important way of finding genes – what Jean-Michel Claverie, the author of chapter 19, calls 'software trapping'. An account of databases and their function is in my opinion an absolute requirement for any book on gene mapping and isolation and the chapter, intended as a guide to the databases, will be very useful. However, I felt that possible pitfalls of database searches should have been given more emphasis, particularly with reference to the genetic and radiation hybrid maps. The different map construction methodologies inevitably lead to local ambiguities regarding relative gene order and location. Which is to be believed? Direct experimentation will often be required to establish the veracity of what are intended as global transcript maps but which should not be taken as the ultimate truth.

Although there is some repetition between chapters, they are all individually worth reading. The writing is generally clear and concise, with concentration on methods which have been tried and tested and are known to work. Each chapter is backed up with an up-to-date reference list for a more in-depth picture. The great strength of this book lies in its Notes section which provides the kind of information which only comes from actual experience of working with the various techniques. My only concern with Boultwood's compilation is that it will soon need updating, particularly, perhaps, the chapters on databases which will assume increasing importance as the quantity of genetic information held explodes, a point made by one of the authors, Martin Bishop. With this reservation I shall have little hesitation in recommending it to my peers who, I am sure, will be grateful for the soft ring spiral bound format, which provides a practical method of tying the book down to the bench without which it might well be permanently borrowed.

JULIE WILSON-ANNAN
MRC Human Genetics Unit,
Western General Hospital, *Edinburgh*

Human Genetics: *Problems and Approaches*. By F. VOGEL and A. G. MOTULSKY, 3rd Edition. Springer 1996. 851 pages, Price £69. ISBN 3 540 60290 9.

The first edition of Vogel and Motulsky appeared in 1979 and immediately became the dominant text in human genetics of the time. I remember using it as the sole reference book for both an honours course in medical genetics and a masters course in human genetics, so effectively did it cover all aspects of the subject. The authors took something of a risk in not revising their book until 1986, but human genetics was still moving comparatively slowly, and the second edition comfortably resumed its dominance of the field. But not for long, By 1990 most of us had been compelled to drop it from the reading lists we gave out to undergraduate and post-graduate students alike. It had a dated feel and there were many better books on the market.

So how does one respond to the appearance of the third edition, ten years later? First, with surprise that it has taken so long. Then with eager anticipation, for few human geneticists have the breadth of knowledge and the length of experience of Vogel and Motulsky. Finally, and I'm sorry to say it, with disappointment. The wait has not been worthwhile.

The difficulty is that the authors remain locked into a format that served well in the 1980s but which will not do for today. Most of what has happened in human genetics in the last ten years has been the result of the astonishing manipulative power of molecular biology. It is no good pretending otherwise, even if your first love is mathematical genetics. Thus a template that gives much more space to the latter than to the former has to be ditched. The authors claim that the third edition is 'completely revised', and this at first sight appears true, with 19 chapters in the new edition versus 9 in the previous one. Closer inspection, however, shows that this has been achieved by simply dividing most chapters in two. In fact the new 19-chapter Vogel and Motulsky is only 5% longer (851 pp. *v*. 807 pp.) than the old 9-chapter one.

There is, furthermore, astonishingly little new material to account for the activities of the horde of researchers who have been attracted to the subject by the technological advances of the last 15 years. The chapters on developmental genetics and on somatic genetics are substantially revised, but apart from that one can go for hundreds of pages without spotting a significant alteration. There are other new bits on PCR, positional cloning, immune function genes and gene therapy, but none of these topics is covered in sufficient depth to make one want to trade in the second edition. The chapter on genetic counselling and prenatal diagnosis, which I always found unsatisfactory, has not been improved.

Books published by Springer are usually at the expensive end of the market. The reader has a right to expect that 'completely revised' editions will be just that and not rehashed old ones. I shall advise my librarian that there is little to be gained by splashing out on the third edition.

DAVID BROCK
Human Genetics Unit
University of Edinburgh

Human Genome Evolution. Edited by M. JACKSON, T. STRACHAN and G. DOVER. BIOS Scientific Publishers, 1996. 306 + x pages. Price £60.00 ($120). ISBN 1 859960 95 2.

Human Genome Evolution is a big title that arouses high expectations. What is it about our genome that makes us peculiarly human? How different are we at the level of the genome from our closest living relatives among the primates? What can the genome tell us about the history of human populations? Of these major evolutionary questions only the last is really addressed here, and even here the answer is tentative. There is a very good reason for this; namely that analysis of the human genome is in its infancy. Book titles must of course be snappy, and it is clear that this book more accurately entitled 'A Preliminary Assessment of our Understanding of the Forces that Affect Genome Evolution Using the Human Genome as an Example' would not necessarily sell well. This is not to suggest that *Human Genome Evolution* is without value; in fact the book covers a wide range of interesting and topical areas and is a very useful summary of our understanding of this complicated issue. It is a pity in my opinion that the book lacks an editorial overview highlighting the really important questions that could not yet be addressed. The one page Preface is not really a substitute.

The book begins with a chapter on mutational processes by Krawczak and Cooper. The authors are known for detecting the prevalence of CpG mutations among human genetic diseases, and they provide a valuable summary of present data on this subject as well as a 'broad-brush' survey of other mechanisms of mutagenesis. I found their theoretical treatment of the relationship between rates of 5-methylcystosine deamination and G+C base composition over time much less convincing. The model for decay of CpG from an imaginary starting point 450 million years ago appears flawed, as it considers loss of the dinucleotide but not its creation. Discussion of the rate at which CpG mutates might have referred to three estimates from other labs that preceded the one referred to here, including one by another contributor to this book.

The chapter on exon shuffling provides a refreshing angle on what appears to the outsider to be a somewhat fraught subject. On one hand, the modular construction of proteins argues that functional units have been exchanged repeatedly in the construction of genes. On the other hand, ancestral prokaryotes do not have exons and there is precious little evidence

that they ever did. Patthy takes us through the arguments step by step leading (unarguably in my opinion) to the conclusion that exon shuffling has often been an important process in the evolution of many eukaryotic genes. He stresses that this conclusion does not mean that all genes arose as functionally discrete exons near the origin of life. By separating arguments about the existence of exon shuffling from arguments about whether intron arose early or late in the evolution of life, Patthy makes a persuasive case that this need not any more be a contentious area.

If one accepts that the evolution of humans was to a great extent a result of changes in genes, then it is perhaps surprising that only two chapters in the book deal with gene evolution. In fact our understanding of genes is far too primitive to allow a meaningful discussion of what genotype makes a human being. As it is, the gene chapters describe interesting and informative examples (the HLA complex and the G protein-coupled receptor genes). These have been well studied in humans, and both are represented by a large family of related gene sequences.

Chapters 5–9, representing about one third of the book, are devoted to repeated sequences of one sort or another. These sequences do not encode RNA or protein products that are developmentally or metabolically necessary for humans (as far as is known), and are therefore not genes, at least in a molecular biologist's sense. They are however relatively dynamic in an evolutionary sense, and their constant churning generates significant variation within a species and dramatic changes between species. This means that there is always something to study. Most interesting are the telomere repeats, as they have what few other non-genic repetitive sequences have: an accepted biological rationale. In fact experiments that prove the importance of telomeres are indirect, but the ubiquity of simple G-rich repeats (*pace Drosophila*) argues for fundamental importance in defining the ends of chromosomes. Royle sets out the story clearly and for good measure treats us to the telomere hypothesis of cellular senescence and immortalization. It may not in the end be correct, but the mere possibility is sufficiently exciting to deserve retelling. Sub-telomeric repeats are not quite so interesting, although they raise some intriguing conundrums. Why are minisatellites concentrated near telomeres? Why are they often G + C-rich? Has the high frequency of recombination near chromosome ends anything to do with it? Unfortunately as yet we do not know.

Chapters 5 (Warburton and Willard), 7 (Armour), 8 (Hancock) deal with tandem repeats ranging from satellites (specifically α satellite) through mini-satellites to micro-satellites. Here biological relevance is less easy to fathom. Is α satellite functionally involved in the construction of centromeres? We are not enlightened on this question. Mini-satellites initially acquired interest for sociological rather than biological reasons, but this is changing due to detailed analysis on modes of mutation and structure in specific examples as Armour's chapter makes clear. The article by Hancock concentrates on methods of detecting simple sequences in genomes. I found it difficult to extract any biological generalizations from the results of his survey among a variety of life forms. The data would have been easier to assess if a model had been formulated that either does or does not fit with the observations. Britten provides an excellent review of Alu retroposons and shows how careful analysis of the vast number of Alu sequences that are in the database can lead to important conclusions about the nature of the small number of 'source genes' that retain the capacity to transpose. On the functional side, little is said except to assert that 'the view that Alu sequences are purely parasitic or selfish is no longer tenable'. The important word here may be 'purely'. Even if the occasional random integration turns out to be evolutionarily creative for the host genome, I cannot see that the essentially 'selfish' strategy of Alu elements can be seriously questioned.

The last three chapters deal with the evolution of sex chromosomes and of mitochondria. The chapter by Ellis is a very useful summary of the biology of sex chromosomes, concentrating on the evolutionary problem. The origin of heteromorphic sex chromosomes, dosage compensation, the pseudo-autosomal region and the likely basis for Ohno's law are all given erudite treatment. Chapters on mitochondrial DNA variation (Stoneking) and the Y chromosome (Jobling) deal with these non-recombining genetic units as tools for studying human evolution. Stoneking is at pains to lay out impartially the contending hypotheses. At one extreme there is the opinion that all modern humans originated from an ancestor in Africa a hundred or so years ago. At the other extreme is the 'candelabra theory' which holds that significant evolution occurred after migration out of Africa. Stoneking debunks the idea that the female from which all current mitochondrial DNA is derived was 'Eve', stressing that the important part of the story is to know when and where she lived. Although this is clearly still a contentious area, the data assembled here point overwhelmingly to a recent African ancestor who lived on the order of two hundred thousand years ago. By comparison the candelabra theory seems eccentrically unlikely. The Y chromosome could theoretically do for the male lineage what mitochondrial genome has done for the female lineage. But, as Jobling concludes, the data so far only support the idea that there is a relatively recent common ancestor for all human Y chromosomes. It does not yet say where the owner of that chromosome lived. The smart money is surely on Africa.

Altogether this is an interesting book that gives an up-to-date picture of the way in which human genome evolution is being approached. It is published at a time of frenzied DNA sequencing activity which will

provide the basis for all biology in the future. The challenge now is to use DNA sequence, which by itself conveys little biological information, to get at the big issues of biology. Does the explosive arrival of the sequencing era mean that a major synthesis is just around the corner? I wonder.

ADRIAN BIRD
Institute of Cell and Molecular Biology
University of Edinburgh

Molecular Biology of Parasitic Protozoa. Edited by DEBORAH F. SMITH and MARILYN PARSONS. Oxford University Press 1996. 233 + xvi pages. Price £29.50. ISBN 0 19 963601 X.

Molecular parasitology is an expanding field which is attracting ever increasing numbers of researchers. This is partly because the problems posed by the parasites and by host–parasite relations are scientifically interesting in their own right, but mainly because it is recognized that without a better understanding of the cellular and molecular biology of both host and parasite the control of some very widespread human diseases will never be achieved. It is therefore timely that a new book on the subject should be published in a series designed to report on front-line molecular biological research.

A book of this size cannot, of course, hope to be comprehensive over such a broad field, and the editors have chosen to focus on the best studied and perhaps most important of the parasitic protozoa. These are mainly the Apicomplexans, *Plasmodium* and *Toxoplasma*, with the Sarcomastigophora represented by *Trypanosoma*, *Leishmania* and *Crithidia*. This restriction still leaves plenty of scope for a really stimulating book, but it has to be said that the chapter headings have a rather old and familiar sound. The field is so new that perhaps almost any part of it can qualify as cutting-edge science, but I could not help thinking that the excitement of some of the topics had faded somewhat. This in no way impugns the quality of the contributions, all of which have been written with care and attention to detail. It is just that there is little in the book that will be new to the parasitologist and not enough to excite the newcomer to the field.

However, there are some useful contributions. John Swindle and Andrew Tait's account of Trypanosomatid genetics is illuminating and comprehensive, and David Sibley's description of *Toxoplasma* and its use as a model genetic system is wideranging. It is a tribute to the ingenuity and perseverance of parasitologists that they are prepared to adopt as a model organism one that goes through the sexual stages of its life cycle in the intestines of the cat. What effect, one wonders, would such a restriction have had on the development of classical genetics? Among the other chapters that caught my eye were those on the complexities of kinetoplast structure and replication and the mechanism of *trans*-splicing in Trypanosomatid protozoa, described with typical clarity by Elizabeth Ullu and her associates. Jean Feagin and Michael Lanzer describe the three genomes – one nuclear and two extranuclear – of the malaria parasite, with detailed discussion of their organization and functions so far as these are known. In this chapter the tantalising possibility that the 35 kb element has plastid affinities is once again raised, but with no suggestions as to its origin. Dyann Wirth and Alan Cowman deal with mechanisms of drug resistance in a number of parasites, both from the genetic point of view and in a wider biological context. Possible genetic mechanisms discussed by the authors include effects on enzymes targeted by the drug – either increases in levels or decreases in drug-sensitivity – and effects on proteins concerned with drug transport through the parasite membranes. This is one area of current excitement that *is* included in the book. Other chapters deal with developmental regulation of gene expression in African trypanosomes, RNA editing and the restructuring of genetic information, the biogenesis of glycosomes and hydrogenosomes, and the role of glycosylphosphatidylinositols in determining the architecture of the protozoan cellsurface.

All these are worthy and by no means exhausted fields of investigation, but some important topics are left out. A chapter on strategies for *Plasmodium* vaccine development might have been well worthwhile. Progress here has admittedly been disappointing, but a critical evaluation of current approaches and a discussion of recent field trials would have made interesting reading. Linked with that, there might have been a more extensive account of *Plasmodium* surface variation and immune evasion than the brief mention in the chapter by Feagin and Lanzer. There are other new areas of work developing as a result of the successful introduction of exogenous DNA into the malarial parasite, and this might have been mentioned, perhaps as part of a more general review of recent initiatives. These comments reflect, of course, my own interest in the malaria parasite, but I suspect that similar suggestions might be made for other areas also.

To summarize, this is a good book, but not very exciting. I wish the editors had been just a little more adventurous.

BRIAN J. KILBEY
Institute of Cell and Molecular Biology
University of Edinburgh