

theoretical background to give a good level of understanding of the basic methodology. Plenty of photographs will help the inexperienced workers to understand the practical aspects of cell culture.

The second part describes applications in cell and molecular biology. Four chapters cover the isolation of lymphocytes, establishment of lymphocyte lines, cell fusion techniques and cytotoxicity assays. Some techniques described here may not be necessary for all those readers new to cell culture. However, they are very important tools for cell culture workers in some specialized fields including immunology and haematology.

Finally, transfection, a technique that has become one of the most basic and important technologies in most fields of biology, is described. The authors do not intend to cover in detail all the background and protocols for transfection, but electroporation should be emphasized more. Although electroporation has become a major method for introducing foreign DNA into recipient cells, it is not given sufficient emphasis in this chapter. On the other hand, the protocol of the calcium phosphate co-precipitation method is well written, and sufficient to enable the uninitiated to achieve success.

My overall impression of the book is that it is a very useful introduction to basic culture techniques. I would highly recommend this volume for the inexperienced cell culture worker.

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Human Gene Mutation. By DAVID N. COOPER and MICHAEL KRAWCZAK. BIOS Scientific Publishers. 1993. 402 pages. Price £49.50/US \$99.00. ISBN 1 8872748 41 4.

As the Human Genome Project rolls relentlessly forward, more and more of the estimated 100 000 human genes have been characterized. Most of those responsible for high-prevalence Mendelian disorders have already been cloned; in 1993 alone the sequences of the genes for Huntington's disease, X-linked agammaglobulinaemia, Menkes' disease, Friedreich's ataxia and neurofibromatosis type 2 were reported. With a few exceptions the general rule is that these disorders are extremely heterogeneous at the molecular level. Inevitably, therefore, increasing attention has to be paid to the range of mutations that are to be found and the types of assay that have to be used to detect the variable mutant alleles at these loci.

Human Gene Mutation is one of the first books, and undoubtedly the best, to address itself specifically to this subject. It has useful chapters on genetic disease, on the anatomy of the human genome and on linkage

analysis. But its substance lies in its coverage of mutation, from history through technology to estimation of mutation rates. The data content is huge and impressive, and the appendices which summarize genetic diseases in which molecular detection is possible, single base-pair substitutions, small deletions and splice-site mutations causing Mendelian disorders, would be worth publishing on their own.

Inevitably a book of this name will date rapidly. Its value depends to some extent on how quickly the publishers can get it on to the bookshelves. Cooper and Krawczak claim that their literature survey is complete to December 1992. I don't know exactly when this was published, but it landed on my desk for review before the end of June. That is very impressive, and I wonder once again why so many other publishers – Cambridge University Press being a particularly bad example – find it so difficult to publish a complete manuscript in under a year. Most would benefit from a refresher course at BIOS Scientific.

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Cystic Fibrosis: Current Topics. Volume 1. Edited by J. A. DODGE, D. J. H. BROCK and J. H. WIDDICOMBE. John Wiley & Sons. 1993. 250 pages. Price £59.95. ISBN 0 471 93 1012.

The publication of a new book on cystic fibrosis is welcome news for those of us with graduate students, new post-docs and clinical fellows in a laboratory investigating the molecular and cell biology of this disease. Until the cloning of the CFTR gene in 1989, new students in the CF field were faced with a mass of literature to wade through that had little real science content.

Cystic Fibrosis: Current Topics thus has the potential to fill a definite gap in the market, that is between the lay books on CF and those written for practising physicians. Its price tag of £60 puts it beyond all but the independently wealthy of students, so the decision to purchase is likely to end up on the table of budget-holders or librarians.

A brief scan of the authors reveals contributions from many of the key players in the CF research field since 1989. The book is divided into three sections on genetics, cell biology and clinical aspects. It opens well with a chapter on the structure of the CFTR gene that gives an insight into the tremendous amount of work that went into the isolation of the CF gene by positional cloning. It describes the problems encountered in constructing a full-length CFTR cDNA clone and examines expression of the CFTR gene. An unusual feature of the CFTR mRNA – that of alternative splicing leading to the production of mRNA lacking specific exons – is explored, though its significance remains obscure. Finally the CFTR gene promoter is discussed, essentially revealing how little

is currently known about this aspect of the gene and what might control its expression *in vivo* or confer its quite restricted tissue specificity. Possibly the sole criticism of this chapter is the failure of the authors to quote papers published in European journals, preferring instead to quote North American CF meeting abstracts. This is also a problem with certain later chapters in the book (particularly the chapter on CFTR function), which is a pity given the aims stated in the editor's preface.

Then follows a chapter on mutation analysis in cystic fibrosis, which is largely taken up by useful mutation information in tabular form. Regrettably no consideration is given to the types of mutation that may have been missed as a result of reliance solely on PCR from genomic DNA, by many groups contributing to the CF consortium. Short sections deal with the interesting geographical variation in the prevalence of specific mutations in the CFTR gene, with highly polymorphic microsatellite repeats within the gene and with genotype–phenotype correlation, a topic covered extensively in Chapter 4. This might well have been better placed after the mutation chapter and so it will be considered next. The question of whether disease course can be predicted on the basis of the 2 CFTR mutations a CF patient carries is a very important one, and probably that asked most frequently by CF families and their physicians. The authors of the chapter on genotype/phenotype correlations are rightly cautious in providing such data and stress the difficulty of collecting statistically significant numbers of individuals carrying specific combinations of mutant CFTR genes. With a few exceptions, including $\Delta F508$ and certain other mutations in the first nucleotide-binding fold (NBF) of CFTR, sound data are just not available. However, the chapter describes well the clinical features of the disease and methods of assessing disease severity. In addition, it presents correlations between certain mutations and mild or severe pancreatic disease and meconium ileus. An area of recent controversy has been the phenotypic effects of nonsense mutations in the CFTR gene. Some of the experimental data in support of the arguments that are presented are unlikely to stand the test of time. Finally an important part of this chapter is the consideration of disorders other than CF that are associated with mutations in the CFTR gene – in particular, congenital absence of the vas deferens (CBAVD).

The chapter on prenatal diagnosis of CF, as well as probably being inappropriately located within the book, is too long and takes a rather historic approach to the topic. It might be better integrated into the later chapter on neonatal screening for CF.

The next section deals with the cell biology of CFTR and contains several excellent chapters. The first of these deals with patch-clamp studies of apical membrane chloride channels and assumes a basic knowledge of electrophysiology which many readers

may lack. It investigates which epithelial cell channels mediate cAMP-stimulated chloride secretion and hence might be involved in the disease process in CF: the outward rectifier (ORF), the low-conductance CFTR channel or other chloride channels. An in-depth analysis of conductance, selectivity, kinetics, regulation and pharmacological inhibition is presented for each of the channels. The characterization of the CFTR channel in various expression systems is then examined in detail.

Since the isolation of the CFTR gene in 1989 there has been a growing literature on the significance of the homology of CFTR with members of the ATP-binding cassette (ABC) transporters, otherwise known as traffic ATPases. It is thus appropriate for the next chapter to be a succinct review of the important functional domains of the various ATP transporters and their mechanisms of action. Of particular interest is the examination of the nucleotide-binding folds, since many CF-associated mutations in CFTR are within these domains. A final section examines the differences between channels and transporters and the evidence that one protein may function as both channel and transporter.

A brief chapter on CFTR function presents data on predictions from the primary structure of the CFTR protein and how far experiments on expression and purification of recombinant CFTR have confirmed these predictions. Of particular interest is the question of whether ATP hydrolysis is essential for the chloride channel activity of CFTR. Finally the site of action and possible secondary functions of CFTR are considered. Then follows a chapter which again might be better placed, close to the earlier chapter on mutations in CFTR. Its title, 'Defective intracellular processing of CFTR as the molecular basis of cystic fibrosis', summarizes the general hypothesis that is presented. The biosynthesis of wild-type and mutant CFTR is examined in heterologous expression systems and to a less extent *in vivo*. $\Delta F508$ CFTR is not properly processed, resulting in defective trafficking through the ER and subsequent degradation. A range of other mutants in several functional domains of the CFTR protein have been examined to assess their processing and ability to express a functional, low-conductance chloride ion channel. The conclusions are that mutants that are unable to produce mature, fully glycosylated CFTR lack a cAMP-activated Cl^- conductance. Furthermore, NBF1 is more sensitive than NBF2 to the effects of equivalent mutations. The authors do point out that with the exception of $\Delta F508$ and a couple of other mutations, these data are derived solely from over-expression systems that may not completely reflect the *in vivo* situation. The major problems in obtaining such data from patients with specific mutations are the difficulties in obtaining good primary epithelial cell cultures and the generally poor quality of anti-CFTR antibodies.

The last chapter in this section deals with the

chloride channels of intracellular organelles. The possible involvement of CFTR in pH regulation in intracellular organelles is far from proven. Clearly, given the apparent abnormalities in CF mucin sulphation, fucosylation and sialation, this would be an attractive hypothesis. However, the chapter is far too complex and its relevance uncertain.

Part III of the book addresses clinical aspects of CF. In a book that is so scientifically based, a simple chapter on the medical and social consequences of living with cystic fibrosis would have been a good opening for the clinical section. Instead an attempt is made to cover every aspect of the disease and put it in its historical perspective. This is unsatisfactory, as it inevitably means that topics meriting separate reviews are covered in a couple of paragraphs. The beginner will find it difficult to separate historical beliefs from up-to-date medical practice.

There follows an excellent chapter on pseudomonas infection in CF. The evidence that the host response is as important as characteristics of the invading organism in the pathology of chronic pseudomonas infection is reviewed. Further, the possibilities of intervention to prevent colonization becoming chronic infection and to restrict the damage of chronic infection are outlined.

Neonatal screening for CF has long been controversial, as it has been difficult to fulfil the principle upon which screening programmes are justified, namely that early detection results in a better outcome. Nevertheless, enthusiastic practitioners have convinced local areas to establish screening programmes, and the methods, problems and results are reviewed. It was thought that finding the CF gene would make screening procedures easier, but the multiplicity of mutations has meant that there is no simple screening test. This chapter could usefully have been extended to consider the related topic of population screening for CF carrier testing.

The scientific progress of the past five years has brought great excitement to clinicians and patients. The challenge of translating laboratory advances to progress in clinical care is carefully documented in a chapter on 'New Directions in Treatment'. Careful clinical research will be required to substantiate the long-term benefits of new treatment.

In conclusion, this book is a useful addition to the CF literature, which will undoubtedly improve as the series progresses. The text would benefit from an introductory chapter that explains the contents of each section and its relevance to CF disease. However, even with this addition it is likely that few readers will be able to read and understand all of the book.

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Archibald Garrod and the Individuality of Man. By ALEXANDER G. BEARN. Oxford University Press. 1993. 227 pages. Price £35.00. ISBN 0 19 262145 9.

In his 1958 Nobel Lecture, George Beadle made the comment, 'In this long, roundabout way, first in *Drosophila* and then in *Neurospora*, we had rediscovered what Garrod had so clearly seen so many years before'. Later Beadle was to write, 'Regardless of when it was first written down on paper, or in what form, I myself am convinced that the one gene—one enzyme concept was the product of gradual evolution beginning with Garrod'. Following this tribute, many geneticists including myself have believed that Garrod was the first scientist to have caught a glimpse of what genes actually do, and that it is right and proper that he should be known as the father of biochemical genetics.

The truth is probably less certain. In this meticulously researched and beautifully written biography, A. G. Bearn, who is a distinguished clinical geneticist in his own right, traces the life and times of Garrod and attempts to tease out from the ideas of genetics, biochemistry and medicine that prevailed at the turn of the century just what it was that made Garrodian concepts so unique and insightful.

Archibald Garrod, son of a distinguished rheumatologist, was born in 1857 into the prosperous and self-confident middle class of Victorian England. The family home was in Harley Street and the atmosphere one of striving intellectuality. At the age of ten, young Archibald penned his first booklet on classical architecture. Like many young men of the time his interest in science was stimulated by natural history (his enthusiasm was butterflies), and he went up to Oxford to read Natural Sciences. Despite a First in chemistry, family tradition claimed the young scholar and Garrod returned to London and a career in medicine at Bart's. In the 35 years between gaining his medical degree and his appointment as Regius Professor of Medicine at Oxford (1920), he held a variety of clinical posts at Bart's and co-appointments at the Royal Hospital for Sick Children, Great Ormond Street. He had to wait until he was 55 before becoming a consultant, by which time he was already an FRS.

Although a practising clinician for most of his career, Garrod's first love remained chemistry. His fascination with urinary pigments, pursued in collaboration with Frederick Gowland Hopkins, led him inevitably to 'black urine disease' or alkaptonuria. It was already known that the black pigment was homogentisic acid; Garrod's contribution was to suggest that alkaptonuria was the result of a chemical aberration in the tissues, present at birth, or as he was later to call it, an inborn error of metabolism. He was quick to grasp the concept of biochemical individuality, but his dogged pursuit of this theme (later