Genet. Res., Camb. (1988), **51**, *pp.* 165–170 *Printed in Great Britain*

Book reviews

Advanced Methods in Protein Microsequence Analysis. Edited by BRIGITTE WITTMANN-LIEBOLD, JOHAN SALNIKOW and VOLKER A. ERDMANN. Berlin: Springer-Verlag. 1986. 423 pages. DM 198. ISBN 3 540 16997 0.

The scope and role of protein sequencing has changed in the last ten years or so. Up to 1977 it was the only method for elucidating the exact primary structure of a protein. When the methods for rapid DNA sequencing became available, amino acid sequencing was avoided whenever possible, as being tedious, unreliable for large proteins, and requiring more material than could often be obtained. More recently the balance has again changed, with the development of extremely sensitive methods and instruments for protein sequencing, and it is now possible to combine DNA and protein sequencing in designing rapid and highly efficient strategies for tackling a wide variety of biological problems. Moreover, there is an absolute requirement to adopt a protein approach to investigate such topics as active-site labelling, or post-synthetic modification, or isoenzyme expression, to name but a few.

The determination of protein sequences is a field which has traditionally shared the details of its methods by word of mouth and informal lab notes. There has long been a great need for a practical manual – a 'Maniatis' of protein sequencing. I am therefore very pleased to be able to report that this book does indeed go at least part of the way towards satisfying this need. However, it is a remarkably variable book, and there are several disappointing omissions as well as the inclusion of quite a bit of material of marginal relevance.

The book is derived from a FEBS Advanced Course on Microsequence Analysis held in September 1985. The course was apparently heavily oversubscribed, and this book is an attempt to satisfy the ever-increasing demand for highly sensitive methods for the analysis of proteins. The title of the book has logically been derived from that of the course, but in fact seems quite misleading as many of the methods are not advanced, and many are not even concerned with protein sequencing. The editors state in the introduction that some of the '...experimental protocols are suitable for use in the laboratory for student courses..., as well as for use by researchers who are new to the field of protein microsequence analysis'. The sections dealing with methods for protein cleavage, separation of peptides by HPLC and manual microsequencing are truly excellent in this respect. How useful it is, for example, to have it explained that ammonium acetate buffers for HPLC separations should be prepared from ammonia and acetic acid, because the salt is not pure enough – and that the buffer once prepared is only stable for a few days.

The availability of rapid and high sensitivity protein sequencing techniques means that these should be the methods of choice for many applications. However, it is frequently the case that a scientist requiring these techniques has little experience with handling proteins. There is an obvious need for advice concerning the pros and cons of the different sequencing methods and the different types of equipment available. It is disappointing that there is no section of this sort in the book. Moreover, the sections on automated sequencing are heavily biased towards descriptions of instruments constructed in the laboratories concerned, and there is little mention of the commercially available machines. There can only be relatively few laboratories which have both the capability and inclination to construct their own instruments – a statement which is justified when one considers the phenomenal success of the Applied Biosystems gas-phase sequencer.

In summary, the main strength of this book is as an excellent laboratory manual for many of the high sensitivity methods required for the analysis of proteins. With this in mind, it would be more useful (and presumably much cheaper!) if the book had a soft cover/spiral-bound format.

LINDA A. FOTHERGILL-GILMORE
Department of Biochemistry
University of Edinburgh

Cancer Cells 5: Papillomaviruses. Edited by B. STEINBERG, J. BRANDSMA and L. TAICHMAN. New York: Cold Spring Harbor Laboratory 1987. 423 pages. Paper, $80.00. ISBN 0 87969 301 0.

This book is a collection of papers delivered at the annual scientific meeting entitled 'The Papillomaviruses', which was held at Cold Spring Harbor in the summer of 1986.

In keeping with the Cancer Cells series the presentations are related to molecular mechanisms

involved in replication, expression, transformation and tumorigenicity in addition to the relationship of the papillomaviruses to disease, the immune response and therapy. The presentations cover bovine, rabbit and human papillomaviruses. The introduction, written by Peter Howley, is an invaluable background to the book.

The introduction emphasizes the enormous expansion in the study of papillomaviruses since the first meeting organized at Cold Spring Harbor in 1982 which attracted only 100 participants, and attributes the great increase in popularity to two main reasons:

(1) the availability of recombinant agents and *in vitro* systems to begin to study the biology of this virus;

(2) the strong association of specific papillomaviruses with certain carcinomas in humans.

These features elevate the originally common wart virus (HPV) to an oncogenic virus with complex molecular biology.

The importance of the first point requires the initial recognition that the papillomaviruses cannot be cultured in the laboratory, i.e. no *in vitro* tissue culture model system for their replication has been established. Indeed, it is only the recent sophisticated advances in genetic manipulation that have allowed these viruses to be dissected and the functions of the gene products, enhancer sequences and promoter regions to be examined in detail in biological systems.

In Peter Howley's laboratory the bovine papillomavirus type 1 (BPV-1) is the virus studied. This virus induces fibropapillomas. Detailed knowledge of its functions have now been elucidated. Like the HPVs of which there are some 46 types, the genome has a coding capacity for seven early (E) and two late (L) proteins. BPV-1, a dsDNA virus, replicates extrachromosomally and the message is transcribed from only one strand. The viral functions have been identified by sequence data and subsequent analysis of the open reading frames (ORFs). The function of the various ORFs is based on genetic manipulation of the coding region into expression vectors and the subsequent characterization in, for example, the transformed cell. The transformed cell will harbour the virus but not replicate it. From such studies it has been possible to determine that BPV-1 which transforms cells in culture expresses the E5 ORF, a highly conserved gene associated with fibroblast proliferation. Two independent oncogenes have been defined in the BPV-1, E5 and E6. However, these oncogenes readily transform only established cells and not primary cells. So BPV-1 does not code for an immortalizing oncogene analogous to the polyoma large T antigen or myc. The E6 oncogene is conserved in human as well as bovine strains. Although the human strains HPV-5, HPV-16 and HPV-18 transform cells in culture the actual gene responsible has not yet been determined, but the E6 gene is considered a good candidate. The E2 gene of BPV-1 contains a transactivator whose regulation is controlled by two E2 responsive elements in the long control region (LCR). However, the carboxy terminal domain of the E2 ORF also codes for a transcriptional repressor.

These points give some insight into the complexity of gene control in the papillomaviruses. Full replication of the virus is thought only to take place in terminally differentiating keratinocytes: thus cell associated factors are involved in the control of virus replication. Virus can be recovered from bovine papillomas and also from some human warts of the common skin types, e.g. HPV-1.

To deal more precisely with the second reason why Peter Howley sees a rapid increase in the study of papillomaviruses, this involves the proposal that HPV-16 and HPV-18 are strongly associated with malignant cervical disease, whereas HPV-6 and HPV-11 are strongly associated with premalignant disease – i.e. cervical intra-epithelial neoplasia (CIN). Several continuous squamous cell carcinoma cell lines have been studied to determine the role of HPV-16 and HPV-18 subtypes. The genome is integrated at specific sites within the E1 or E2 genes, resulting in the subsequent deregulation of viral promoters upstream from the E6 and E7 ORFs. Both E6 and E7 are transcribed; but a shortened E6 gene product is found in these carcinoma cells due to an extra splice site. This characteristic is thought to be peculiar to HPV genomes associated with malignancy, e.g. HPV-16 and HPV-18. Thus chimaeric transcripts are detected in Hela cells which encompass the 5′ end of E6, E7 and E1 ORFs together with 3′ terminal host cell sequences. One problem with the relationship of HPV-16 to oncogenesis is the high proportion of histologically normal cells which harbour the genome. This strongly suggests that cofactors are important in the progression to malignancy and these may be cocarcinogens or impaired immunity.

Work in the laboratory of Schwartz analyses Hela × normal keratinocyte hybrids and shows that although these cells appear morphologically transformed they do not form tumours in nude mice. This indicates that transformation *in vitro* and tumorigenicity *in vivo* are controlled by separate genetic elements. It is not clear whether HPV-16 and HPV-18 code for any tumour function; their association with malignancy may be due to deregulation of normal cell genes or epigenetic means.

Indeed in a study from Crum's group the HPV genome is transcribed in only a very small proportion of premalignant tumours, indicating that no HPV-16 function requires to be continuously expressed.

So to whom is the volume on the papillomaviruses a useful reference book? Mainly I feel to those with a desire to understand the latest ideas on genome organization, transcription patterns and control genes. The background given in this review emphasizes the complexity of the papillomaviridae. A certain elementary knowledge of virology and molecular

biology is necessary to understand the presentations. The book is therefore useful mainly to final-year undergraduates, postgraduates, molecular biologists and virologists. Each chapter contains references which will allow the reader to carry out background reading, but the main emphasis of the text is on research work carried out by the different groups involved in the meeting. Is it good value? Probably it is a good and reasonably up-to-date reference for any library attached to an appropriate research laboratory.

JOAN C. M. MACNAB
MRC Virology Unit
Institute of Virology
Glasgow

Genetic Takeover and the Mineral Origins of Life. By A. G. CAIRNS-SMITH (first published 1982, first paperback edition 1987). Cambridge University Press. ISBN 0 521 34682 7.

Since the early writings of A. I. Oparin and of J. B. S. Haldane in the 1920s, virtually all scientists have accepted that the molecules of life arose by spontaneous synthesis on Earth, in strongly reducing conditions. There has been a prevailing view that small organic molecules forming from primordial gases became concentrated in various ways, that polymerization eventually led to long-chain molecules, that reactions between different kinds of such molecules resulted in self-replication, and finally that simple systems emerged, able to reproduce and evolve by natural selection. This conception of chemical evolution has been supported by the many experimental syntheses, done since Miller's classic work of 1953, of organic molecules in conditions simulating those of the early Earth. Impressively, many of the nitrogen-containing compounds vital to the biochemistry of living organisms can be made abiotically. But this is only the first step. For despite experimental demonstrations of polymerization, the rest of the story is far less clear. And to Andrew Cairns-Smith parts of it, at least, are despairingly implausible.

The author begins his text by setting out, very fairly in my view, the standard view on chemical evolution. Then he proceeds to explain, with singular clarity, why he does not believe it. There are too many difficulties. Consider, for example, prevital nucleic acid. Even allowing for the abiotic formation of purines and pyrimidines, nucleotides cannot be assembled from these components by any kind of easy synthesis. Cairns-Smith gives no less than 19 reasons why not. The next problem is that of multiple interdependence. We seem to be dealing with endless interrelated chicken-and-egg questions. How, in fact, are all the various bits of biochemical mechanism set up when the significance of each component depends upon the existence of all the others? We should consider, too, the origins of chirality. Why are only L-amino acids found in living bodies? These are only a few of the difficulties of the conventional view. Going further, there lies the ultimate spectre – the origin of the machinery of heredity.

The problems being thus defined, Cairns-Smith develops in great detail the argument he has already championed in his earlier books – that of the clay–crystalline origins of life. 'For a picture of first life do not think about cells, think instead about a kind of mud, an assemblage of clays actively crystallising from solution. . .' Yet this goes far beyond the ideas of Bernal and others, of clays involved in early evolution simply because they concentrated and catalysed organic molecules. To Cairns-Smith clay minerals were the actual materials, and perhaps the only ones, out of which the earliest organisms were constructed. Genes, controlling the chemistry of the immediate environment, came early, but they were mineral, and not of nucleic acid. They existed in immense numbers. These colloidal inorganic minerals were able accurately to replicate themselves as they grew; any defects would likewise be replicated. This clay-based life could fix carbon and nitrogen, could harness sunlight, and could consistently synthesize particular molecules. It came to use the readily available free organic molecules in the environment as phenotypic components. They were to begin with no more than 'optional extras'. But they built up by steps into organic genes. The organic genes were secondary, but since they were so much more effective than the 'clay genes' they became dominant. This is the 'genetic takeover' referred to in the title. And as a result life, with its now effective hereditary mechanism based upon nucleic acids, escaped from its clay base.

Each chapter argues different elements of the case at length. Primary genes, takeover, first biochemicals, first life, and the entry of carbon into the evolving system are considered in turn. In the process the author covers a very broad field, but with singular erudition. Cairns-Smith writes extremely well. His prose is lucid and superbly constructed, and he has been able to make even the difficult bits more or less comprehensible. The text is illustrated by many attractive diagrams of chemical and crystal structure, and there are a fair number of fine electron micrographs. At one point the author introduces an imaginary dialogue between Dr Advo, a champion of genetic takeover, and the sceptical Dr Kritic. It is really very well done. The concepts developed here may be heterodox, but they are based upon a vast knowledge of crystal structure and biochemistry, so clearly illustrated throughout the whole book. Cairns-Smith has defined the impasse which current studies in the origin of life have reached, and he has set forward his own case clearly, and in the final chapter points to ways in which future research might go. Now there may well be weaknesses in the argument, but whether any such are fundamental was not immediately evident to this reviewer. I found it intensely thought-