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**BOOK REVIEWS**

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**Annual Review of Biochemistry**, Vol. 57, 1988, pp. 1122, (eds.) C. C. Richardson, P. D. Boyer, I. B. David and A. Meister, (Published by Annual Reviews Inc., 4139 El Camino Way, Palo Alto, CA 94306, USA), Price: USA, \$35; elsewhere, \$39.

The 1988 *Annual Review of Biochemistry* has a prefatory article by F. Sanger entitled 'Sequences, sequences and sequences'. The story of the development of methods for sequencing proteins and nucleic acids has been told in a deceptively simple way. Some of the experiences described by Sanger, who made signal contributions to the progress of biochemistry and molecular biology and won two Nobel Prizes, are worth recording. He states that he is 'ashamed' of only one paper, which was published jointly with A. Tiselius in Uppsala, Sweden, since he (Tiselius) 'had not really contributed anything'—and this in contrast to Chibnall in England, who allowed him to publish a paper on his own even though the work was initiated by Chibnall and the latter could have justifiably put his name. Sanger also discounts the popular idea that 'scientific progress depends on sudden breakthroughs or moments of sudden exhilaration'. Unusually he also 'decided to retire and give up research' on reaching the age of 65 as he thought it would be something of an anticlimax after his successful completion of the DNA sequencing method and having had wonderful opportunities for research for 40 years.

The 28 reviews are a mixture of classical biochemistry and newer aspects of molecular and cellular biology, and have references numbering 100–500. Together they form a resource of work done mostly in the last decade in the areas chosen by the editors for this year. *Annual Review of Biochemistry* continues to be the single most important book to be possessed by all laboratories interested in biochemical research.

DNA can be modified by activated oxygen species, common metabolites of glucose, and diverse inorganic and organic electrophiles, including metals, alkylating agents and polycyclic aromatic hydrocarbons. Yet it is quite stable. Amazingly, a 3.4-kb DNA fragment was cloned from a 2400-year-old mummy! The genetic integrity and functional stability of DNA depends on the repair enzymes. Work on DNA repair has attracted a great deal of

attention and has been reviewed under the subjects direct base excision, nucleotide excision, recombination, cross-links, and SOS and adaptive response to oxidative stress. The adaptive response to alkylating agents receives special attention in another review in view of the carcinogenic potential implicit in this process. The mechanism of 'repair of the highly mutagenic DNA lesion O<sup>6</sup>-methylguanine' has largely been solved and an 'outline of the regulation of the inducible pathway' is now available. More will be heard in future on the *ada* gene, the regulatory gene of the adaptive response to alkylation damage. This produces a 39-kb Ada protein capable of self-methylation, transferring methyl groups from O-methylated DNA, and as a consequence converting it from 'a weak to a strong activator of transcription'.

The structure and function of bacterial sigma factors, which bind reversibly to the active site of RNA polymerase and play the determining role in the specificity of transcription initiation, are described. The sigma factors form a structurally complex, homologous protein family, sharing the property of binding to the core of RNA polymerase. In another article the current knowledge on transcription by RNA polymerase III, responsible for synthesis of a variety of small RNAs, has been presented.

Eukaryotic chromosomes 'participate in transcription, replication, meiotic and mitotic condensation, pairing, recombination and segregation' through specific 'interactions between nuclear proteins and DNA sequences'. Nuclease-hypersensitive sites in chromatin are the 'open windows' that allow access to *cis*-acting DNA sequences to *trans*-acting factors, and 'occur around centromeres, silencers, recombination sequences, replication origins, upstream activation sequences and promoter elements'.

Another interesting and provocative article covers post-transcriptional regulation of gene expression, especially at the level of translation initiation, elongation and mRNA splicing. The author sees translation initiation as a simple process and the ribosome as 'just a large ribozyme/enzyme' with active sites for its 'substrates', mRNA and Met-tRNA, with the information necessary for its binding to mRNA contained in a sequence of 35 bases.

The cell needs a balanced supply of the four dNTPs to replicate and this depends on the enzyme

ribonucleotide reductase. The enzyme has the general structure  $\alpha_2\beta_2$ . The  $\alpha$  and  $\beta$  subunits have  $M_r$  85,000 and 45,000 respectively, and the small subunit has the characteristic iron-tyrosyl radical centre. The interactions between synthesis of dNTPs and DNA are discussed in considerable detail.

The identification and isolation of *E. coli* DNA polymerase III, the complex enzyme responsible for the replication of the chromosome, was made possible by the use of natural replicative templates in the assay. The current status and future directions of this topic are given in another article.

Proteins and their reactions occupy a central place and this subject is covered in 11 articles. Acylation of specific cellular proteins is ubiquitous. It can occur post-translationally, with fatty acid (primarily palmitate) linked in a thioester or ester bond to cysteine, serine or threonine, or cotranslationally by myristoylation of N-terminal glycine, or carboxy-terminal addition of phosphatidylinositol containing a glycan moiety. The enzyme that catalyses N-myristoylation, the best-understood protein acylation process, is the subject of one full article. Fibronectin is a multifunctional extracellular matrix protein with the 'most celebrated activity' of promoting cell adhesion. One review focuses on its cell-surface receptors, called integrins, with which the adhesion protein forms a recognition system that determines 'the information cells need to acquire and maintain the proper position, polarity, stage of differentiation and growth rate'. There is a sentence in this article which, when read in isolation, gives a wierd meaning: 'The cDNA sequence is human and the protein sequence bovine.' (!) The molecular organization and function of the complement system, with its 20 plasma proteins that play an important role in host defence in infection and inflammation, have been comprehensively covered. The glycoproteins of the zona pellucida, the thick, transparent coat of mammalian eggs, and their participation in the process of fertilization have been described with illustrations.

A few selected topics related to the class II sub-region of the human major histocompatibility complex, its genetic organization, polymorphism of the genes and proteins, and regulation of their expression have been covered in another article.

One article focuses on insights into the evolution and expression of lens crystallins. The lens crystallins provide an excellent system for studies on tissue-specific gene expression. The crystallins are abundant soluble proteins and constitute 20–60% of the wet

weight of the tissue in which they are expressed. The last decade has seen much development in the molecular and cellular biology of intermediate filaments, the prominent components of the cytoskeleton and nuclear envelope, the structural proteins of which are involved in specialized functions related to differentiation and signal transduction. A review brings this rather special, fast developing subject to the attention of biochemists. Another less-known area, that of peptide toxins from venomous snails, has been presented in sufficient detail.

An article on viral proteinases explains the importance of proteinases in the processing of precursor polypeptides, which yields active products necessary in the viral replication cycle, and also the usefulness of these studies in the development of specific protein inhibitors as antiviral agents. The synthesis of peptides and proteins has been of continual interest in biochemical studies and the current interest in biologically active peptides seems to have prompted inclusion of a review to 'provide an interpretive overview of synthetic methods that a non-specialist can use as a guide, but that an expert will not find seriously deficient'. The review justifies the need for chemical approaches in future biological studies.

Work in the last five years has revealed modes of attachment of membrane-bound proteins through non-protein anchors other than through acylation. A glycosylphosphatidylinositol linkage to the carboxy-terminus through ethanolamine has been shown. Treatment with bacterial phospholipase C, specific for cleaving phosphatidylinositol, released from the membrane surface alkaline phosphatase, acetylcholine esterase and 5'-nucleotidase, which then could not rebind. The finding of this mode of attachment resolved the enigma that proteins with no obvious hydrophobic sequences (needed for membrane localization) can be attached to membranes and function as localized molecules; examples are the Thy-1 antigen and the *Trypanosoma* variant surface glycoproteins. A review on this topic deals with structural and biosynthetic aspects of this anchor mechanism and offers useful guides for further research.

The article on growth factor receptor tyrosine kinases is an excellent overview of this rapidly expanding field that includes growth factors, protein kinases, transcriptional activation of specific genes, and oncogenes and cellular transformation. Interestingly the seven receptor tyrosine kinases studied

have a common architecture and membrane topology—an extracellular, large ligand-binding domain and a large, intracellular catalytic domain (about 500 amino acids) linked by a single hydrophobic transmembrane segment. It is expected that exciting information will be forthcoming on how the ligand binding to the receptor generates the signal and how the signal is transmitted through the membrane and transduced as ATP-dependent phosphorylation of protein tyrosine (845 in human EGF-R). Another article introduces cachectin, a macrophage-derived protein that functions as an essential mediator of the inflammatory response and is capable of evoking a 'shock' state and inducing anorexia and wasting and haemorrhagic necrosis of tumours.

Several compounds that inhibit essential biosynthetic reactions are useful as herbicides and those that affect 'photosynthesis and essential amino acid biosynthesis, unique to plants and microbes,' are more appropriate and likely to be less toxic to animals. There is a review of the current understanding of plant enzymes and the genes involved in the biosynthesis of amino acids, and the possibility of using herbicides targeted at them. Although studied from the beginning of biochemistry, regulation of carbohydrate metabolism is still an actively studied field. Hormonal regulation of hepatic gluconeogenesis and glycolysis is reviewed, including studies on pyruvate kinase, 1- and 2-kinases of fructose 6-phosphate, and phosphatases of 1,6- and 2,6-biphosphates of fructose.

Some general subjects have been included. One of these is an article on bacterial electron transport chains, by no means a new area but one that is now studied using genetic and molecular-biological approaches. This article describes bacterial aerobic respiratory chains and cytochromes, extensively covering the systems in *E. coli* and *P. denitrificans*. While there is some survey of peculiar electron transfer components, the omission of Indian work on *Agrobacterium tumefaciens* is glaring. The latter showed the presence of ubiquinone with 10 isoprene units in the side chain and antimycin-sensitive oxidation of NADH, both unusual for bacteria. Polyphosphates occur widely, and although a universal role for these has not been demonstrated, one of their roles seems to be to act as phosphorylating agents. This is described in one review. Another article is devoted to carnitine, its enzymology, and its impact on short-term metabolic control. The enzyme dopamine- $\beta$ -hydroxylase, which catalyses the conversion of dopamine to the neurotransmitter

and hormone norepinephrine, present in chromaffin granules of adrenal medulla and synaptic vesicles of sympathetic nervous system, is the subject of a review that attempts to integrate advances in studies on the nature of the enzyme with its function in the granules. A review with the novel title 'Glycobiology' discusses the current theories concerning the role of N-linked oligosaccharides in protein-specific biological activity. Blood clotting has attracted attention for several years, and the recent 'dramatic advances on sequences of cDNA coding for factor VIII, factor V, tissue factor and prothrombin' seem to have prompted a review on 'current perceptions of the multicomponent complexes associated with blood clotting with particular emphasis on the structural and functional aspects of the membrane-related cofactors'.

There has been a large growth in the literature of biochemistry and related areas and the trend is for more growth. Each year, with a selected few topics for these reviews, the *Annual Review of Biochemistry* provides a comprehensive presentation of the advancing frontiers. This year's volume, with 30 pages and possibly about 10,000 references contributed by about that many authors (list running to 82 pages), confirms the continuing expansion of interest in this subject. It is to the credit of the editors that a blend of classical and molecular-biological approaches has been presented, and subjects that are not so popular, but are still important, have not been ignored. This reviewer would like to see more illustrations and summary tables of data and less descriptive matter. With specialization for each worker becoming narrow, even these reviews have tended to become too large to comprehend, and alternatives are awaited.

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*Annual Review of Cell Biology*, vol. 4, 1988, pp. 754, (eds.) G. E. Palade, B. M. Alberts and J. A. Spudich. (Published by Annual Reviews Inc., 4139 El Camino way, Palo Alto, CA 94306, USA). Price: US\$39.

The field of cell biology is fast expanding in many directions and encompasses all aspects of organization

and function of living cells. The editors have rightly pointed out that 'it is not easy to generate a well-balanced Annual Review'. This volume has 24 articles covering widely different topics that look like a collection of those available. Realizing that it is not easy to give any themes by combining some of these articles, the reviewer decided to give an overview of these in the same sequence. The first article describes recent crystal studies of DNA for the comprehension of biologists, and includes the excitement of left-handed DNA, partly generated from Indian work. The current knowledge of adaptation to the environment in *E. coli* with respect to the outer membrane proteins (omp), which act as pores, has been reviewed. Not many would be familiar with 'growth cones, the specialized motile structures at the elongating tip of neurons', although the subject has been well reviewed during the eighties. The review here focuses on work during 1985-88, especially 11 papers of about 60 quoted, without any pretension of impartiality. Hair cells, the epithelial receptor cells that carry out transduction of mechanical stimuli into electrical responses in the auditory system, are now amenable to experiment, and a review on the topic describes how this difficult area is now yielding information. Regulation and physiological functions of cell-associated plasminogen activation that leads to formation of a serine proteinase, plasmin, are reviewed. The finding that DNA sequences lying a considerable distance upstream of transcriptional start sites are involved in transcriptional regulation has led to the concept of 'enhancers' distinct from 'promoters' and of their general occurrence as cellular transcription control elements. A description of their modular organization, their positive, negative and inducible regulation, and the involvement of protein-protein interactions have been summarized in a crisp article that is worth reading.

Mitochondrial membrane potential is known to be derived from respiratory chain electron transport and is considered to drive the 'proton turbine' of  $F_0F_1$ -ATPase to synthesize ATP. New data with the use of a unique probe, rhodamine 123, a highly specific fluorescent dye, are discussed, which now indicate that such potentials are indeed obtained in living cells. Using inherent self-assembly properties of the components, living cells generate ordered supra-molecular arrays. This fascinating problem of cell biology has been analysed with particular reference to the extracellular matrix.

Flowering plants have a requirement of outcrossing

and those that are hermaphroditic also possess a mechanism for preventing self-fertilization. This mechanism is known as self-incompatibility, and is controlled by the S-gene. An article describes recent work, using recombinant DNA technology, on this subject.

Proteoglycans are proteins that carry sulphated carbohydrate components, glycosaminoglycan, with functions in cellular processes as diverse as matrix assembly, cell adhesion, differentiation and proliferation. Studies on their structure and biology are brought together in one review.

The endoplasmic reticulum (ER), an extensive membrane-bound organelle in the cytoplasm, is the site of synthesis of proteins. The sorting of proteins that are resident in the ER, such as those that synthesize some lipids and oligosaccharides, microsomal redox systems, and enzymes involved in correct protein folding, of those exported outside the cell, and of those targeted to lysosomes, mitochondria, plasma membrane and the cytosol is a very active field now, and this subject is covered by a comprehensive review. In another article the focus is on mitochondrial biogenesis, dealing essentially with genes of mitochondrial DNA and the integration of nuclear and mitochondrially synthesized proteins in the membrane structures of this organelle. Following this, another review deals exclusively with the functional organization of the nuclear envelope, especially important in eukaryotic cells to separate, 'spatially and temporally', the transcription and maturation of mRNA in the nucleus from its translation in the cytoplasm. The envelope is now known to consist of a double membrane and pore complexes with a lining of fibrous protein meshwork (lamina), which together regulate nucleocytoplasmic transport, a selective, vectorial process. Another article summarizes work on the mechanism of intervention of the embryonic microenvironment in establishing phenotypic diversity during neural crest ontogeny. This is an example of a classical anatomical descriptive approach to a specialized process like emergence of the peripheral nervous system.

A great deal of interest has been generated recently on membrane receptors and signal processing. Beta-adrenergic receptor, adenylyl cyclase G-proteins and the desensitization phenomenon have been discussed in a well-organized review. The process of conjugation in *Saccharomyces cerevisiae* is the basis of another article, with a view to understand the genes involved and their products. Under the interesting

title 'From egg to epithelium', the anatomical changes associated with emergent epithelial cells, and the development of cytocortex and cytoskeleton as well as intercellular contacts, junctions and matrices, and intracellular organelles, are described. It is now possible to narrow down the areas on the plasma membrane responsible for the adhesion of cells to the underlying substrate in tissue culture, called adhesion plaques or focal contacts. Work on this less-known subject is summarized and this should stimulate further work. The kinetochore, the structure responsible for the attachment of mitotic chromosomes to the spindle and for their correct segregation, and its interaction with microtubules are the subject of another review.

The article 'New collagens' is likely to evoke much response, given the long-standing interest in work on collagens in India. Collagens, the structural proteins found in extracellular space, are now recognized to be a group of twelve distinct proteins encoded by different genes. Their major structural feature is the triple-helical conformation.

Lipids in membranes play the dual role of providing a permeability barrier and regulating the activity of membrane-associated enzymes. The biosynthesis of lipids and their transmembrane and intermembrane mobility have been reviewed. One omission in this review seems to be that of ubiquinone (coenzyme Q), and some earlier work from our laboratory and later work from Hackenbrock on its mobility could well have found a place. Post-translational modification of proteins through

acylation of side-chains of amino acids by fatty acids is now recognized to be of wide occurrence. A review is devoted to the process of fatty acylation of proteins, which is an example how a single biosynthetic process can affect a wide variety of cellular processes.

Eukaryotic chemotaxis is an intriguing biological phenomenon. A review, covering the basic features of this process in biochemical terms, includes receptors, signal transduction, phospholipid-induced messengers, cyclic nucleotides, motility factors, G-proteins and cytoskeletal structures. Lastly, there is a review covering the structure and utilization of isotypes of tubulin, the subunit protein of microtubules. Tubulin is a heterodimer of two 50 kDa proteins that self-associate into hollow cylinders.

This volume will be highly useful to workers in biochemistry, biophysics, and cell and molecular biology. It is worth spending time reading these reviews. The awesome pace at which progress is being made in these areas changes the styles and capabilities in cell biology research. These reviews convey a feel of these changes. It is no wonder that Annual Reviews are the best-read and best-quoted work.

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