Annual Review of Immunology 1996. Wilson E. Paul ed. Annual Reviews Inc., 4139 El Camino Way, P. B. No. 10139, Palo Alto, California 94303-0139, USA. Vol. 14. 718 pp. Price: $56, elsewhere $61.

The *Annual Review of Immunology 1996* contains 26 articles. They deal with the general areas of early T cell development and differentiation, T cell activation and TCR-mediated signaling, B7/CD28 and CD40/gp39 mediated co-stimulatory events, Class I MHC mediated antigen presentation, regulation of Class II gene expression, interactions involving endothelial cells and mucosal barriers, arthritis and salmonellosis, CTL-mediated disease protection, immunotoxin action, action of viral-derived immunoregulatory molecules and the macrolide antibiotic rapamycin. Articles on tyrosine kinase mediated signaling, variable region gene assembly and the nature of somatic hypermutation cover the area of B cell biology. The volume opens with a short article by M. Koshland describing the strong influence that Karl Landsteiner had on her. Particularly interesting is her concern for the problems faced by women scientists and the need to encourage creative thinking in present-day science.

Three articles discuss events related to progenitor development and their early differentiation and signaling. K. Shortman and L. Wu in their article 'Early T lymphocyte progenitors' describe early steps occurring during the differentiation of multipotent hemopoietic stem cells and early T cell progenitors into cells that have completed their TCR gene rearrangements. Contrary to older assumptions, significant differences have now been shown to exist between fetal and adult lymphopoiesis. The surface expression of markers such as Sca-1, Lin, Thy 1.1, c-kit, human CD34 and CD45, CD4 and CD8, the status of TCR gene rearrangements as well as the expression of RAG-1 and RAG-2 genes in early progenitor T cells are discussed. In a complimentary article 'Cellular interactions in thymocyte development', G. Anderson *et al.* describe the influence of thymic stromal components during positive and negative selection in the thymus. Thymocytes and stromal components seem to interact in a mutually interdependent manner. Although stromal components are known to influence thymocyte maturation, it is now increasingly evident that thymocytes also influence stromal cell function. Data gathered from mice deficient for TCR-alpha subunit, RAG-1, RAG-2, $p56^{lck}$ genes, SCID and CD3-epsilon transgenic mice are described. The roles of $P56^{lck}$, a putative $p21^{ras}$ exchange protein called Vav, CD45 phosphatase as well as ZAP-70 during positive and negative selection are discussed. Emerging evidences support the conclusion that the events of positive and negative selection are mediated by distinctly different biochemical signaling pathways. The participation of tyrosine kinase-mediated signaling pathways in B cell development and lymphopoiesis is discussed in their article on B cell development by A. Sutterthwaite and O. Witte. The effects of gain as well as loss of function mutations of selected tyrosine kinases on B cell development are summarized. An additional article included in the general area of B cell biology has been written by S. D. Wagner and M. S. Neuberger on the topic of somatic hypermutation. The article deals with the mechanism of somatic hypermutation in B cell development, a process that results in affinity maturation. The possible molecular nature is discussed with respect to the observed pattern of nucleotide substitution and the regions mutated. Information regarding the mechanism of V(D)J gene rearrangement during TCR and Ig assembly is available in the article written by B. P. Sleckman, J. R. Gorman and F. W. Alt. The various factors that govern the accessibility of recombining sequences within the TCR and Ig genes are discussed with special reference to the different stages of lymphocyte development.

Three articles cover the general area of T cell recognition and activation. J. Sloan-Lancaster and P.M. Allen in their article 'Altered peptide ligand-induced partial T cell activation' describe the information obtained regarding the induction of T cell anergy by TCR binding of peptide analogs of immunogenic peptides. These 'altered peptide ligands' (APL) are generated by selective replacement of specific amino acid residues in the immunogenic peptide. APL and agonistic peptides seem to differ from each other in the pattern of tyrosine phosphorylations they induce on the TCR-gamma subunit. The number of tyrosines phosphorylated in the TCR/CD3 are, in turn linked to the nature of ligand bound by the TCR. In contrast to being an all or none phenomenon, T cell activation seems to progressively depend on the number of signaling molecules recruited downstream to differential phosphorylation events. The article describes these events lucidly and proposes several models to explain them. Endogenously occurring APL may thus play an important role not only in thymic maturation and various disease processes but may influence T cell immunity as well. While the above article deals with T cell activation, G. A. Bently and R. A. Mariuzza describe details of the crystallographic studies of the TCR to confirm the similarities between the TCR and immunoglobulin structures. It must, however, be mentioned that more recent information has been published subsequent to their article 'The structure of the T cell antigen receptor' published in this Annual Review. The role of TCR-mediated signal transduction pathways in cytokine gene regulation is discussed in the article 'T cell antigen receptor signal transduction pathways' by D. Cantrell. The regulation of phospholipase C-γ and phosphatidylinositol 3'-hydroxylase as well as the roles of $p21^{ras}$, Grb2 and Grk molecules during TCR signaling are covered. The downstream induction of various transcription factors especially NFAT, AP-1, NF-kB and Oct-1 as well as the regulation of MAP and JUN kinases by the TCR and CD28 molecules are discussed in detail. A separate article by Y. Chein *et al.* is devoted to gamma–delta T cell function. The differences between $\alpha\beta$ and $\gamma\delta$ T cell types with respect to their requirements for activation, antigen recognition, absence of the need to process antigen before its recognition by the $\gamma\delta$ TCR as well as the properties of recognized antigens such as prenylation and phosphate bearing nonapeptides are discussed. While the above articles deal with normal T cells, a comprehensive article by A. Moretta *et al.* deals with receptors on human natural killer (NK) cells. NK cells are not MHC restricted and therefore, differ from normal T cells. Rather than possessing antigen-specific receptors, recent information suggests that specialized receptors for different MHC alleles are found clonally distributed on NK cells. The recognition of epitopes shared by groups of MHC alleles found on normal self-MHC molecules lead to inhibitory signals that inhibit NK killing. However, the masking or alteration of these epitopes that are present on self MHC-Class I leads to activating signals that

result in successful NK recognition and killing. Receptors that recognize HLA-B and HLA-C alleles have been identified, their genes cloned and the receptor structures delineated. Interestingly, both activating and inhibitory type receptors for HLA-C alleles have been discovered and represent new members of the immunoglubulin superfamily. The differences between murine Ly49 and human NK receptor molecules are discussed. Detailed information about the mechanism of cytotoxicity by NK and MHC-restricted cytotoxic T cells (CTL) is found in another article by D. Kagi *et al.* Besides describing both perforin-mediated and Fas antigen-mediated mechanisms, the article also emphasizes the relative roles played by these pathways during immunopathology and immunological protection. The importance of these two cytotoxic mechanisms during infection with cytopathic versus non-cytopathic viruses, bacterial infections, autoimmmune and allograft rejection reactions is dealt with.

Information regarding co-stimulatory signals that accompany lymphocyte activation is found in two articles, one on CD28/B7 mediated-signals and the other on CD40/gp39-mediated immune regulation. The first article by D. J. Lenschow *et al.* discusses the important role of CD28/B7 interactions in the activation and suppression of humoral immune responses, transplantation and autoimmune disease. The general properties of CD28 and CTLA4 molecules, their participation in TH1 and TH2 differentiation, the differential cellular distribution, expression and regulation of B7-1 and B7-2 are described along with a temporal model for their regulation. The second article 'Immune regulation by CD40 and its ligand GP39' by T. M. Foy *et al.* describes the central role of CD40 and gp39 in B cell expansion and differentiation, humoral immune responses to T dependent antigens, germinal center formation and in the peripheral and thymic induction of T cell tolerance. The advances made in the molecular analyses of CD40 receptor/gp39 ligand binding are described in the article. Antigen-mediated regulation of gp39 expression on T cells from normal and transgenic mice that constitutively express specific antigen is also described.

Information gathered in the area of leukocyte–endothelial cell interactions and subsequent leukocyte migration and immune surveillance of mucosal barriers is available in two articles. Immune surveillance depends to a large extent on the successful migration of specific leukocyte subsets to the location at which inflammation occurs. The recirculation of leukocytes from the blood into peripheral tissues is controlled by endothelial cells. The mechanisms by which this control is exerted are described in the article 'Orchestrated information transfer underlying leukocyte endothelial interactions' by K. Ebnet. The induction and production of various chemokines by endothelial cells and the specific interactions involving adhesion molecules such as P-selectins and integrins are discussed, especially with regard to their control of leukocyte migration. The mechanisms by which antigens are sampled and presented across epithelial and mucosal barriers have assumed great importance in contemporary immunology and the knowledge accumulated is becoming increasingly relevant in development of therapeutic strategies. The article by M. R. Neutra *et al.* covers transepithelial transport of antigen by specialized epithelial cells called M cells. Several pathogens have the ability to utilize the properties of M cells to gain access and invade mucosal tissues. The mechanisms by which this invasion is achieved has been described with special reference to reovirus, poliovirus, MMTV, HIV as well as bacteria such as *E. coli*, *Vibrio cholerae*, *Salmonella*, *Shigella* and *Yersinia*.

Two articles deal with the Major Histocompatibility Complex. The article by I. A. York and K. L Rock concentrates on the recent molecular details of antigen processing and presentation by MHC Class I. The role of TAP proteins, ubiquitin and chaperones in antigen presentation as well as the subcellular compartments involved are covered in detail. The article 'Regulation of MHC Class II genes: Lessons from a disease' by B. Mach *et al.* describes the clinical study of patients suffering from BLS (Bare Lymphocyte Syndrome). BLS is characterized by defective regulation of MHC-II surface expression due to defects in two MHC-II transactivators called CIITA and RFX5. This clinical discovery, the first of its kind to be shown to involve genetic lesions in transactivator genes was confirmed by complementation cloning studies. The mechanism of action of these two transactivators in modulating Class II genes is described. Information regarding the regulation of MHC-II by various cytokines, MHC-II promoter and the DNA-binding proteins that bind to it are summarized in a comprehensive table. The last article in the volume 'The NF-kB and I-kB proteins' written by A. S. Baldwin Jr describes in detail the action of the well-known transcriptional factor, NF-kB and its inhibitory protein I-kB. NF-kB is normally found associated with Ik-B in the cytoplasm. During immune and inflammatory responses, activating stimuli lead to the release of NF-kB from I-kB followed by its translocation into the nucleus. NF-kB-binding sites serve as transcriptional regulatory elements that are inducible by LPS, TNF, GM-CSF, IL-1, IL-2, IL-6 and ICAM-1. Advances regarding the biology of NF-kB/Rel family of proteins, the crystal structure of NF-kB, mechanism of its activation and the genes it regulates as revealed by recent gene knockout studies are described.

The article by R. T. Abraham and G. J. Weiderrecht describes the immunopharmacology of rapamycin. The mechanism of immunosuppressive action brought about by this macrolide as well as its analogue FK506 through the formation of rapamycin-binding complexes is reviewed. Recent information regarding the interaction of these complexes with its target protein called mTOR and the participation of a new signal pathway in IL-2 activated T cells is covered. The use of immunotoxins for cancer and disease is now a well-defined approach. The clinical advantages of targeted immunotoxin therapy is discussed in an article on 'Immunotoxins' by G. R. Thrush *et al.* A ready reference table summarizing clinical trials that have used immunotoxins has been included. This article also describes the use of bispecific antibodies as well as various toxin moieties to target B and T cell subsets. The use of cytokine and growth factor-based immunotoxins in bone-marrow transplantation, autoimmune disease, AIDS as well as graft vs host disease are discussed. The development of more efficient drugs and therapeutic strategies to strengthen the immune system is seemingly accompanied by a parallel effort on the part of viruses to evolve novel mechanisms to evade the immune system. The article 'One step ahead of the game' by M. K. Spriggs confirms just this. Viruses co-evolve along with the evolution of higher mammals that are the targets for their infection. Many viruses have now been shown to synthesize many immune modulators which, in turn, regulate the processes of antigen presentation, complement and cytokine

function as well as apoptosis. The mechanism by which the ICP47 gene product, US11 of human cytomegalovirus as well as the gp19 protein of adenovirus inhibit MHC Class I transport is summarized. The action of the BZLF2 gene of EBV on MHC Class II presentation is discussed. Human IL-10 and the BCRF1 gene product of EBV seem to show similar actions, thus making it possible for this viral protein to disturb nomal cytokine networks. Pox viruses also encode soluble receptors for Type I and Type II IFN (B18 receptor protein), TNF, IL-1 as well as other proteins and chemokines that regulate programmed cell death. The similarity of pox virus-encoded ORFs and growth factors to the EGF family of proteins is discussed. The information discussed is very pertinent to the control of viral infections.

Three articles relate to disease processes. The discussion about M cells found in the article on mucosal barriers is dealt in more detail in the article on 'Salmonellosis: Host immune responses and bacterial virulence determinants'. This article by B. D. Jones and S. Falkow describes the genes, inv A,-B,-C and inv-D that control the ability of Salmonella to invade the mucosal tissue. Other invasion genes such as *hil*, *prgH* and *orgA* are also dealt with along with genes responsible for the pathogenesis and survival of the parasite within phagocytes. In summary, several products that are important for the invasion of pathogenic Salmonella along with their genes and the host immune responses to them are described.

The article 'Role of cytokines in rheumatoid arthritis' by M. Feldmann *et al.* reviews information gathered about the pathogenesis of rheumatoid arthritis. Analysis of cytokine mRNA and protein is lately being utilized to understand the basic nature of this disease. Much emphasis has been laid on the expression patterns of pro-inflammatory cytokines including IL-12 and anti-inflammatory cytokines such as IL-10 and TGF-β. The expression of chemokines such as IL-8, GROa, ENA 78, RANTES, MCP-1a during disease as well as the recent therapeutic approaches that include anti-TNF, IL-1 and IL-6 antagonists are detailed. The article 'The interleukin-2 receptor γ chain: Its role in the multiple cytokine receptor complexes and T cell development in XSCID' by K. Sugamura *et al.* describes additional information about the already well-studied IL-2 receptor structure. The new found additional γ subunit of this receptor also participates as a structural constituent of other cytokine receptors such as IL-4, IL-7 and IL-9. Substantial information has been gathered about the human X-linked severe combined immunodeficiency (XSCID) syndrome as a result of structural and molecular analyses of this subunit. A more lucid and detailed comparison of B and T cell defects in XCID and knockout mice for IL-2Rγ gene is found in this article. IL-7 seems to play an important role in early T cell development.

Much needed information about immunological memory can be found updated in a very interesting article by the 1996 Nobel recepient Rolf Zinkernagel. The article exhaustively covers the information available about immunological memory and the effector mechanisms needed for its establishment. These are discussed with particular reference to cytopathic and non-cytopathic viruses and $CD8^+$ T cells. The roles of CTL precursor frequencies and T cell activation as well as the mechanism of antigen persistence during the establishment of memory are dealt with.

Thus, the articles in this well-compiled volume have concentrated relatively on T cell biology and selected disease processes while covering some new topics such as endothelial cell–leukocyte interactions and somatic hypermutations. Some topics that have been covered in previous volumes have also been updated.

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Annual Review of Plant Physiology and Plant Molecular Biology 1996. Jones, R. L., Sommerville, C. R. and Walbot, V. eds. Annual Reviews Inc., 4139 El Camino Way, P. B. No. 10139, Palo Alto, California 94303-0139, USA. Vol. 47. 787 pp. Price: $52, elsewhere $57.

Like Christmas or the New Year, people like me look forward eagerly to the new Annual Review Volume. Without doubt, the Annual Reviews are to be counted among the most significant scientific publications of our times, every volume bringing in a wealth of information and new perspectives. The publication of the first volume of *Annual Review of Plant Physiology* (*ARPP*) coincided with my entry in the Honours Course of Botany. Though the style was a bit forbidding and appeared incomprehensible, the Annual Reviews have since then been a constant companion and a source of invaluable information. A few years ago, in consonance with changing times, the *ARPP* became *ARPP & MB*. In its next incarnation one might even call it the 'Annual Review of Plant Biology' because questions even in such traditional subdisciplines as morphology, anatomy, classical plant embryology, taxonomy can now be addressed in a molecular fashion. For a time, molecular biology meant exclusive preoccupation with nucleic acids, but quite rightly we have a more mature outlook now and presently the field embraces action at the molecular level by all actors, big or small. Instead, as days go by, we are turning a full circle – 'molecular' biology is now turning more 'cellular' and already whole plant physiology (or call it plant biology) is back in fashion.

Now to the current volume. Over the years, the Annual Reviews open with an autobiographical article. These articles are a source of inspiration and strength and I have been using information of personal kind to enliven interest amongst youngsters and generate the value of patience and persistence (it is surprising how close many great scientists have been to bankruptcy or despondency such as of a 'no job' or 'dismissal' situation). And having met Jake MacMillan, it was particularly interesting to learn how he meandered from colchicine to become the world's most noted authority on chemistry of gibberellins. Of course, his caveat and lasting stamp has been in the application of GC–MS for identification and assay of these molecules (ironically, however, the introduction of this expensive technology made me quit work on gibberellins after publishing a couple of papers).

If we try to broadly classify the contents (not at all an easy job because of the growing complexity of any area and the intricate relationships to other enquiries), the majority of the 26 articles belong to what can be called the area of 'Metabolism and its regulation', with four articles relating to chloroplasts or photosynthesis, one on respiration (glycolysis), two on lipids, one each on N-metabolism, DNA damage and repair, the 14–3–3 proteins,

sucrose phosphate synthase, carbohydrate gene expression and phosphatases. The general area of 'Cell and sub-cell' includes four articles: one each on cell walls (albeit of grasses), apoplastic cell space, compartmentation of proteins (in endomembranes) and two on transport across membranes. The area of 'Growth and Development' has three articles which includes one each on light control of seedling development, xylogenesis, and chimeras. The area of 'Stress molecular biology' includes two articles – one on chilling sensitivity and another on dehydration tolerance. Much research on modern day plant molecular biology is being driven by the promise of 'Biotechnology' and this is represented by a key article of great current interest, i.e. gene silencing. Then there are various other articles of the 'Miscellaneous' category.

Among the various reviews, I found those on chloroplasts or photosynthesis, the quizzical 14–3–3 proteins, the phosphatases, light control of seedling development, molecular basis of dehydration tolerance and chilling sensitivity of great interest from the viewpoint of my own research and teaching. Photosynthesis increasingly (and appropriately too) deserves more than one article, and all the four articles are very timely. For a long time, despite the importance and the advances concerning the 'Z' scheme of photosynthesis, no one precisely understood the photosynthetic units (systems if you like) and have an idea of how excitons and electrons move in space. Thanks now to a variety of approaches, biochemical and specially biophysical such as electron diffraction and X-ray crystallography, we can now achieve a resolution of as few as 2 or 3 Å in deciphering architecture of 3-D mega complexes. The progress is salutary and remarkable when we compare the current notions with those prevalent in the sixties or even the seventies when the monomolecular layer of chlorophyll pigments dominated all thinking. The review by Green and Dunford summarizes the progress in respect of LHC II and other chl *a/b* complexes and brings out the intricacies of the geometrical configurations (or orientation) of chlorophylls and carotenoids (nothing is left of the earlier models). Similarly, the article by Cramer's group brings us up with the advances in respect of cyt b6 & f complex with emphasis throughout on structure–function relationship. The chapter by Horton and coworkers catches a glimpse of the new area of regulation of photosynthesis, the focus here being on the protection of the photosynthetic apparatus from excess light through mechanisms such as represented by the xanthophyll cycle. Finally, like Rubisco (its counterpart in C3 plants which has in past been the focus of a vast amount of research), attention is paid to PEP carboxylase in a review by Chollet and co-workers, the emphasis being on regulation strategies such as phosphorylation. Phosphorylation brings us also to dephosphorylation and thus to phosphatases (covered by Smith and Walker) which until now have been neglected compared to kinases which have so far stolen the limelight. Yet, to me the most interesting development concerns the 14–3–3 proteins. Like the name itself, function is also intriguing. The proteins apparently provide the means of a bewildering array of interactions amongst various proteins of diverse signal transduction chains, influence phosphorylations and seem to be like a major component of what may be called the plant CPU (central processing unit) as also in animals.

In the area of 'Plant Growth and Development', easily the most interesting article is by Arnim and Deng bringing alive to the reader the growing field of light control of development. The burning question currently is, what are the precise roles of different phytochromes (of which now there seem to be about half-a-dozen)? The review shows how mutants are leading the way towards understanding of their mode of action.

Closer to human survival, 'Plant Biotechnology' and 'Stress Molecular Biology' constitute other areas of present-day thrust. One of the unpleasant surprises met by a genetic engineer is that plants fight back introduced foreign genes and tend to throw them out. The review by Meyer and Saedler covers this aspect and attempts to explain why this is so. Two other reviews deal with the subject of chilling sensitivity and tolerance to dehydration. If one could understand these, one could visualize present day crops being extended to far wider areas and also the deserts becoming green.

Finally, each of the Annual Reviews does a signal service by drawing to centre-stage a somewhat neglected area, and bringing it alive from obscurity. The potpourri of articles such as on production of wax, glutathione transferases, and perhaps also xylogenesis and chimeras could be grouped in this category and they bring new and unexpected insights. A particularly valuable review is on dioxygenases which are responsible for biosynthesis of a wide spectrum of biomolecules from pigments such as anthocyanins to hormones such as gibberellins.

In the various reviews of the 'Miscellaneous' as well as other groups, one cannot help pondering over the remarkable changes in methodologies and approaches in the last decades. Everywhere, genetic engineering (overexpression, anti-sense and gene knock-out technology, site-directed mutagenesis, etc.) is expected to bring new insights. Genetic engineering in times to come has to be learnt by all researchers like chromatography, PAGE, centrifugation or spectroscopic methods, regardless of whether one decides later to go in for agricultural biotechnology or not.

To conclude, in keeping with the tradition of all Annual Reviews, the volume lives up to the highest academic standards. Nonetheless, I have a few suggestions for editors. This is in keeping with changing times. The Annual Reviews should prepare for the new century and now go for a new format of somewhat easier and more user-friendly style, with more expanded introductions and historical background (as in the reviews by Ferl or by Szymkowiak and Sussex, or Tanner and Caspari). There should also be more diagrams and in colour. In my experience, the real value of these reviews is for those working in fields other than those of the reviewers and with increasing specialization every article has to be made more readable. Rebecca Chasan was doing a splendid job for the Plant Cell. We need some more of her style, which I think – with a strong will and an editorial mandate – can be done without necessarily compromising technical quality. Also with a wider readership, the economics of more illustrations and also of colour printing can still be worked out satisfactorily. Otherwise, the Annual Reviews may gradually lose their unchallenged position to other upcoming journals and serials, some of them already doing a good job of dissemination of knowledge of plant biology.

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Medicinal and Pharmaceutical Chemistry. Harkishan Singh and V. K. Kapoor. Vallabh Prakashan, Delhi 110 034, India. 1996. (i)-(viii) + 671 pp. Price: Rs 560 or US $ 70.

This classic monograph on *Medicinal and Pharmaceutical Chemistry* is the product of labour of love of two outstanding teachers of India. That our country has made rapid progress in the pursuit of excellence in the practice of medicinal and pharmaceutical chemistry is not in doubt. In some measure, both Singh and Kapoor are responsible for this achievement by training a generation of medicinal chemists in the country.

The book is divided in 46 chapters which covers almost all the areas of medicinal chemistry starting with chemical nomenclature, international non-proprietory names (INNs), physicochemical and stereochemical aspects of drug action. The authors systematically deal with principles of pharmacokinetics and chemistry of various therapeutic classes of drugs. The areas covered are many such as anaesthetics, hypnotics, sedatives-opioid analgesics, antitussives, psychoactives, CNS stimulants and depressants, anti-Parkinson drugs, sympathomimetic, cholinergic and anticholinergic drugs, muscle relaxants, and anticonvulsants. There are separate chapters on endocrine disorders such as hypoglycaemia, hyper and hypothyroidism and others. The chapters on antihistamines, non-steroidal anti-inflammatory agents, cardiovascular drugs and diuretics are especially interesting since they describe modern advances in the fields. One of the major achievements of this monograph is that it traces the basic concepts in medicinal and pharmaceutical chemistry and then leads the reader to most recent advances in each therapeutic area. The style of presentation is lucid and absorbing and would help both students and teachers of medicinal and pharmaceutical chemistry. The book was found to be free of printing errors, which itself speaks volumes for thoroughness in its publication.

I recommend this excellent monograph to all the students and teachers of medicinal and pharmaceutical chemistry.

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