BOOK REVIEW

Advances in Applied Toxicology

Edited by A.D. Dayan and A.J. Paine

Published by Taylor and Frances, London, New York and Philadelphia, 1989. Price £30; 228 pages.

Books with catching titles and a large variety of apparently unconnected multi-authored chapters tend not to keep the promise encapsulated in the title. It is usually the general lack of focus which renders such books only peripherally interesting to most scientists. To some extent this verdict seems to be also applicable to this new book which creates the impression that it may well be the first volume of a new series, even though the publishers do not state their intention concerning further volumes.

The overall ambitious objective of the book as described by the editors in the preface is to create a bridge between scientific understanding and political and legal experience in the field of toxicology in order to arrive at a reasoned and well-informed judgement. Thus, the general approach taken in the ten chapters is to overview a subject and to come to some clear and practical recommendations or conclusions.

The presented topics can be conveniently placed into four different groups; new techniques ("Practical approach to immunotoxicity testing" by Van Loveren and Vos, "Cultured human hepatocytes as a model system" by Guillouzo et al., "In vitro techniques for assessing teratogenic potential" by Neubert), environmental carcinogens ("Testing chemicals for carcinogenicity" by Roe, "Mutagens, carcinogens and tumor promoters in food" by Wakabayashi et al., " Safety studies of irradiated food" by Elias), new biological products ("Toxicity tests" by Bangham, "Hazards of biotechnology" by Aickin) and two chapters on the toxicity of contraceptive steroids (by Gunzel et al. and Lehmann et al.).

On the whole the chapters are most informative, well written and useful. The chapter on immunotoxicity outlines the complexity of the immune system and the wide variety of agents which have been shown

to modulate it. TCDD and organotin compounds are examples of immunotoxicants and the author recommends that a flexible tiered approach should be adopted in the safety assessment of the potential immunotoxicity of chemicals. There are, however, still considerable gaps in the relevant methodology. The methodology associated with the isolation of hepatocytes and their use in pharmacotoxicological research has been described frequently in recent years and chapter 8 in the book traces the progress in this area in the last few years. It is a good introduction for the novice and appropriately refers back to a number of other recent book chapters dealing with this subject.

In vitro techniques occupy an important among methods currently available to assess the tetratogenic potential of chemicals. Chapter 9 discusses these methods and forwards proposals for studies which would form the basis for the informed judgement as to what extent such methods are suitable to replace currently used *in vivo* tests.

The book starts with a most vivid account of what is wrong with the way chemicals are tested for carcinogenic activity. In line with a campaign pursued by Bruce Ames in recent years, the author tries to change our perception of the carcinogenic risk of chemicals by stressing lifestyle and hormonal factors and the importance of non-genotoxic mechanisms of carcinogenesis. He illustrates his message with results according to which a change in the diet of rodents from unlimited food to restricted access to food had a profound influence on the incidence of malignancies. This interesting chapter is complemented by an overview of the wide range of chemical structures of genotoxins or tumour promotors occurring in foodstuffs. It is intriguing that 0.5 mg hydrogen peroxide is released per cup (150ml) of instant coffee made from roasted beans. Appropriately the authors draw attention to the importance of the quantitation of the content of genotoxins in food for a proper evaluation of the risk associated with exposure to them.

The major changes in food caused by irradiation to control microbiological health hazards result from reaction with free radicals formed primarily from the water content in food, and effect also caused by heating of food. The conclusion of this rather unexciting chapter is that adverse health effects resulting from food irradiation seem to be absent.

The most interesting chapters of this book are concerned with the toxicity and risk of products of novel biotechnological methods. Chapter 6 addresses the the risk associated with such products, e.g.

viruses, vaccines and polypeptide hormones. It draws attention to the impurities which often accompany these products and to the fact that each batch may contain different amounts of different impurities. In 1987 there were 25 licensed products consisting of synthetic peptides available in the U.K., all of them contain impurities, e.g.truncated, deaminated or oxidised peptides ("error peptides"). In the case of products recombinant DNA it is important to note that the stress associated with their production in bulk culture can give rise to molecular variants of the intended protein substance due to mutations in the plasmid of vector. It is merit of this chapter that it focusses on the different thinking required when one deals with the toxicity of such products. The conclusion of the last chapter is that the historical information concerning the nature and extent of the hazards associated with products of modern biotechnology simply does not exist. In a poignant aside, the author ruminates on the potential consequences of the now infamous study by Davanas et al. (Nature *333*, 816, 1988) in which it was shown that solutions of antiimmunoglobin E retain biological activity on dilution far below the Avogadro limit. If the paper had not been discredited it would have cast profound uncertainty on the perception of the risk associated with biotechnological products.

The message emanating from the two chapters on toxicological aspects of steroid hormones concerns the stunning difference between rodents and humans in their susceptibility to the adverse effects associated with the use of contraceptives. No single animal species used in the preclinical testing programme for sex steroids adequately predicted the human response.

Overall the book covers a rather large spectrum of different topics, all of which are of high interest to toxicologists. The book is excellently produced, sensibly indexed and deserves a place in the library of pharmacological and toxicological research departments in industry and academia.

Reviewed by Dr. Andreas Gescher, Pharmaceutical Sciences Institute, Aston University, Birmingham.

BOOK REVIEW

Biochemical and Pharmacological Aspects of Depression

Edited by K.F. Tipton and M.B.H. Youdim

Volume 3 of Topics in Neurochemistry and Neuropharmacology. General Editors M.B.H. Youdim, W. Lovenberg and K.F. Tipton. Published by Taylor and Francis, London, New York, and Philadelphia, 1989. Price £30. 146 pages.

The most interesting works with titles of this sort are written by a single author and give a new and interesting perspective on the topic. However, such books, like "The Neuropsychology of Anxiety" by Jeffrey Gray are few and far between. The book under review is a more typical volume, multi-authored, somewhat lacking in coherence, and with nothing very original in each chapter. However, I learned more about some aspects of the subject from it, and I imagine most other readers would also. In particular, this book has the great virtue of being short and clearly written. It is possible to sit down and read through it at a stretch, and gain a good overview of the current state of the subject.

The biochemistry of depression is a tantalising subject. Many of the people working in the field must have hoped that it would turn out to be like Parkinson's Disease. A clear neurochemical deficit would be found, equivalent to the striatal lack of dopamine, and this would lead to the rational design of a treatment, analogous to giving the precursor L-dopa. However, it has not turned out like that. The first relevant observations came by chance in the 1950s when it was noticed that certain drugs had an effect on mood. The compound iproniazid, developed for the treatment of tuberculosis, was found to cause euphoria. It was also shown to inhibit monoamine oxidase, and enzyme known to inactivate certain neurotransmitters, such as noradrenaline and 5-HT. This provided the first link between depression and the molecular action of a specific drug. At the same period it was also shown that reserpine, the alkaloid from the snake plant, Rauwolfa serpentina, long used in Indian medicine to treat hysteria, made depletion of monoamine neurotransmitters from their storage sites. Finally it was found that the tricyclic drug, imipramine, could relieve

depression, and also reduce the uptake of the biogenic amine neurotransmitters into nerve terminals. All this laid the basis for the biogenic amine theories of depression, propounded in the 1960s, which state that depressive symptoms are due to a decrease in the functional concentrations of noradrenaline and/or 5-HT at receptor sites in the brain.

The research of the last 30 years, as is well described in this book has explored and modified this hypothesis from many directions. Much evidence has been accumulated for the disturbance of monoamine systems in depression, from post mortem brain, CSF and platelet studies. For example many studies have shown that platelets taken from patients who are depressed are less effective than others in taking up 5-HT. However, none of these studies have clearly identified a primary basic lesion and there is usually a considerable overlap between patient and control values. Also it is not clear to what extent platelets, or post mortem material, reflect the living brain.

The major development in the 1970s was to shift attention onto the neurotransmitter receptors. A problem with original monoamine theory of depression was that it did not explain why, although the tricyclics and monoamine oxidase inhibitors had immediate biochemical action their clinical effects took two or three weeks to develop. It was thought that this problem might have been resolved when it was shown, using animal models, that both these classes of drugs, as well as electro-convulsive shock treatment, had effects on neurotransmitter receptors, such as the beta adrenergic receptor, that took this sort of time to develop. It was suggested that the basic lesion in depression might lie in such receptors. More recent research has shown how complex the receptor responses to these drugs can be, depending on dose used, time of administration, and the brain region examined. However, these complexities did not undermine the basic theory. What was needed was some way of evaluating brain neurotransmitter function in live patients while they were depressed.

In the 1980s researchers have tried to approachg this problem by challenge studies. As P. Cowen describes, in one of the best chapters of this book, the secretion of several pituitary hormones is partly regulated by monoamine neurones. It is possible to use a specific drug challenge, or probe, such as the 5-HT precursor L-tryptophan, and measure the resulting change in plasma hormone level. This gives an indication of the functional activity of the pathway with which the

drug interacts. This approach has provided convincing evidence for abnormalities in both 5-HT and noradrenaline mediated neuroendocrine responses in depression and confirms what more indirect approaches had suggested earlier. However, the differences found are still usually statistical ones between groups. Also, as was the case with the earlier studies, it is still not clear to what extent the changes found are causal. Nor have the biochemical studies led to the rational development of any clearly effective new drugs.

Recently, as outlined at the end of this book, other biochemical systems have been examined n depression, including the neurotransmitter GABA, and second messengers such as phosphatidylinositol, and cyclic AMP. Even though these have thrown up some interesting observations, it is still too early to say how significant they will turn out to be The monoamines remain, for the moment, at the centre of the stage. Maybe newer techniques, such as molecular genetics and PET scanning, will finally resolve the questions of the biochemistry of depression in the 1990s. But for a reasonable view of where things are at now one can turn to this book.

Reviewed by Dr. Vivette Glover, Queen Charlotte's and Chelsea Hospital, London.