

FOREIGN COMPOUND METABOLISM

By J. Caldwell and G.D. Paulson, editors

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Price £32.00

This volume contains the keynote lectures and invited papers presented in the plenary sessions of the First International Symposium on Foreign Compound Metabolism. This symposium was held in West Palm Beach, Florida in October-November, 1983 and was organized by the International Society for the Study of Xenobiotics (ISSX).

The book deals with five main themes: cell biology of xenobiotic metabolism; prediction of metabolic pathways; comparative xenobiotic metabolism in plants, bacteria, aquatic species and mammals; the metabolic basis of chemical toxicity; and, physiological control of metabolism. Each section has from four to seven articles, giving a total of 27. An index of 20 pages is also included.

The first section discusses cellular aspects of xenobiochemistry including the involvement of organelles other than the endoplasmic reticulum, the topography of the monooxygenases in the endoplasmic reticulum, the intralobular localizations and distributions of the enzymes within the liver, and the distribution of xenobiotic-metabolizing enzymes in tissues. The last paper specifically covered the P-450-dependent monooxygenases, glutathione transferases and epoxide hydrolase, emphasizing their concentrations in the various tissues, their inter- and intracellular locations, the presence of isozymic forms and the regulation of their levels. Section two deals with the pathways of metabolism of halogenated hydrocarbons, organo-sulphur and -nitrogen compounds as well as stereochemical considerations in drug biotransformation and disposition. The subject of unmetabolized compounds, mainly from the point of view of the accumulation of hydrophobic compounds in fish, was addressed and then the subject of predicting (or "forecasting", with the subtle semantic difference this implies carefully noted) metabolic pathways was briefly reviewed. The third section, covering comparative xenobiochemistry, opened with a consideration of economic, toxicological and environmental factors. Subsequent separate papers covered comparative aspects of oxidative, hydrolytic and conjugative reactions. The latter subject was continued with a further chapter devoted to the formation and metabolism of glutathione conjugates in animal and plant species. The fourth section consists of a wide-ranging coverage of the metabolic basis for chemical toxicity.

Opening with a chapter which discusses the problems and uncertainties which arise in studies on safety evaluation, the section continues with a review of the enzymic control of the formation of reactive metabolites through oxidative processes. Bioactivation by reductive mechanisms is then treated from the viewpoint of nitro reduction. The following paper deals with sulphation and glucuronidation, bringing together newer knowledge which shows that these classical reactions of detoxication may also lead to the formation of toxic metabolites. The following contribution addresses itself to the larger subject of the balance between metabolic activation and inactivation and how this balance, seen in the specific case of menadione metabolism in isolated hepatocytes or liver microsomes, may or may not result in toxicity. The final paper in section four concisely summarizes the studies which show that bay-region diol epoxides adequately account for carcinogenicity of polycyclic hydrocarbons. The importance of steric and other spatial factors rather than gross chemical reactivity in the toxicity of these metabolites is emphasized. The fifth section of the book is devoted to physiological factors controlling metabolism. The three chapters cover androgenic regulation of cytochrome P-450 and the effects of aging and of infection on the hepatic metabolism of xenobiotics.

The book has been produced using camera-ready copy, thus providing for rapid publication. A further advantage of this technique is the moderate price of the book. The obvious drawback with this approach is the use of several different typefaces; however, these are generally reproduced with good quality and the result is therefore typographically pleasing. Each major section of the book is preceded by a page of photographs (serious and not-so-serious) of many of the participants, a pleasant touch which no recaptures the flavour of the meeting for those who attended. This book contains a selection of timely contributions to xenobiochemistry. These cover many interesting and important areas of the overall subject and both the scientific programme committee and the many distinguished speakers must receive credit for the high standards shown in the book. While definitely a specialist volume, this book should be of interest and usefulness to all workers in the field of xenobiochemistry.

reviewed by R. Scheline

PROGRESS IN DRUG METABOLISM

J.W. Bridges and L.F. Chasseaud, eds.

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It was somewhat of a surprise to see the latest volume in this well established series – the dust jacket is green instead of the more traditional vivid pink colour. The reason for this change becomes apparent on closer inspection – a change in publishing house from Wiley to Taylor and Francis. However, the style and format inside have not been changed. In fact, the whole production is very much up to the excellent standard expected of this series.

Volume 8 contains five review articles covering a range of topics within the broadest definition of Drug Metabolism. Apart from the opening two articles, which both cover aspects of metabolic sulphate conjugation, there has been no attempt to provide a theme for this volume. This follows very much the pattern set by the previous volumes. Readers may see this as an advantage or disadvantage. It will probably increase the readership of each volume, but will probably deter the personal buyer, who may well have a particular interest in only one or two of the articles.

The book opens then with a shortish commentary by Jakoby's group (W.B. Jakoby, M.W. Duffel, E.S. Lyon and S. Ramaswamy) entitled 'Sulfotransferases Active with Xenobiotics – Comments on Mechanism'. This divides the enzymes into aryl, alcohol and amine sulfotransferases, and considers each in terms of the enzymes which have been isolated and characterised. It goes on to describe specificity of each of the enzymes and includes a discussion of present knowledge of mechanisms of the transferase reaction. This forms a concise and excellent introduction to the second, more lengthy, article in the volume, which is written by G.J. Mulder entitled 'Sulfation – Metabolic Aspects'.

In this article, after a short introduction describing the identification of sulphate conjugates in body fluids and methods for studying sulfation reactions, the author considers most aspects of sulfation or sulfonation, as he correctly states the reaction should be called. These include the bioactivation of sulfate and its availability in the body, xenobiotics which become metabolised by this route, the importance of sulfation in the metabolism of steroids, bile salts, and biogenic amines, species differences in sulfation and the competition between sulfation and glucuronidation for various substrates. This makes for a very

readable up to date account of the state of the art in this field.

The next review turns to a completely different subject in discussing the role of xenobiotic metabolism in the design of pesticides. Written by G.T. Brooks, this paper introduces the reader to the concept of foreign compound metabolism by non-mammalian species and then describes the implications of this metabolism to pesticide design under three main headings: bioactivation as a guide in design; derivatization of pesticides or their active metabolites; detoxication as an aid in pesticide design. The main themes are well illustrated with copious examples covering the entire range of pesticides, the emphasis being on molecular modification of existing compounds to develop new agents with a greater selectivity of action and/or a decreased environmental persistence. The resultant story gives a most interesting insight to this topic for readers whose main interests probably are in mammalian metabolism of therapeutic drugs. However, pesticide chemists themselves, who are perhaps less familiar with xenobiochemistry, must surely find a great deal here of major importance.

The next article, likewise, does not deal with therapeutic drug-metabolism, being a discourse on pharmacokinetics and metabolism of styrene. The authors are H. Vainio, E. Hietanen and G. Belvedere. This review discusses the modes of entry of environmental pollutants into humans and emphasises the role of drug-metabolism in their elimination. The text goes on to detail the present knowledge relating specifically to styrene, not only an important industrial chemical, but also one which is found in exhaust fumes from motor vehicles, cigarette smoke and polystyrene packing materials. The role of metabolism in styrene induced toxicity is also included. This should thus appeal mainly to industrial health and safety personnel, but should be of considerable interest to most scientists involved in many other aspects of drug metabolism as well.

The final paper of over 140 pages is an excellent attempt to bring together the wealth of knowledge on the pharmacokinetics of the benzodiazepines collected since their introduction in the early 1960's. This is no mean task and T.W. Guentert is to be congratulated on his efforts. Not surprisingly perhaps, he represents the drug company who have made the front running in this field. The details are there for the therapeutic drug expert who wishes to check a specific point. However, as with the other articles in this volume, anyone with an interest in any aspects of drug metabolism will find in this story a fascinating account of the importance of metabolism in the disposition of a series of related

compounds.

As with previous volumes, the quality of presentation of the book is superb. It has been typeset, which is always better than camera ready author produced typescripts. Despite this, the price is not excessive. An exhaustive subject index covering some 21 pages has been provided. This certainly improves the book's value as a reference source. Maybe the editors should consider a cumulative subject index in the future to cover all the volumes of this excellent series. In conclusion then, this is a book which will find a place in all Departments with an interest in any aspect of xenobiochemistry. It is certainly a must for libraries to buy, but I imagine that only a few individuals would feel able to justify the purchase of a personal copy.

Reviewed by D.J. Temple