

BOOK REVIEWS

Toxic Compounds: From Metabolism Studies to Prediction

Foreign Compound Metabolism. Edited by J. CALDWELL and P. C. PAULSON. Taylor and Francis, 1984. Pp. 328. £32.

By Wendell W. Weber

Contamination of the environment with chemicals is an increasingly burdensome problem for all forms of life. Is it possible for us to forecast the disposition of these agents in humans and other forms of life exposed to them? Can we use this information to avoid the unwanted biological consequences these agents may cause? Both of these questions are of particular interest to basic and clinical biological scientists, but ultimately the latter one is of utmost concern to everyone. This book tries to answer these questions. After an exhaustive examination of the data brought forth, the book conveys the impression that the answers are extremely difficult to attain and for now are, on the whole, more negative than positive.

Some three dozen scientists, mostly pharmacologists and toxicologists with expertise in the biotransformation and disposition of xenobiotics, addressed this and related questions at the first meeting of the International Society for the Study of Xenobiotics (ISSX) held in 1983. Presentations dealt with the cell biology of xenobiotic metabolism, prediction of metabolic pathways, comparative metabolism, the metabolic basis of chemical toxicity, and the physiological control of metabolism. The book, a report of papers read, is divided accordingly.

In part 1, Estabrook sets the stage for later discussions with an introduction to the range of adaptive cellular responses invoked by environmental chemicals. Within this framework, Bresnick discusses the components of cellular organelles, other than the enzymes of the nuclear envelope, as an architectural feature of importance in xenobiotic metabolism that the cell can apply to these stresses. Baron and colleagues draw on their immunohistochemical studies in liver to explain the additional levels of complexity which can influence xenobiotic metabolic machinery.

In part 2, the metabolic disposition of several important classes of xenobiotics is discussed. Thus, Wiersma *et al.* draw attention to observations on the microsomal P-450 metabolism of halogenated

hydrocarbons, suggesting that epoxide dehalogenated products are major precursors of DNA adducts, while aldehyde derivatives are major precursors of protein adducts. Hanzlik begins his discussion of sulfur compounds with a mini-tour de force on organosulfur chemistry, emphasizing relationships between the chemistry of these compounds and their biological effects. Cho *et al.* review the physicochemical properties of some major organonitrogen compounds as background for a discussion of oxidative and reductive biotransformations they undergo. Trager and Testa outline the gamut of differences in drug biotransformation and distribution in human and animal subjects that might be expected from differences in their stereochemical properties. Caldwell and Hutt explain how the biological consequences of Phase I oxidative reactions are much more difficult to predict than those of reductive, hydrolytic or Phase II reactions, and note a number of structural relationships between drugs which have been found to be useful in predicting differences in their metabolic fate.

In part 3, Paulson and Stegeman demonstrate the economic and toxicological significance of comparative metabolic studies to agriculture, oceanography, and human medicine using the production of metabolites more toxic than the parent compound. In Paulson's paper, the conclusion that isoniazid leads selectively to greater toxicity in genetically human rapid acetylators is put in doubt. Nevertheless, they make a convincing case for studying, understanding and using comparative metabolism in the development and safe use of xenobiotics. Wilkinson discusses metabolism and selective toxicity with the objective of determining whether there exist broad evolutionary patterns or trends that are inapparent from studies of individual systems, and of evaluating how the metabolic capabilities of different groups of individuals or organisms equip them to survive the threat of an increasingly hazardous chemical environment. An abundance of fascinating ideas is presented, including the notion that P-450 genes originated in an ancient genome which probably existed before molecular oxygen appeared on earth, and that evolution has had a favorable influence on the attainment of a high level of cytochrome P-450. Other comparative metabolism papers by Dauterman on

hydrolytic reactions, by Eadsforth and Hutson on carbohydrate and sulfate conjugations, and by Lamoureux and Bakke on glutathione conjugations document the concept that bacterial metabolism of xenobiotics is dominated by hydrolytic, oxidative and reductive reactions, whereas conjugation is much less common than in plants and higher animals.

In part 4, on the metabolic basis of chemical toxicity, a series of seven papers conclude that toxicity usually cannot be attributed to any single enzyme or enzyme system, but is due to a critical balance between metabolic activation and inactivation. In support of this conclusion, Oesch describes how differences in epoxide hydrolase, dihydrodiol dehydrogenase and glutathione transferase acting on prototypic epoxides can bring about differences in their metabolism; Mulder describes the differential effects of biotransformation by sulfate and glucuronide conjugation of lithocholic acid and arylhydroxamid acids, and Orrenius *et al.* describe how the metabolism of menadione by competing pathways can lead to toxicity differences. In the latter instance, Orrenius explains that agents that promote menadione reduction via a *one electron* pathway and *promote* toxicity are to be contrasted with agents that promote its reduction via a *two electron* pathway and *protect against* toxicity. The final paper in this section by Jerina and colleagues is an incisive review of theoretical and experimental studies leading to the first identification of the bay region diol epoxides as ultimate carcinogens for polycyclic arylhydrocarbons such as benzopyrene. Jerina explains that the diastereomeric and enantiomeric conformation of these substances is a far more important factor in the expression of their tumorigenic activity than their gross chemical reactivity.

Part 5 deals with selected aspects of physiological control of drug-metabolizing enzymes. The significance of forms of androgen-inducible P-450s which have been characterized in rats and sex-related differences in their activities is briefly reviewed by Kato and Kamataki. Katani provides a balanced critical and comprehensive assessment of age-dependent liver metabolism in man and animals. The paper of Renton and Peterson summarizes the influence of infection on metabolism of drugs, an area of investigation which may be

BOOK REVIEWS

unfamiliar to many pharmacologists and toxicologists. Thus, impaired metabolism of drugs and their subsequent elimination in man and experimental animals attributable to a wide variety of viral and bacterial infections, interferon, and a factor, or factors, released from Kupffer cells during infection is described. The effects of dietary regulation on human drug and hormone metabolism are discussed by Anderson and Kappas, who observe that dietary factors such as high protein intake, ingestion of cruciferous vegetables, and methods of food preparation enhance drug metabolism and contribute significantly to individual variation in drug elimination.

On the whole, the book is well organized and indexed. Coverage of the metabolism of environmental compounds and relevant bio-organic chemistry is extensive and of high quality, ranging from historical perspectives to experimental and theoretical molecular studies. Most of the papers are rather specialized and are of greatest interest to basic life scientists at advanced levels. Several papers can be recommended to basic science graduate students because of the lucidity or fundamental approach to their topic. These include the papers by Trager and Testa, by Caldwell and Hutt, by Paulson, by Wilkinson, by Jerina and colleagues, and by Renton and Peterson. Unfortunately, there is no concluding section that provides an overall conclusion.

We are left with the impression that metabolic studies have rather low value for predicting patterns of metabolism and toxicity of environmental chemicals in biological organisms. It is doubtful that the majority of conference participants would agree with this conclusion and it seems too pessimistic to this reviewer. It may thus be important to point out that numerous studies have appeared in the literature of human pharmacology during the past few years which provide a measure of optimism on this issue. Hereditary factors also have definite effects on the disposition of xenobiotics in man and in animal models for man. If there is a point on which the discussion in this book might be criticized, it is on the relatively limited attention paid to such studies in man, or in human tissues. Human pharmacogenetic studies have demonstrated that hereditary factors affect oxidative, hydrolytic and conjugative pathways to a very significant extent, and that these traits can predispose individuals to disorders induced by numerous drugs and probably other

environmental chemicals. However, a much broader base of such knowledge is needed to attain the high degree of predictive capability that we desire in regard to environmental chemicals.

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Insect Biology in Depth

Insect Ultrastructure, vols. 1 and 2. Edited by R. C. KING and H. AKAI. Plenum Press, 1982 and 1984. Pp. 485 and 624. \$55 (vol. 1), \$85 (vol. 2).

By N. J. Lane

Insect Ultrastructure is a two-volume edition, published by Plenum Press, containing 31 chapters produced by the efforts of 49 contributors. The books are edited by R. C. King and H. Akai, and are based in part on a conference on *The Ultrastructure and Functioning of Insect Cells*, held in 1982 in Sapporo, Japan. As the title intimates, the volumes are collections of articles on insect fine structure and present up-to-date, well-illustrated reviews. Inevitably, limitations of space decreed that studies on only certain aspects of insect tissues could be chosen for perusal in the two books. Moreover, the reader is forcefully reminded of the other limitation imposed on the subjects chosen when the editors estimate that representatives of less than 0.01% of the known species of insects have thus far been investigated under the electron microscope! The topics that have been included, in the event, include insect gametogenesis, developing somatic cells, structure, function and development of a range of specialized tissues and organs, and insect cells under certain pathological conditions. Those subjects which are covered in the resultant two volumes are, it emerges, expertly handled. The illustrations are, on the whole, of a high standard and the chapters are well written and organized, bringing together all the most recent developments. There are many useful diagrams and the subdivisions and subtitles which characterize each chapter are a great asset, since these make it possible for the reader to find any given aspect of a subject with great ease. Happily, the editors have managed to persuade many of the major investigators in the various fields to contribute a chapter to these volumes. They include

David S. Smith, who in a sense was the progenitor of these books when, back in 1968, he published *Insect Cells: Their Structure and Function*, dealing with the fine structure of insect tissues. It is striking how far the field has developed since that time, for Smith's book was, in effect, a short atlas of the different insect tissue types as viewed in ultra-thin sections, with but a brief commentary on function in each type. Now in these two larger new books we have not only the fine-structural features of insect tissues assessed in thin section, but also a whole range of other approaches to their detailed substructure. These include scanning electron microscopy, freeze-fracture replicas, isolation of cellular constituents, stereo-imaging of high-voltage micrographs, and so on. Moreover, the calibre of assessment is not limited to pure morphology, and many physiological and inventive experimental approaches have been taken to try to make order out of what is often a complex array of structures.

As for the potential readership of these volumes: clearly research workers in the various specialized fields of entomology will want to own these books, as may graduate students in the same situation. Access to these will be imperative for advanced undergraduate students doing projects in the fields of insect physiology, cell biology, pharmacology and biochemistry, as they provide the essential up-to-date background information for embarking on such research. Certainly any laboratory carrying out fine-structural investigations on insect tissues will also need these volumes, although they are too specialized for university students in the first years of study. The retail prices, US \$55 and \$85 per hardback copy respectively for Vols. I and II, may prove prohibitive to many individuals, but it is to be hoped that libraries will purchase them, as the books are certainly worth that price in terms of their splendid layout and carefully written texts.

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