Heart Association Symposium, "Regulation of Catecholamine Metabolism in the Sympathetic Nervous System," held in February 1972. The 18 papers were devoted to various aspects of catecholamine activity. This is one of the most recent reviews of this subject.

The September 1972 issue contains three reviews, one of which is "Purinergic Nerves," by G. Burnstock. This review contains data concerning a component of the autonomic nervous system which is neither adrenergic nor cholinergic but tentatively is called "purinergic" because the principal active substance released has been identified as a purine nucleotide. This is a highly interesting review worthy of careful study.

In general, both *Annual Review of Pharmacology* and *Pharmacological Reviews* contain excellent reviews and are good sources of information for anesthesiologists. However, it is noteworthy that the types of reviews in the two are different. *Annual Review of Pharmacology* tends to cover a broad range of subjects with relatively short reviews, while *Pharmacological Reviews* covers a more limited range of topics but with a more detailed discussion of each. Nevertheless, each publishes many reviews of importance and interest to anesthesiologists.

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Fundamentals of Drug Metabolism and Drug Disposition. EDITED BY B. N. LADU, H. G. MANDEL, AND E. L. WAY. Baltimore, Williams and Wilkins, 1971. Pp. 615. $19.75.

In a previous issue of this journal (ANESTHESIOLOGY 38: 516, 1973), *Fundamentals of Drug Metabolism and Drug Disposition* was reviewed, and it was recommended that this multi-authored volume be used as a textbook. Because there are a variety of environmental and genetic factors that influence the activity of the enzymes that metabolize anesthetic drugs, and because these may be relevant to the clinical practice of anesthesia, the editors thought it appropriate to have certain chapters of this book reviewed in greater detail than previously. It is hoped that the reader, in studying these chapters, may obtain a perspective necessary for understanding the metabolism of anesthetic drugs as discussed in this symposium issue.

In their highly informative and readable chapter, "The Value of Determining the Plasma Concentration of Drugs in Animals and Man," B. B. Brodie and W. D. Reid ask why drugs are metabolized at all. Their answer is that "drug metabolizing enzymes . . . were developed in evolution to permit the organism to dispose of liposoluble substances—hydrocarbons, terpenes, sterols and alkaloids—ingested in food which would accumulate to enormous levels if they were not converted to excretable derivatives." These authors speculate that "new drugs are metabolized because they simulate classes of foreign organic compounds to which animals have always been exposed." This teleologic argument is appealing because it explains why a myriad of drugs, including anesthetic vapors, can be metabolized by an enzyme system localized in the endoplasmic reticulum of the liver cell.

The chapter by H. G. Mandel, "Pathways of Drug Biotransformation: Biochemical Conjugations," and the chapter by R. T. Williams, "Species Variation in Drug Biotransformations," should be read as a unit. The chapter by Williams describes the variety of oxidative reactions catalyzed by the microsomal drug-metabolizing enzymes and the usual consequence of these reactions, namely, formation of more polar and water-soluble derivatives which are more rapidly excreted than the parent compounds. Williams also indicates that many drugs are metabolized by more than one oxidative reaction. This results in the formation of a wide variety of metabolites. This is pertinent to anesthetic drugs, because inhalational anesthetics can undergo more than one kind of oxidation reaction, *e.g.*, o-dealkylation and dehalogenation of methoxyflurane. The chapter by Mandel describes the metabolic reactions involved in the conjugation of drugs. Mandel points out that glucuronide formation is one of the more common routes of metabolism and that the activity of the microsomal enzyme system responsible for glucuronide conjugation is influenced by drugs. Glucuronide formation is an important route of metabolism for some volatile anesthetics. *In-vitro* studies have shown that several volatile anesthetics inhibit glucuronide formation at clinically useful concentrations.

Mandel also indicates that drug metabolism does not necessarily imply detoxication. This means that a metabolite can be more, or less, active pharmacologically than the parent drug, or that biotransformation may result in a product with no change in its pharmacologic properties. The significance of this is that changes in the activity of drug-metabolizing enzymes may influence the intensity or duration of action of drugs, depending on whether biotransformation results in products that have pharmacologic properties similar to, greater than, or less than, those of the parent drug. The volatile anesthetic, trichloroethylene, is metabolized by the microsomal enzyme system to metabolites that possess pharmacologic activity.

Of all the chapters considered in this review, the one by G. J. Mannering, "Microsomal Enzyme Systems Which Catalyze Drug Metabolism," and the one by H. V. Gelboin, "Mechanism of Induction of Drug Metabolism Enzymes," are the most difficult to read, because they require more than a superficial background in enzyme and protein chemistry, and both authors use experimental data to illustrate each point. Mannering discusses the

mechanism of microsomal enzymes involved in oxidative and reductive reactions and describes in detail the properties of the components of the microsomal drug-metabolizing system. There is an extensive discussion of the binding of drugs with the heme enzyme, which appears to be essential for oxidative and some reductive reactions. Whether there are two or more heme enzymes that have unique binding properties is also extensively discussed. Gelboin discusses the evidence for increased synthesis of several microsomal enzymes by drugs and presents evidence that the induction process may be mediated by an increase in RNA synthesis. The discussions in both chapters are significant because only when we understand the mechanism of drug metabolism and enzyme induction will we be able to predict a drug interaction.

How the activity of drug-metabolizing enzymes in liver microsomes is influenced by the administration of various drugs, foreign chemicals, and natural body constituents is described in the chapter, "Environmental Factors Influencing Drug Metabolism," by A. H. Conney. The importance of these factors in the development and evaluation of drugs is the subject of a chapter, "Application of Metabolic Disposition and Studies in Development and Evaluation of Drugs," by J. J. Burn. Both authors stress the importance of the environmental and genetic factors in influencing the activity of drug-metabolizing enzymes in animals and its relevance to man. Whether these factors are also relevant to *clinical* anesthesia is, at present, unknown.

Careful reading of the chapters discussed in this review should serve as a background for understanding the metabolism of anesthetics and related drugs and evaluating reports on the biotransformation of current and future anesthetics in animals and man.

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Cellular Biology and Toxicity of Anesthetics. Edited by B. Raymond Fink. Baltimore, Williams and Wilkins, 1972. Pp. 328, $20.50.

A symposium held in Seattle, May 11–12, 1970, marked another endeavor of an interdisciplinary research group to delve into the methodical study for the application of anesthesia research to cell function. The conference on "Toxic Effects of Anesthetics," held in Seattle in May of 1967, set the precedent for the organization of this 1970 symposium, in which the participants relate excitability and configurational changes in membranes to effects of inhalation anesthetics or metabolism.

The first of three sections, "Excitable Membranes," concentrates on the neuronal cell membrane as the site of action of anesthetics. K. Krnjević proposes a scheme for inhibition of mitochondrial activity. Comparative pharmacologic studies concentrate on reduction and excitability at the neuronal synapse and postjunctional membrane. H. Wollman's studies of cerebral oxygen consumption in man conclude that anesthetic dose is more important than the specific anesthetic in determining cerebral blood flow. Also, metabolic alterations, paralleling those of hypoxia, were produced by hypocarbia.

In chapter two of "Excitable Membranes," ("The Role of Divalent Cations and Certain Drugs in the Activation and Inactivation of Muscle Postjunctional Receptors"), W. L. Nastuk, J. D. Koester, and A. J. Gissen address themselves to a subject which has long been perplexing to the pharmacologist and clinician—namely, receptor desensitization on the molecular level. Despite their extensive efforts, it is noted that, "Desensitization is not usually assumed to be of prime importance." However, *in-vitro* experimentation does provide some evidence in support of this contention. In short, receptor desensitization remains highly speculative.

"Non-excitable Membranes" provides a perspective of energy transduction to structured systems of a cell and relates the coupling function of membranes to structures produced by anesthetics. Mitochondrial membrane-carrier functions are discussed in this section and R. Miller notes that these organelles "are found in each cell of the nervous system and are actually *"excitable."*

Specific examples of biotransformation of halothane and hepatic microsomal enzyme induction in animals and man are presented in "Cell Systems." The significance of species specificity is discussed.

Publication from the proceedings of the 1967 conference, *Toxicity of Anesthetics*, also edited by B. Raymond Fink, established a thorough and comprehensive format for presentation of experimental data and research on anesthetic toxicity. Similarly, both texts relate the toxic effects of anesthetics to cellular biology; both texts attempt to further research in this particular field; both are monographs; and both are valuable reference sources for the effects of anesthetics on cellular biology. However, in *Toxicity of Anesthetics*, a "Discussion after Presentation" concludes each chapter, making provision for insight into the thoughts of those who were fortunate enough to attend that meeting. It is suggested that this method of "Discussion after Presentation" would enhance the interpretation of *Cellular Biology and Toxicity of Anesthetics*. This volume is an excellent handbook and source of reference in this fast-moving field of research.

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