The Anesthesiologist's Bookshelf

Edited by MEREL H. HARMEL

Toxicity of Anesthetics. Proceedings of a Research Symposium, Seattle, May 1967. EDITED BY B. R. FINK. Baltimore, The Williams and Wilkins Co., 1968.

It would have been more appropriate to call this volume "The Toxicity of Anesthetic Drugs." Devoid of the word "drugs," the title tends to perpetuate an idea, prevalent in the minds of most students and physicians, that anesthetic drugs are a special category with nothing more than a propensity for inducing a form of unconsciousness which allows for surgical intervention, and that consciousness automatically supervenes upon cessation of administration of the anesthetic agent. It seems to be a dim realization, if at all, that it is necessary to recognize that during the course of anesthesia we are concerned not only with the effects of anesthesia but also with the effects of the anesthetic drug. The present volume is timely in the latter context by bringing together a series of papers which focus attention on what I prefer to call the pharmacologic actions of anesthetic drugs which are not necessarily, in the case of most of the papers, concerned with their propensity for producing anesthesia. As with every other class of drugs, there is a spectrum of pharmacologic effects of anesthetic agents on physiologic and biochemical systems, and this would emphasize that the induction of anesthesia with some of the agents in current vogue is not a simple, unadorned blessing for the patient. For too long, there have been those who have been charmed by the illusion that anesthetic agents are innocuous. This is probably because of the millions of persons each year who undergo some form of anesthesia for one purpose or another, and most seem to recover from the experience with no distinguishable ill effects. This, however, would appear to be more of a tribute to the remarkable capacity of the protective mechanisms of the body to cope with the insult to its integrity than to the so-called innocuousness of these drugs.

This volume, like any publication which attempts to tie together a diverse series of papers presented at a symposium, is uneven in the character of the written form of the presentation, and the quality of the work, but this does not detract from its value. The 26 papers are divided into the following categories: I. Effects in Model Cell Systems; II. Regional Cellular Effects; III. Effect on Organ Function; IV. Teratogenic Effects. Interestingly, nine of the 26 presentations have halothane or fluorocarbon explicitly stated in their titles, while studies with these are included also in other papers. This would seem to attest to the fact that despite the wide use of halothane, for example, we remain woefully deficient in our understanding of the more subtle aspects of the pharmacology of fluorocarbon anesthetic drugs.

In the first category of papers, those by Cohen and Marshall, Fink and Kenny, and Corssen explore the effects of anesthetic concentrations of halothane on mitochondrial metabolism, in the first instance, and on cell-culture metabolism in the latter instances. These investigators view their studies as being possibly pursued to the point where the depth of anesthesia may be quantitated in terms of the effects of these agents on biochemical mechanisms at a cellular level. This reviewer feels that such an objective can be realized only if such studies can be carried over to *in vivo* brain metabolism, correlated with the electrical activity of the brain at various depths of anesthesia, and, in turn, these correlated with certain reflex activities that might be elicitable under the experimental conditions. This not, incidentally, impossible.

In category II, Van Dyke recapitulates the interesting studies on metabolic transformation of anesthetic drugs that have been carried out in Chenoweth's laboratory at the Dow Chemical Co. Prior to the interesting findings of these investigators, it was common to speak of the gaseous and volatile anesthetic drugs as being inert in that they did not undergo any alteration in the body and were eliminated unchanged. Due to the work of Chenoweth and colleagues, this idea has been dispelled convincingly. The presentation by Chenoweth and Brewer in this volume on the impurities and breakdown products of various anesthetic agents cites the results of their continuing investigation into this little-recognized but important matter. The paper by Clayton on fluorocarbon toxicity is a detailed presentation of the present status of this area. This author concludes his paper by setting forth a program of the type of studies required to give a full understanding of the pharmacologic properties of these interesting compounds. The remaining papers in this category report on the effects of prolonged anesthetic inhalation, the effects on nucleic acids, and barbiturates, on catecholamine-activated lipid metabolism, and finally, the electrophysiologic changes in cardiac muscle wrought by halothane, thiopental and methoxyflurane.

The papers in category III are a varied lot, but those concerned with the aspects of hepatic toxicity of the fluorocarbons are of principal interest. Klatskin emphasizes the importance of distinguishing between true hepatotoxins and those drugs which produce sensitization reactions; as these two classes of agents differ with respect to the types of hepatic lesions and clinical manifestations they produce. Klatskin feels that halothane is probably a sensitizing agent capable of producing hepatic necrosis in susceptible individuals. He feels that even though the risk of fatal hepatitis with halothane is small compared with the overall mortality following major surgery: (1) the use of halothane should be restricted to major surgical procedures, (2) it should not be used repetitively in staged surgical procedures and (3) under no circumstances should halothane be used in a patient who has had a previous reaction to it. This, of course, points up the relevance of knowing or eliciting the anesthetic history of the patient. Klatskin does not believe there is any present justification for the abandonment of the use of halothane. This is a realistic appraisal if the use of halothane is attended with circumspection and a realization of its potentialities. Also in category III, Smuckler, Bombeck and Nyhus report on structural and functional changes in the isolated perfused liver by halothane and by chloroform. Aside from showing that the effects on the liver are not exactly similar with these two agents, they pose an interesting hypothesis with respect to the hepatic necrosis observed after repeated exposure of the liver to halothane. Since the effect of halothane on the liver is to produce an alteration in the smooth endoplasmic reticulum and its function, it is possible that halothane induces an increase in the quantity and function of this cellular organelle. As a result of this, the system may metabolize either the halothane itself or some unrecognized component with this metabolic product, establishing the series of events which lead to cellular necrosis. Greene presents a case for the use of monosaccharide transport studies in red blood cells as a model approach for investigations of the effects of anesthetic drugs on membrane transport mechanisms. Other papers in category III are concerned with fluorothane toxicity, effects of anesthetic drugs on catecholamine biotransformation, Spermidine levels as a means of assessing liver injury, intra-arterial hydrogen peroxide as an adjunct to external irradiation therapy of human malignancies, and the narcotic effects of helium and hydrogen in situations simulating depths of 1,500 to 4,000 feet of sea water. Finally, category IV contains papers about the problems encountered in assessing the teratogenic effects of diethyl ether, nitrous oxide, cyclopropane, and halothane during embryonic development.

Anyone using anesthetic drugs for whatever purpose should be aware of the studies presented in this volume by the investigators who contributed to the symposium.

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Obstetrics

THE UTERUS AND PROPRANOLOL Adrenergic blocking agents were studied to determine how they affect the actions of epinephrine and norepinephrine on the uterus during induced or spontaneous labor. The beta-blocking agent, propranolol, was infused intravenously on 24 occasions in 21 subjects. The effects of propranolol on the actions of norepinephrine were studied in five subjects. Three subjects received the alpha-blocking agent, phentolamine, prior to infusion of norepinephrine. The results demonstrated the ability of propranolol to reverse the usual uterine inhibitory and cardioaccelerator actions of epinephrine, the inability of propanolol to block the uterine stimulatory action of epinephrine and norepinephrine, and the ability of phentolamine to block the uterine stimulatory action of norepinephrine. The results suggest the investigational use of a beta-blocking agent to determine potential inhibitory effects of endogenous epinephrine upon labor. *(Barden, T. P., and Stander, R. W.: Effects of Adrenergic Blocking Agents and Catecholamines in Human Pregnancy, Amer. J. Obstet. Gynec. 102: 226 (Sept.) 1968.)*