Reports of Scientific Meetings

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Metabolic Effects of Anesthesia

The Faculty of Anaesthetists of the Royal College of Surgeons of England held a symposium on the "Metabolic Effects of Anesthesia" in London on September 18 and 19, 1970. Fifteen participants from both sides of the Atlantic presented material on subjects as diverse as the metabolism of anesthetic drugs and the effects of anesthetics on cell division and membrane transport mechanisms. The breadth and scope of the program defy summarization. How could one possibly recapitulate a talk such as that by the University of Liverpool's Dr. I. C. Geddes on aerobic and anaerobic metabolic mechanisms? Fortunately, abstracts are to appear in the near future in *The Annals of the Royal College of Surgeons of England*. However, some of the material presented was of such topical and pressing interest to anesthetists that its prompt reporting is justified, even at the expense of arbitrarily omitting much of value that was also presented.

In a discussion of the effects of temperature on cell membranes and metabolism, Dr. P. J. Goodford, head of the Biophysics and Biochemistry Laboratory of the Wellcome Research Laboratories, emphasized the importance of the fact that enzyme systems do not all respond in the same way to changes in temperature. A plot of enzymic activity as a function of temperature may result in positive exponential curves with either an almost-zero early slope or a relatively steep early slope at lower temperatures, or it may result in a bell-shaped curve. It cannot be assumed that lower body temperatures merely mean that metabolism is normal but at a slower rate. At normal temperatures, metabolic processes are *a priori* in balance. Because different enzymes have different responses to the same change in temperature, at a given level of hypothermia certain enzymes are affected more than others. The result may be that normal steady-state metabolic balances are not altered, but the rate at which they are achieved is affected, or it may be that the ability to maintain normal steady-state metabolic balances is impaired, depending upon the degree of hypothermia. Since metabolic processes are not related linearly to temperature, metabolic responses to a 5 C decrease in temperature from 37 to 32 C differ from those observed when the temperature decreases 5 C from 32 to 27 C. Dr. Goodford also stated the hypothesis that changes in membrane excitability induced by hypothermia are caused solely by changes in membrane permeability.

In discussing drug metabolism, Dr. Ellis Cohen, of the Department of Anesthesiology at Stanford University School of Medicine, noted the localization of curare metabolites in the lungs, an example, in the reviewer's opinion, of the increasing body of evidence that the lungs have nonventilatory functions of major metabolic and anesthetic importance. Dr. Cohen also noted a fundamental difference between biotransformation of diethyl ether and biotransformation of halothane *in vivo*. Ether metabolism includes the formation of nontoxic, progressively more simple metabolites, including breakdown to CO_2. These metabolites may even be incorporated into a number of normally occurring compounds. The ^{14}C of labelled ether, for example, may be found in exhaled CO_2, as well as in substances such as cholesterol. Halothane metabolism, on the other hand, involves formation of nonvolatile trifluorinated hydrocarbons, none of which enter normal metabolic pathways. Metabolism of halothane starts within moments of its administration, it involves a significant amount of the drug (9 per cent of halothane administered intravenously in animals may be accounted for as metabolites two hours later) and the excretion of metabolites is a slow process requiring days for completion. Dr. Cohen emphasized there is no proof that halothane metabolites are hepatoxic.

Dr. L. Strunin of the Department of Anaesthetics, the London Hospital, also emphasized

in the course of his discussion of metabolism of drugs by the liver that, with the exception of chloroform, there is no evidence that any of the metabolites of inhalation anesthetics are hepatoxic. In fact, a compound such as disulfiram (Antabuse), which inhibits microsomal enzymes as well as enzymic induction, *prevents* the central hepatic lobular necrosis and the increase in serum SGOT associated with chloroform anesthesia.

Dr. M. B. Chenoweth, Research Scientist in the Biochemical Research Laboratory of the Dow Chemical Co., also commented on the lack of relation between hepatic drug metabolism and hepatic toxicity. He noted, for example, that inhibition of ethanol metabolism results in hepatotoxicity while there is no toxicity when ethanol is metabolized normally.

The consensus of the symposium participants was their halothane metabolism may be related to those rare instances in which halothane is associated with hepatic damage, but that there is presently no evidence to support such a hypothesis. It is, however, a hypothesis which deserves careful consideration and investigation. The concensus drifted further from unanimity in considering development of a sensitization reaction to halothane (or its metabolites) as an explanation for halothane-induced hepatic reactions. This reviewer admits to his bias in favor of the sensitization theory on the basis of compelling personal experience; he gained the impression that some of the reluctance to accept the possibility that halothane-induced hepatitis is a sensitization phenomenon is related to inability to accept the concept that sensitization reactions exist which fall far short of the classic Shwartzman reaction.

Dr. B. A. Britt, Research Associate in the Department of Pharmacology, University of Toronto, discussed the etiology of malignant hyperpyrexia. In doing so she made a strong clinical and biochemical case for differentiation between patients who develop hyperpyrexia in the absence of anesthetically-induced muscle rigidity and patients who develop rigidity after succinylcholine and/or halothane. The former, a minority, are easier to treat, the mortality is not as great, and the hyperthermia not as severe. Hyperpyrexia preceded by rigidity represents a genetically transmitted, highly lethal condition. Dr. Britt and her associates have been able to perform a unique study of the syndrome based upon biochemical and electron microscopic analyses of vastus lateralis muscle biopsies obtained from patients who had survived hyperpyrexia episodes. Their most important finding was that halothane produced a significant decrease in calcium uptake by sarcoplasmic reticulum in patients with the rigid type of hyperpyrexia. They hypothesize that this results in abnormal energy production and utilization, associated with heat production great enough to cause marked elevations of temperature. The basis for the abnormal calcium uptake induced by halothane in these patients remains unexplained; it was not observed in biopsies obtained from normal control patients or from one individual who had experienced the non-rigid type of hyperpyrexia. Equally important was their fortuitous observation that the intravenous infusion of procainamide produced a rapid lowering of temperature (from 107 F to below 98 F within 15 minutes) in a patient with the rigid type of hyperpyrexia. If confirmed in other patients, this will represent a most important contribution to the management of this potentially lethal complication of general anesthesia.

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Surgery

SHIVERING Shivering occurred in 52 per cent of 716 patients following anesthesia with halothane. Small doses of narcotic analgesics were found to be the best method of treatment. Antianalgesic drugs caused an increased incidence of shivering. The loss of heat due to peripheral vasodilatation and the antianalgesic property of halothane are thought to be the causes of the shivering. Because shivering increases oxygen requirements, maintenance of a constant body temperature during surgical operation is recommended. (*Gozon, F.: Cause and Treatment of Spasticity following Halothane Anesthesia, Der Anaesthesist 18: 257 (Aug.) 1969.*)