# Reports of Scientific Meetings

*Nicholas M. Greene, M.D., Editor*

## Conference on Cellular Toxicity

The conference on Cellular Toxicity of Anesthetics, held in Seattle, May 11–12, 1970, at the University of Washington, represented an unusual opportunity for workers in several disciplines to exchange information about the actions of anesthetics. Organized by B. R. Fink of the University of Washington, the meeting included presentations by physical chemists, biochemists, pharmacologists, and anesthesiologists from the United States, Canada, and Great Britain. The participants were drawn from universities, research institutes, and the pharmaceutical industry.

*Anesthetic Biotransformation and Toxicity.* Additional evidence in support of the concept that biotransformation plays a significant role in the elimination of halogenated anesthetics was presented. E. N. Cohen presented data from extensive studies of nonvolatile metabolites of halothane which accumulated in the livers of mice and monkeys. These trifluorinated carbon fragments were principally bound to large molecules in the nuclei and mitochondrial fractions of hepatic cells. The fact that repeated exposure to halothane increased the metabolism of this drug suggested that enzyme induction took place. H. F. Cascorbi also reported prolonged urinary excretion of trifluoroacetic acid after intravenous administration of tracer quantities of $^{14}C$-labeled halothane to volunteers. Although anesthesiologists tended to have a higher degree of biotransformation than persons not regularly exposed to halothane, this was not invariably true. The excretion of labeled products was also related to the total quantity of all types of drugs ingested. R. A. Van Dyke reviewed possible enzymatic mechanisms of halothane biotransformation and suggested the cytochrome P 450 system as the most likely pathway. It was the consensus of several participants that the trifluorinated breakdown products of halothane may be the substances which produce acute hepatic toxicity from this agent. However, sufficient quantities of these substances for toxicity studies were not yet available.

The chronic toxicity of volatile anesthetics in guinea pigs, rabbits, and rats was summarized by M. B. Chenoweth. These animals were exposed to 0.1 MAC of ether, halothane, or methoxyflurane for seven hours a day, five days a week for six weeks. Although ether produced no ill effects, the halogenated drugs reduced growth, increased liver weight and produced hepatic cellular damage. Thus, this study supported the concept that long-term toxic effects may occur in operating room personnel and suggested that the environment there be controlled to reduce chronic exposure to these agents.

*Effects of Anesthetics on Cell Membranes.* K. Krnjevic reviewed the actions of local anesthetics on the neuronal membrane and suggested that they act to block sodium movement. He noted that the mechanism of action of general anesthetics is more obscure, but suggested that they act by depressing neuronal oxygen consumption, reducing ATP stores and thereby increasing membrane permeability to potassium. G. B. Frank continued the discussion with a review of the current theories of narcosis and advanced the hypothesis that these agents produce general anesthesia by a selective action on certain key cells within the central nervous system. His suggestion that general anesthetics impair sodium transport was supported by B. R. Fink's observations in heteroploid cell cultures exposed to halothane or amobarbital.

*Effects on Subcellular Structures.* D. E. Green discussed the architectural changes which occur in mitochondria with energy transformation. The tripartite repeating units of the inner mitochondrial membrane proceed through a regular configuration cycle as electron transfer, phosphate binding, and ATP formation occur. C. A. Taylor then reported that halothane profoundly affects the configurational cycle of mitochondria exposed to this agent *in situ* by "freezing" the membrane in an uncoupled state. This study thus suggested that malignant hyperpyrexia is secondary to an action of anesthetics at the mitochondrial level. D. E. Gatz then raised hopes that drug therapy to prevent this devastating condition might be developed. He presented evidence that haloperidol protected brain mitochondria

from the uncoupling action of dinitrophenol and was effective in preventing malignant hyperpyrexia in animals given dinitrophenol during halothane anesthesia. The drug was not effective unless administered 18 hours prior to exposure to halothane.

P. J. Cohen reported that clinical concentrations of halothane, methoxyflurane, ethylene, and diethyl ether all inhibited the respiration of rat liver mitochondria by blocking oxidation of NADH and NADH-linked substrates. Higher concentrations of these agents blocked respiratory control. Finally, J. F. Nunn reported on his intriguing studies of the effects of anesthetics on the microtubular systems of cells. Microtubules are a morphologic expression of a temporary protein framework which supports the interior of cells. Exposure of bean plants, sea urchin eggs or multinucleated protozoa to halothane was followed by reversible disappearance of microtubules. Nunn attributed the inhibition of cell division during anesthesia to this phenomenon, and suggested that these changes might serve as a model for the action of anesthetics in other locations.

*Cellular Responses to Anesthetics.* Cyclopropane has two effects on mitosis in the chick embryo. S. L. Snegireff reported that this drug produced an arrest of mitosis in the metaphase and a decreased entrance of cells into mitosis. Only metaphase arrest was present when cyclopropane concentration was 20 per cent; both changes were found with 35 per cent of this agent, while only a reduction of mitosis was seen when 50 per cent was present.

A new method of measuring the potency of anesthetic agents by the use of luminous bacteria was reported by D. C. White. The light output of the luminous marine organism *Photobacterium phosphoreum* was depressed by exposure to volatile anesthetic agents in the concentrations used in clinical anesthesia; the depression of light output was proportional to the logarithm of the concentration of the agent. The results obtained were comparable to estimates of the potency of the agents obtained by other methods, including MAC for humans. White suggested that his preparation is particularly suitable for experiments designed to test the validity of current theories of narcosis.

*Cerebral Metabolism during Anesthesia.* H. Wollman summarized the data obtained in human subjects in his laboratory with five agents: All general anesthetics studied reduced brain oxygen consumption, but the diminutions were not proportional to depth of anesthesia. No alteration in the pathways of brain glucose metabolism were detected.

J. D. Michenfelder summarized data which he obtained in the dog. Although 70 per cent $N_2O$ increased cerebral metabolic rate 11 per cent, all other agents reduced cerebral metabolism. Brain ATP, lactate and pyruvate concentrations were not altered by anesthesia without hypocapnia. With profound hypocapnia, however, brain ATP was reduced and lactate concentration, as well as the lactate/pyruvate ratio, was increased. These data thus provided further evidence that profound hypocapnia impairs cerebral oxygenation.

Michenfelder also reported the effects of anesthesia on the rate of brain ATP depletion and lactate production following decapitation. Despite the fact that cerebral metabolic rate varied with the anesthetic utilized, ATP depletion and lactate accumulation were not influenced by anesthetic agent. In contrast, hypothermia (30 C) significantly reduced ATP depletion and lactate accumulation. Thus, these data suggested that anesthetics and hypothermia reduced cerebral metabolism by different mechanisms. Furthermore, anesthesia did not appear to protect the brain from anoxia.

This section of the conference was concluded by E. A. Brunner's report of his studies of the effects of volatile anesthetics on cerebral metabolism in mice. Although all agents reduced the cerebral metabolic rate, no significant alterations of phosphocreatine ATP or lactate concentration were noted. These results thus corroborated the findings of Michenfelder in the dog. In addition, Brunner noted time-related increases in cerebral glycogen concentration with all agents. Likewise, all anesthetics increased the brain/blood glucose ratio.

The significance of these observations must await further investigation.

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