

Anesthetics and Metabolism

FOLLOWING THE ESTABLISHMENT of the foundations of modern biochemistry 50 years ago, the metabolic effects of anesthetics have intermittently attracted the attention of biochemists. The majority of this research was conducted by biochemists, because anesthetists, by and large, had neither the interest in nor the training for such work. The results were often less than satisfactory. This was due in part to limitations inherent in the development of the science of biochemistry. In part, it was due to the tendency of investigators to study nonvolatile, nonspecific and esoteric neuronal depressants. The use of narcotics, hypnotics and alcohols was explicable on the basis of their ease of handling under laboratory conditions, but the value of the study of such agents frequently was impaired by overenthusiastic and, in retrospect, simplistic use of the results to support unitarian explanations for the mode of action of anesthetics: because butanol, for example, was observed to have a particular metabolic effect, its narcotic effect was said to be the result of this effect, and, furthermore, this effect was offered as the explanation for the mode of action of *all* neuronal depressants. The significance of this type of research was further impaired because the drugs studied often were not accepted as true anesthetics by those concerned with the production of clinical anesthesia, and by the fact that the drugs employed were used in concentrations well beyond the therapeutic range.

Within the last decade the situation has changed radically. Biochemical techniques have advanced to a stage of accuracy and sophistication undreamed of 20 years ago. Equally important, research into the biochemical effects of anesthetics is now being conducted by a number of anesthesiologists who are not only acquainted with the clinical use of the drugs they are studying but are both biochemically knowledgeable and trained in modern investigative techniques. A result of this has been the appearance of an increasing number of biochemical articles of major significance and originality in recent volumes of

ANESTHESIOLOGY, including the article in the present issue by Fink and Kenny.

With the increasing interest in biochemical aspects of anesthesia, the question has been raised as to the relevance of such research. Does it represent merely abstract gathering of data for its own sake? It can, unfortunately, but it also has the potential for the derivation of information necessary for a complete understanding of the anesthetic state. In the first place, the metabolic changes produced by anesthetics may be a cause and not a result of the state of anesthesia, popular theories currently in vogue to the contrary. This possibility has been suggested by Quastel and others, but in recent years it has fallen into disfavor as an explanation for the mode of action of anesthetics as attention has been focused on biophysical interactions taking place between anesthetic molecules and cell membranes. Fink and Kenney allude to the possibility that the biochemical changes they have observed are a cause of anesthesia rather than a result, but with understandable caution they do not commit themselves. The question is not yet closed and warrants further investigation. Eventually, it may develop that the physical effects of anesthetics on membranes include interference with membrane transport of metabolic substrates, and that the result of impaired membrane transport mechanisms is alteration of metabolism to the extent that tissue depression ("narcosis") results. As Fink and Kenny, as well as others, have pointed out, anesthetics may be expected to affect all biologic membranes, not just those membranes separating cytoplasm from extracellular fluid ("cell membranes"), but also membranes investing mitochondria. Impairment of the latter would have particular biochemical significance, for within mitochondria are located many of the enzymes responsible for energy production and utilization.

The second means by which research into the biochemical effects of anesthetics may lead to a fuller understanding of anesthesia is by

offering an explanation for some of the adverse effects of anesthetics. The effect of general anesthetic agents is most manifest, of course, in the response of the central nervous system. Anesthetics, however, act not only upon nerve tissue, but upon all sorts and conditions of cells. The non-anesthetic adverse effects of anesthetics are clinically most apparent in the response of the cardiovascular system to general anesthesia. The negative inotropism characteristic of general anesthetics

may, for example, be associated with changes in cellular metabolism, even though the anesthetic state itself may be the result of biophysical events involving membranes within the central nervous system. More work is required before definitive answers can be supplied regarding the nature and significance of metabolic changes during anesthesia. But the outlook for such answers is increasingly optimistic.

NICHOLAS M. GREENE, M.D.

On the Hering-Breuer Reflex and Breathing during Anesthesia

THIS YEAR marks the hundredth anniversary of the description by Hering and Breuer of the respiratory responses to inflation and deflation of the lungs. The reflex bearing their names has been of considerable interest to anesthesiologists and to physiologists studying the control of breathing. Nerve endings in the lungs act as sensors for the regulating centers in the central nervous system to modulate the frequency and amplitude of breathing. It is now well known that this reflex is but one of the many factors influencing the act of breathing.

Breathing during anesthesia and the effect of central depressants on breathing are of primary concern to clinicians and many research workers. The Hering-Breuer reflex has been invoked to explain the rapid and shallow breathing observed during anesthesia with diethyl ether and trichloroethylene. Two or three decades ago, students of anesthesia were taught that "controlled respiration" affects the Hering-Breuer reflex and inhibits inspiration, resulting in apnea. Apparently, this teaching was a misconception and a misinterpretation of clinical observations according to current knowledge.

In this issue of the Journal, Paskin, Skovsted and Smith present evidence derived from stud-

ies in man that the Hering-Breuer reflex does not account for tachypnea encountered during anesthesia. A typical response to inflation of the lungs by imposition of an inspiratory load consisted of a decrease in tidal volume and insignificant or minor changes in respiratory frequency. Of particular interest is the observation that inflation of the lung did not evoke appreciable inspiratory inhibition except on occasions during cyclopropane anesthesia, given after premedication with morphine. Their experimental approach is admirable in its simplicity, and the results may remove yet another misconception concerning the respiratory effects of certain anesthetics.

Paskin, Skovsted and Smith properly point out that general anesthetics depress the respiratory control mechanism. This view has been supported amply by recent studies in animals and in man, some of which are referred to by the authors. The extent of depression depends on the anesthetics used and the level of anesthesia achieved.

Failure to demonstrate the reflex response is explained by the hypothesis that the Hering-Breuer reflex is not active in man or that a depressed control mechanism cannot respond even though the pulmonary stretch receptors may be sensitized. Anesthetic sensitization of