whose members are critical observers of anesthetic procedures, will provide us with a meaningful index of "anesthetic risk."

ARTHUR S. KEATS, M.D.
Chief
Division of Cardiovascular Anesthesia
Texas Heart Institute
Houston, Texas

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Halothane and Regulation of Respiration

CONDUCTING RESEARCH on man is potentially hazardous, and often impractical under modern constraints. Nevertheless, physiologic differences among species dictate that pharmacologic and physiologic information learned in laboratory animals be independently verified in man.

The report from London, Ontario, presented elsewhere in this issue of ANESTHESIOLOGY,[1] confirms in man important data gathered in dogs, first in San Francisco,[2] and later in Denver.[3] It is of some pragmatic value for the clinician to know that halothane depresses the ventilatory response to hypoxia in man. As further guidelines, codes and regulations for human research continue to evolve,[4] it may become less likely that we will have repeated opportunities to confirm, in man, the work reported by Drs. Knill and Gelb. It is, therefore, all the more important that this report, and the authors' conclusions, be examined carefully.

One may take issue with some of the methods used. Anesthesia was induced with a barbiturate, which may depress hypoxic stimulation of ventilation for a considerable period.[5] The hypotension seen in the anesthetized subjects may alter chemically induced changes in ventilation.[6,7] Repetitive hypoxic, hypercapnic, or "isocapnic" hypoxic testing may alter central P_{CO_2} for longer than the time allowed between tests.[8] These objections are relatively minor and do not qualitatively invalidate the results. It remains clear that Drs. Knill and Gelb have demonstrated in man that 0.1 MAC halothane blunts the ventilatory response to hypoxia, while 1.1 and 2.0 MAC halothane severely depress or abolish that response.

Anesthetic concentrations of halothane depress the ventilatory responses to hypercapnia–acidosis (CO_2–$[H^+]$) and hypoxia. It may be debated whether

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one response is depressed to a greater extent than the other. In dogs, the interaction of hypoxia and CO_2–$[H^+]$ in driving ventilation is destroyed by halothane anesthesia.[2] Drs. Knill and Gelb reported that they measured the hypoxic hypercapnic responses during 1.1 MAC halothane in eight subjects, and found a decrease in slope of $\dot{V}_E$ *vs.* P_{CO_2} from 0.25 $l \cdot min^{-1} \cdot torr^{-1}$ during normoxia to 0.18 $l \cdot min^{-1} \cdot torr^{-1}$ during hypoxia. Unfortunately they did not include either individual data or statistical assessment to allow the reader critically to evaluate the data.

Perhaps the most interesting and surprising information they present is that in a concentration as low as 0.1 MAC halothane greatly decreases the ventilatory response to hypoxia, while failing to alter the ventilatory response to CO_2–$[H^+]$. Yacoub *et al.*[9] obtained similar results in human subjects breathing nitrous oxide, 30–50 per cent.

Despite the finding of Drs. Knill and Gelb that halothane also blunts the ventilatory response to doxapram, we should be careful about concluding that halothane exerts its ventilatory effects solely through the carotid body. Although doxapram appears to stimulate ventilation in parallel with hypoxia,*[10] it is not certain that in man the pharmacologic action of doxapram is mediated through the carotid body. Biscoe and Millar failed to show a decrease in firing of the carotid sinus nerve in response to hypoxia when halothane was added to pentobarbital anesthesia in cats,[6] although that result may have been caused by a limitation of their experimental design. Human subjects, following denervation[11] of their carotid chemoreceptors, show respiratory depression with hypoxia. The cause may be frank central neural depression or cerebral blood flow-mediated decrease in CO_2–$[H^+]$ stimulation.[8] Those subjects[11] did not (with two exceptions), manifest depression of slope of $\dot{V}_E$ *vs.* P_{CO_2} when challenged with hypoxia. Weiskopf *et al.*[2] did demonstrate such depression in dogs, with halothane. The nature of the response shown by the subjects of Knill and Gelb is not clear from the data presented. If all their subjects manifested depression similar to that which I was able to calculate for the single subject whose data are presented in their figure 2, then it would appear that halothane in man causes depression greater than that caused by complete loss of carotid-body function. Thus, whereas the depression of the chemical drive to ventilation may, in part, include a mechanism involving the carotid body, it would appear that at least one additional site of action must also be involved, as we have previously observed.[2]

Evidence for such an additional site may now be found in the work of Derenne *et al.*,[12] Tusiewicz *et al.*,[13] and Jones *et al.*[14] Derenne *et al.*[12] found during methoxyflurane anesthesia, in man, a relatively unchanged central drive producing a decreased tidal volume as a result of an increased effective elastance of the respiratory system. Tusiewicz *et al.*[13] and Jones *et al.*[14] showed that halothane depresses the increase in that part of the ventilatory response to CO_2–$[H^+]$ performed by the intercostal muscles. This may, in part, be due to elimination of non-respiratory-related neural input to the alpha motor neurons of the intercostal muscles.

Much of Drs. Knill and Gelb's discussion regarding the function of the carotid body and the effects of anesthetics is speculative. Physiologists do not agree how the carotid body transduces low P_{O_2}, or high P_{CO_2}–low $[H^+]$, into increased ascending neural traffic. It is difficult to describe effects of anesthetic agents upon a poorly understood physiologic process. Nevertheless, the clinician should be aware of a few important points. Halothane in anesthetic and subanesthetic concentrations depresses man's ventilatory response to hypoxia. Nitrous oxide has a similar effect in concentrations of less than 50 per cent. Low doses of narcotics and barbiturates have similar effects. The clinician should be alerted that the old dictum hailing the carotid body as the "ultimum moriens" (last to die)[15] can no longer be functionally applied to the practice of anesthesia. A patient who is anesthetized with a general anesthetic, or who is recovering from general anesthesia or premedication, should be regarded as having greatly diminished, if not absent, ventilatory chemoreflexes, and he should be attended to accordingly.

Richard B. Weiskopf, M.D., LTC, MC
Chief, Division of Combat and Experimental Surgery
Department of Surgery
Letterman Army Institute of Research
Presidio of San Francisco, California 94129

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