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Of Coliforms and Cancer

THE DISCOVERY that general anesthetics undergo significant metabolism *in vivo* and the mounting evidence that products of this metabolism may produce significant adverse effects surely rank as a major challenge to our specialty. Although the liver is considered to be of predominant importance in this respect, it is by no means unique, since microsomal enzymes may also be found in the kidney, lung, gastrointestinal tract, thyroid, testis and adrenal.[1] In this month's issue of ANESTHESIOLOGY, Hong and associates[2] present the fascinating possibility that normal intestinal flora may contribute significantly to the biotransformation of nitrous oxide. With impeccable analytic methodology, they have demonstrated convincingly that it is bacteria rather than the enzymes of intestinal cells that are able to reduce N_2O to N_2. Furthermore, they give reasonable evidence that conditions pertaining in the normal intestine permit extrapolation of these *in-vitro* findings to the intact organism, be it man or mouse.

Do these findings have implications for clinical practice? It is unfortunate that the authors have left us dangling in this respect. They cite evidence that "the metabolic route from nitrous oxide may include free radical intermediates" and express the belief that such "free radicals are important in the etiology of carcinogenesis, teratogenesis and associated tissue damage." They also suggest that production of potentially carcinogenic or teratogenic N-nitroso compounds from "metabolism of nitrous oxide might be potentially toxic even if this were to occur in very small amounts." They thus imply that there is new evidence for the mutagenicity of N_2O. In today's climate of political, ecologic, and regulatory concern, this implication must be put in proper perspective.

The relationship of N_2O to adverse cellular effects is most controversial. The literature abounds on all sides of the question, and is sufficiently familiar not to warrant review at this time. However, in considering the specter that has been raised, a number of questions must be addressed. It is obvious that neither potentially hazardous free radicals nor N-nitroso compounds have been identified; that was not the purpose of the investigation. For this reason, one cannot yet make definitive statements concerning either the existence, duration of existence, or specific mutogenic properties of the suspected intermediates.

Perhaps more to the point, if we accept the potential hazard resulting from biotransformation within the intestine, how much *increased* risk does this phenomenon actually impose? Do similar metabolic processes occur in normal unanesthetized man? Recently, Tannenbaum and co-workers[3] demonstrated that nitrite and nitrate are produced by endogenous synthesis in the human intestine. They concluded that this results from "heterotrophic nitrification of ammonia or organic nitrogen compounds" in the upper aerobic intestine. Passage of the material into the more anaerobic portion of the gut then allows production of nitrite and nitrate. In a manner parallel to that taken by the Stanford group, Tannenbaum *et al.* concluded that "some of the nitrite may react to form N-nitroso compounds," "human exposure to nitrite is much greater than previously recognized," and "intestinal nitrification may contribute to the etiology of cancer in humans."

It would appear that both groups of investigators have proposed a potentially serious hazard deriving from what may be similar pathways in the metabolism of nitrogenous compounds within the human intestine. What is the magnitude of this metabolism in awake man as compared with the findings of the Stanford group? Tannenbaum *et al.*[3] studied six healthy males receiving a protein-free diet during a ten-day period. Their average daily urinary nitrate excretion was 1,265 μmol, while the average nitrate intake was only 67 μmol. The highest daily nitrate excretion exceeded intake by more than 1,700 μmol. Let us compare these figures with those that may be derived from the data of Hong *et al.*[2] If each gram of human large intestinal contents produces 103 nmol of N_2 in 16 hours, and if human gut contents represent 3.3 per cent of total body weight, a 70-kg man continuously exposed to N_2O should produce 300–400 μmol of N_2 in a 24-hour period. This corresponds closely to the 1.0 ml of N_2 that Hong *et al.* have postulated would result from the action of intestinal bacteria on the N_2O taken up during a three-hour period of anesthesia. This represents *only* 25–33 per cent of the continuously occurring metabolism of nitrogenous compounds described by Tannenbaum.[3]

It may be simplistic to relate the biotransformation of N_2O to endogenous nitrite and nitrate production. Nonetheless, there are metabolic similarities in the two processes, both of which have been indicted as potentially harmful. If these similarities are real, should the colonic metabolism of N_2O, quantitatively insignificant when compared with background bio-

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transformation, constitute a serious threat to its clinical use?

In perhaps a lighter vein, Brice *et al.*[4] have stated that nitrous oxide is a normal atmospheric contaminant (0.3 ppm). Thus, even unpolluted air may be hazardous to the health, from its content of either N_2O or N_2, the latter having been shown by Winter *et al.*[5] to produce a slight anesthetic effect.

Hong and colleagues have performed a valuable service in bringing an important concept to the anesthetic literature. It is to be hoped that the issues they have raised do not cloud the most important question of delayed anesthetic toxicity resulting from biotransformation. Only continuing research as fastidious as that demonstrated by their analytic techniques will be able to furnish the desired information.

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