to those in our published work comparing thumb adduction with inspiratory force. That is, the *d*-tubocurarine requirement for 90 per cent depression of diaphragm activity was double that needed for 90 per cent depression of hand muscles.

We agree that all neuromuscular studies should use standard stimulus patterns, and those presented by Ali and Savarese could serve as a useful model. In addition, we feel that dosage schedules should be similar when it is clinically possible.

JOHN H. EISELE, JR., M.D.
Professor
Departments of Anesthesiology and Human Physiology
University of California at Davis Medical School
Davis, California 95616

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Chronic Anesthetic Exposure—What Is the Margin of Safety?

To the Editor:—The problem of evaluating the risks associated with chronic low-dose anesthetic exposure is clearly difficult and of immediate concern. We believe that the opinion voiced in a recent editorial,[1] namely, that there is a considerable margin of safety in this area and that halothane is probably not the cause of the increased incidence of congenital abnormalities and spontaneous abortions reported for operating room personnel,[2,3] is both premature and counterproductive for the implementation of efficient gas scavenging procedures. The editorial statement referred to above was based on the lack of observable teratologic effects during a study in which mice were chronically exposed to several doses of halothane prior to mating and throughout pregnancy.[4] While no genetic effect was observed in this particular study, there are several lines of evidence that indicate that halothane may give rise to mutagenic metabolites. Garro and Phillips[5] have reported that 2-bromo-2-chloro-1,1-difluoroethylene (BCD) a presumed halothane metabolite,[6] induced mutations in both the Ames Salmonella test and in a direct DNA mutagenesis assay. Furthermore, investigators at Stanford have found that a second halothane metabolite, 1,1-difluoro-2-chloroethylene, also is mutagenic by the Ames test.[7] The Stanford group also observed that BCD can be generated non-metabolically from halothane in anesthesia machines equipped with soda-lime canisters.[8] The possibility that halothane may produce genetic effects in some species, particularly when administered with other anesthetic agents, must be considered in light of a report that has been submitted by Dr. W. B. Coate *et al.*,[9] of Hazleton Laboratories, to the National Institute of Occupational Safety and Health (NIOSH). In the Hazleton study, halothane, 1 part per million (ppm) with nitrous oxide, 50 ppm (twice the recommended exposure limits[10]), and halothane, 10 ppm, with nitrous oxide, 500 ppm (the average of unscavenged operating rooms), were administered to rats. The results showed dose-dependent increases in cytogenetic aberrations in both bone marrow and spermatogonial cell populations, as well as a decrease in ovulation and implantation efficiency at the higher level of exposure, and retardation in fetal development at both levels of exposure. Although it is not possible to determine on the basis of this study whether the cytologic and reproductive effects would have been seen if halothane or nitrous oxide had been administered separately, the results do illustrate another question that must be explored in more detail, namely, the problem of multifactor etiology. It has been well established in a variety of systems that exposure to more than one genetically active chemical can have a synergistic effect on morbidity.

Exposure limits are meant to provide a margin of safety. In our opinion, it is not possible at the present time to evaluate how great a margin is encompassed by the recent NIOSH standards.[10] It seems that the most reasonable course to follow in view of the suggestive evidence of problems associated with chronic anesthetic exposure is to strive to decrease to the absolute minimum possible, by currently available technology, the occupational exposure to all anesthetic agents.

ANTHONY J. GARRO, PH.D.
Associate Professor
ROBERT A. PHILLIPS, B.S.
Graduate Student
Department of Microbiology

RALPH A. MILLIKEN, M.D.
Associate Clinical Professor
LESLIE RENDELL-BAKER, M.D.
Professor and Chairman
Department of Anesthesiology
Mount Sinai School of Medicine
New York, New York 10029

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