The Study of Cyclopropane

To the Editor:—I would like to express my appreciation of the editorial, "Thoughts on a Paleoanaesthetic" (Greene, N.M., ANESTHESIOLOGY 40:320–322, 1974), which served as a highly effective and objective introduction to the following article on sympathetic nerve activity during cyclopropane anesthesia by Fukunaga and Epstein.

The articles were brought to my immediate attention by a fellow staff member, one of Doctor Rovenstine's last residents, who elects to remain anonymous. He was surprised to find my name included in the first clinical paper on cyclopropane. Reference to the authors as Stiles, Neff, Rovenstine and Waters on this epochal presentation merits an explanation from the most junior member of the team.

At the conclusion of the cyclopropane study, Dr. Waters, always referred to as the "Chief," asked each of us independently to write the whole paper. This we did. Individual differences of interpretation of the same laboratory and clinical data were beautifully resolved by Dr. Waters and his first assistant, Dr. Rovenstine. The final draft of the paper was read by Dr. John Stiles, a junior resident but senior to me. Not only were residents encouraged to work diligently in the laboratory and operating theaters, but Dr. Waters insisted on giving undue prominence to their contributions at the time of publication.

It is well known that Henderson and Lucas of the University of Toronto discovered the anesthetic properties of cyclopropane quite by accident, during a search for impurities in propylene. Practically unknown is the fact that the same investigators subsequently studied three of its methyl-substituted compounds. Methyl, dimethyl, and trimethyl cyclopropane, prepared for them by E.R. Squibb, proved to be powerful anesthetics. The accompanying untoward effects in animals (cats) were too numerous to indicate that any of the three would ever be suitable for clinical investigation.

Dr. Waters held the work of Henderson and Lucas in such high esteem that he began his clinical investigation of cyclopropane earlier and pursued it with greater intensity than investigations of any of the other anesthetics submitted for study.

The baroreceptive activity demonstrated by Fukunaga and Epstein is a welcome explanation of the well-maintained blood pressure observed during light and profound cyclopropane anaesthesia.

Guedel was the only anesthetist whom I have seen regularly administering 40 per cent cyclopropane in oxygen and demonstrating the return of the heart rate to control ranges, as noted by the authors. Guedel had a great fear of operating with the patient lightly anesthetized with any inhalation agent except nitrous oxide. The muscle relaxation produced by 40 per cent cyclopropane in oxygen with controlled respiration compares favorably with the flaccidity of spinal anesthesia. At this time Guedel's tremor precluded his use of spinal anesthesia.

Harold Griffith, on the other hand, never feared operating with the patient lightly anesthetized with any agent. Prior to the advent of cyclopropane, he did not hesitate to potentiate ethylene anesthesia moderately with weak concentrations of chloroform. It is understandable that Griffith and the surgeons both welcomed the advent of curare for relaxation during light cyclopropane anesthesia.

Although my name has been closely associated with the introduction and promotion of meperidine (Demerol, Pethidine)–nitrous oxide anesthesia, with *d*-tubocurarine for relaxation, because of my continued use of cyclopropane, often under circumstances regarded by Rovenstine as "life saving." I now find myself categorized as an "oddity."

I submit that cyclopropane in nonexplosive concentrations (less than 2 per cent) will fortify the quality of nitrous oxide anesthesia which has been induced with thiopental. Cyclopropane, even in these low concentrations, will provide the freedom from reductions of arterial blood pressure referred to in the editorial.

The reference to Brian Sword and the introduction of the "circle" absorber, which was designed, constructed, and given to him by Dr. Richard V. Foregger, vividly brings to my mind another important event. Brian

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Sword visited the University of Wisconsin during my residency, at which time I witnessed the following conversation between Dr. Sword and Dr. Waters.

Dr. Sword: "Ralph, why do you persist in employing the rather cumbersome "to-and-fro" method of carbon dioxide absorption rather than use my circle filter?"

Dr. Waters: "Brian, I believe one day someone will come up with a pump and I would not be at all surprised if the Venturi principle is employed."

More than a decade later, Revell introduced a pump (turbine) into the carbon dioxide absorption circuit. Later, when a former Stanford resident, Dr. Richard Thompson, suggested using the anesthetic gases as the power source of the pump, we worked together to perfect a Venturi circulating system, thereby implementing a suggestion, if not a recommendation, of Dr. Waters.

It is not only my hope but my expectation that both the editorial and the following cyclopropane study will encourage further laboratory and clinical examination of an anesthetic agent introduced by giants in pharmacology and anesthesia respectively, Velyien Henderson of the University of Toronto and Ralph Waters of Wisconsin.

WILLIAM B. NEFF, M.D.
11 Granite Court
San Carlos, California 94070

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"Halothane Hepatitis"

To the Editor:—It has been postulated that "halothane hepatitis" could be a hypersensitivity response to an antigen resulting from the combination of a metabolite of halothane with protein. Dr. Mathieu and colleagues have demonstrated that a trifluoroacetate–protein conjugate is antigenic in Hartley guinea pigs.[1] These authors rightly express caution, however, about the extrapolation of their results to the clinical situation.

We have, in fact, already completed a study of ten patients and doctors in whose cases we held a high index of suspicion that halothane might be responsible for their hepatic dysfunction. Trifluoroacetate was chemically conjugated with both human serum albumin and liver specific protein. *In-vitro* tests of lymphocyte transformation and leukocyte migration inhibition were performed in the presence of these potential antigens. All of these tests have produced negative results. A full report of this work is in preparation. At the present time, we would suggest, therefore, that there is no evidence to support the concept of hypersensitivity resulting from a metabolite of halothane. On the other hand, it is possible that we have not selected the appropriate antigenic model. The work of Dr. Mathieu's group is, however, of particular interest, since Hitt and colleagues[2] recently demonstrated that isoflurane is also metabolized in man to non-ionic fluoride and the evidence strongly suggests that trifluoroacetate is the metabolite concerned!

B. WALTON, M.B., B.S., F.F.A.R.C.S.
Senior Lecturer
B. R. SIMPSON, D PHIL. (OXOM) F.F.A.R.C.S.
Professor
Anaesthetics Unit
The London Hospital
L. STRUNIN, M.D., F.F.A.R.C.S.
Reader in Anaesthetics
Kings College Hospital
London, England

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