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EDITORIAL VIEWS

Pharmacogenetics and the Halothane Hepatitis Mystery

You can just see a little peep of the Passage in Looking-Glass-House if you leave the door of our drawing room wide open; and it's very like our passage as far as you can see, only you know it may be quite different on beyond. . . .

Lewis Carroll, Through the Looking-Glass

THE ISSUE of the existence and significance of the entity termed "halothane hepatitis" is as recondite as Carroll's obfuscated view. Invectives and half-truths have been hurled like Jovian thunderbolts back and forth between hepatologists, surgeons, anesthesiologists, toxicologists, and other ostensibly erudite professionals, both from academe and the clinical firing line. Such disputations concern the reality, putative toxic mechanism, and incidence of the complication of halogenated anesthetic-induced hepatic necrosis. Patients have meanwhile been sitting as spectators in the proverbial no-man's-land generated by our egregious lack of knowledge. The importance to the specialty and to our wards is weighty since many new, useful and incompletely explored anesthetics are of the halogenated genre.

When halothane was introduced into practice over two decades ago, it represented a quantal leap insofar as safety and versatility of anesthesia was concerned. While not entirely halcyon, it was certainly an auspicious and welcome addition the specialty. One prominent effect was liberation from the manacles of flammability enabling sophisticated and pragmatic electronic monitoring systems to develop. Isolated, anecdotal case reports of unexplained and unpredictable jaundice following otherwise uneventful anesthesia had a dampening effect and reached sufficient pitch by 1960 to launch the National Halothane Study.[1] Unfortunately this Brobdingnagian epidemiologic opus was absolutely inconclusive. Inability to reproduce "halothane hepatitis" in experimental animals, a frustrating turn of events, cast any mechanism of toxicity into the realm of speculation, and placed ultimate diagnosis at the whim of whomever might be the proverbial caster of stones. Predicated on the rather inchoate hint that second or multiple administrations of halothane were associated with a higher incidence of jaundice coupled with the publication of positive "challenge tests", the allergic theory of halothane hepatitis was conceived. A variety of caveats and injunctions, most totally unprejudiced by scientific validation, were promulgated as *ex cathedra* and influenced practice considerably. In the mid-1960s a revelation was introduced concerning the pharmacology of halogenated inhalation anesthetics. Since their introduction, these drugs had been deemed immutable by the body's biochemical machinery. However, advances in analytic techniques produced the amazing if not belated discovery that they are, in fact, rather extensively biotransformed by hepatic microsomal enzymes.[2,3] Almost simultaneously, toxicologists found that "classic" hepatotoxins such as carbon tetrachloride are not destructive by virtue of the parent molecule; conversion to reactive intermediates is the proximate vector of toxicity.[4] Sophisticated biochemical juggling has now produced animal models of hepatotoxicity which are certainly due to halothane metabolism. The essence of toxicity in these presumed facsimilies of the human problem seems due to formation of reactive intermediates from non-oxygen dependent (termed somewhat incorrectly, "reductive") cytochrome P-450 mediated biotransformation. Since alterations of metabolism of xenobiotics can be ascribed to either environmental (drug induction) and/or genetic determinants, Gourlay and his associates from the University of South Australia have quite properly taken a Carrollian peep at genetic differences of halothane biotransformation in three strains of rats in this issue of ANESTHESIOLOGY. As could be predicted, they have found differences using the now classic hypoxic-

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phenobarbital-induced rat model. Immediate transsubstantiation of such data to humans, a dangerous gambit at best, would imply that certain individuals may be more susceptible genetically to this complication than others. Halothane hepatitis would thus be cast in the lot of a multifactorial event, involving variables such as splanchnic blood flow, hepatic oxygenation, qualitative and quantitative aspects of enzyme induction, but pivoting about a pharmacogenetic axis. This speculation is made more appealing because there is information that certain racial characteristics may produce a high rate of jaundice following halothane.*

In spite of advances in knowledge made by the Flinders group and others dedicated to clarifying this arcane issue, the allergy theory is alive and well. A recent publication notes evidence of hepatocyte reacting antibodies gathered from patients who suffered fulminant hepatic failure following halothane anesthesia.[5] The final mosaic produced by melding the biochemical activation hypothesis and the allergy theory, like Carroll's dark and obscure passageway, is certainly not effulgent at this time. It may be, as so often happens, that both these seemingly adversarial concepts are partially true, partially untrue. An initial biochemical event, *e.g.*, increased "reductive" biotransformation, environmental and/or genetic in origin, leads to early hepatocyte damage. This destruction may be aided and abetted by an immune response which intensifies and perpetuates the lesion. Such an hypothesis could not only unravel the Gordian Knot of challenge tests, second administrations, age and obese proclivities etc., but could explain the differences between mild and reversible cases of hepatic disturbance *vs.* the frequently lethal fulminant hepatic destruction observed. Certainly the plenary truth is still obscured, but work such as this of the group from Australia, however irrelevant it may seem to the uninitiated, is accretion of knowledge eventually contributing to patient safety, our ultimate goal.

* Bunker JP: Unpublished observations.

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References

1. Bunker JP, Forest WH, Jr, Mostell F, et al: The National Halothane Study: A study of the possible association between halothane anesthesia and postoperative hepatic necrosis. Bethesda, MD, NIGMS–NIH, 1965
2. Stier A, Alter H, Hessler O, et al: Urinary excretion of bromide in halothane anesthesia. Anesth Analg (Cleve) 43: 723–728, 1964
3. Van Dyke RA, Chenoweth MB, Van Poznak A: Metabolism of volatile anesthetics. I. Conversion *in vivo* of several anesthetics to 14 CO_2 and chloride. Biochem Pharmacol 13:1239–1248, 1964
4. Recknagel R, Ghosal A: Lipoperoxidation as a vector in carbon tetrachloride hepatotoxicity. Lab Invest 15:132–146, 1966
5. Vergani D, Miili-Vergani G, Albert A, et al: Antibodies to the surface of halothane-altered rabbit hepatocytes in patients with severe halothane-associated hepatitis. N Engl J Med 303:66–71, 1980

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Blood Glucose Control during Surgery

THE MANAGEMENT OF DIABETES MELLITUS, including its acute complications of ketoacidosis and hyperosmolar coma, has undergone and is continuing to undergo revision. Rediscovery of old programs, return to rigid control of hyperglycemia, and attempts to achieve normalization of blood glucose have occupied the energies of clinicians and investigators over the past decade. Amidst this whirlwind of activity in diabetes management, it is not surprising that the sacrosanct arbitrary insulin regimens utilized for control of blood glucose during surgery should be scrutinized for their effectiveness and scientific merit. Insulin resistance occurs during surgery due to a combination of factors involving the secretion of hormones antagonistic to insulin action,[1] the administration of glucose solutions during surgery and in the postoperative period, and an apparent cellular hyporesponsiveness to endogenous insulin in nondiabetics[2,3] and to exogenous insulin in diabetic patients.[3] Logically, to meet this challenge of surgery, the insulin dosage to control hyperglycemia should be determined by the level of glucose during surgery as in the routine management of diabetic patients. For convenience, clinicians have accepted the alternative of arbitrary insulin regimens

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