Anesthesiology
V 45, No 6, Dec 1976

Special Article

Pathologic Effects of Chronic Halothane Inhalation:

An Overview

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RECENTLY, an American Society of Anesthesiology-sponsored survey of the effects of the operating room environment on personnel suggested that chronic exposure to trace amounts of anesthetic in the ambient air might constitute a potential hazard.[1] The report of the Ad Hoc Committee complemented other animal and human studies suggesting that prolonged exposure was related to increased incidences of cancer, hepatic disease, spontaneous abortion, and congenital abnormalities.[2–9] These reports supplement existing concerns of possible toxic effects of acute exposure to a variety of anesthetics.

Perhaps the most extensive studies of possible toxicity concern halothane and the liver. Hepatitis following exposure to halothane has been reported frequently.[10–21] Possible etiologies have been reviewed by various investigators.[21–22] Although there are suggestions to the contrary,[21] halothane hepatitis has generally been accepted as a pathologic entity.[23] In addition, recent studies have demonstrated that hepatic lesions similar to those found in man could be induced in rats[24–27] and guinea pigs[28] after single or repeated exposures to halothane.

We have been studying the effects of chronic exposure to halothane in the rat, with particular emphasis on ultrastructural alterations of three organs—the liver, kidney, and brain. Results indicate that the morphologic changes that occur mimic toxic changes caused by other cytogenic substances such as carbon tetrachloride.

This review collates our results with findings reported by others and presents, we feel, a strong case for the toxic potential of halothane. For detailed information concerning individual experimental designs and findings, refer to the original articles.

Pathologic Effects on the Liver

Effects of Anesthetic Concentration

Because of the controversy concerning halothane and hepatic necrosis, a pathology panel was formed as a part of the National Halothane Study (conducted by the National Academy of Sciences–National Research Council) to investigate the pathology of "halothane hepatitis."[29] It was found that the hepatic necrosis had no consistent pattern, varying from minor focal lesions with either random or regular zonal distribution to total parenchymal destruction. In some instances, the necrosis tended to occur in the vicinity of the centrilobular vein. Ultrastructural studies of hepatitis induced by acute exposure to halothane have been performed in both man and animals.[30–37] The general pathologic changes consist of swelling and necrosis of the liver cells, especially in the central zones, with inflammatory infiltrates. The cells appeared dark and shrunken in some areas, swollen and pale in others. Active parenchymal hepatitis with foci of hepatocellular necrosis, alterations in cytoplasmic reticulum and bile canaliculi, mitochondrial changes, and myelin-figure formation have been found.

Received from the Departments of Pathology and Anesthesiology, University of Wisconsin, Madison, Wisconsin 53706. Accepted for publication June 15, 1976. Supported by Public Health Service Grant #GM22685.

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Effects of Subanesthetic Concentrations

In a recent study, Stevens *et al.* compared the toxicities of halothane, isoflurane, and diethyl ether at subanesthetic concentrations in mice, rats, and guinea pigs.[48] It was found that after 35 days of exposure, halothane produced a greater decrement in weight gain and a higher incidence of hepatic degenerative changes than the other agents. In our laboratories, using electron microscopy, we demonstrated cellular changes (such as degeneration of the mitochondria, endoplasmic reticulum, and bile canaliculi) (figs. 1 and 2) in the livers of rats exposed to subclinical levels of halothane, 10–300 ppm, for four to eight weeks.[26] In general, more extensive lesions were found in animals exposed to higher concentrations of halothane. Additionally, pregnant rats were exposed to halothane, 10 ppm, throughout gestation and degenerative changes (such as fatty change, leukocytic infiltration, accumulation of lysosomes, and cellular necrosis) were observed in the livers of the offspring (figs. 3 and 4).[49]

Despite increasing evidence that halothane is hepatotoxic, the incidence of fully recognizable hepatic necrosis in human subjects following halothane anesthesia is very low.[40] However, Stevens *et al.* cautioned that perhaps hepatic injury following halothane anesthesia in man is not so rare as the incidence of massive hepatitis would suggest. Elevations of SGPT and BSP retention have been found following halothane anesthesia,[41,42] suggesting that a mild hepatic injury following exposure to halothane may not be uncommon.

At least two explanations have been suggested for the hepatotoxic effects of halothane. Since granuloma formation and eosinophilia are sometimes associated with halothane hepatitis, hypersensitivity may underlie the pathogenic mechanism.[43–49] A sensitivity phenomenon of the antibody–antigen type could occur if a haptene is formed by conjugation of hepatic protein to the halothane molecule, or a metabolite of it. However, increasing evidence has indicated that halothane, or its metabolite, probably has a direct hepatotoxic effect on the liver. Damage to liver cells following exposure to halothane in dogs,[50] mice,[38,51] guinea pigs,[28,46] and rats[24,26,28,29,52] has been reported. As is the case with the volatile anesthetic chloroform and other halogenated compounds such as carbon tetrachloride, there may be a toxic metabolite that accumulates within biological tissues.[23,53] Cohen and Hood reported accumulations of metabolites from various volatile anesthetics in the mouse, but these metabolites could not be identified because they were bound to tissue constituents from which they could not be extracted.[54,55]

Of interest is the fact that halothane metabolism is apparently concentration-dependent.[56] More metabolism and breakdown of halothane occurred in the livers of animals exposed to lower concentrations of the agent. If the metabolites of halothane are responsible for hepatic damage, chronic exposure to low levels of halothane might then be more toxic than acute exposures.

Pathologic Effects on the Kidney

Methoxyflurane is now known to be nephrotoxic in clinical concentrations.[57–61] There is no evidence that halothane has a similar effect. Raventos,[62] in his classic paper in 1956, reported that some elements of renal damage, primarily dilatation of the proximal convoluted tubules, did occur when animals were subjected to repeated exposures to halothane. In our laboratory we studied the renal morphologic changes following chronic exposure to subanesthetic concentrations of 100 and 300 ppm halothane by light and electron microscopy.[63] In adult rats lesions were demonstrated in the proximal convoluted tubules. Degeneration of the mitochondria with formation of large membranous bodies was frequently found (fig. 5). Accumulation and fusion of lysosomes were also observed in the tubular epithelial cells (fig. 6). Similar changes in the lysosomes have been reported to occur in methoxyflurane nephropathy,[58] choline-deficient rats,[64] manganese-deficient mice,[65] and the Chediak-Higashi syndrome.[66] It has been proposed that these abnormal lysosomal structures are directly related to alternations in lysosomal function.[66]

In addition to the mitochondrial and lysosomal changes, accumulation of spherical particles in the basement membrane (fig. 7), ex-

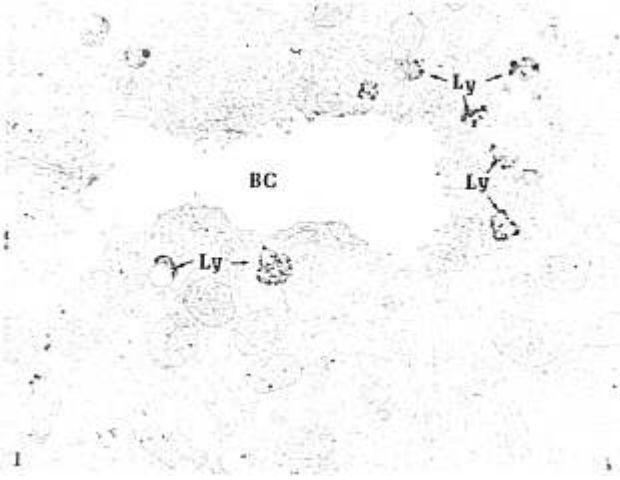

FIG. 1. Liver, adult rat, 500 ppm halothane, 4 weeks. Extensive dilatation of the bile canaliculi (BC) with peribiliary accumulation of lysosome (Ly), indicating cellular injury. Similar ultrastructural changes have been observed in human cases of halothane hepatitis. ×14,500.

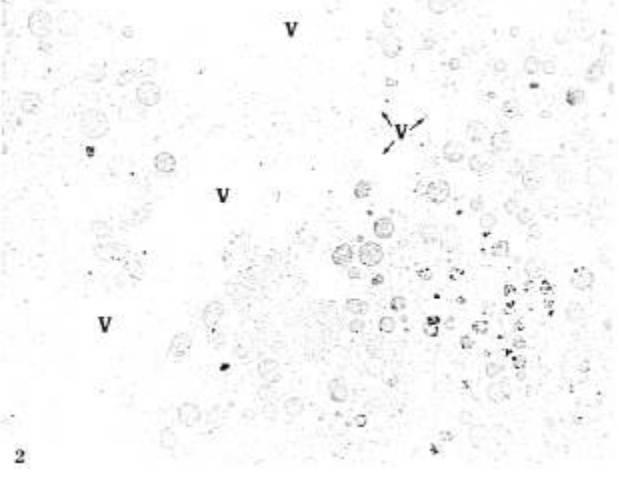

FIG. 2. Liver, adult rat, 500 ppm halothane, 4 weeks. Vacuolar degeneration of the endoplasmic reticulum to form membrane-bound vacuoles (V). ×7,000.

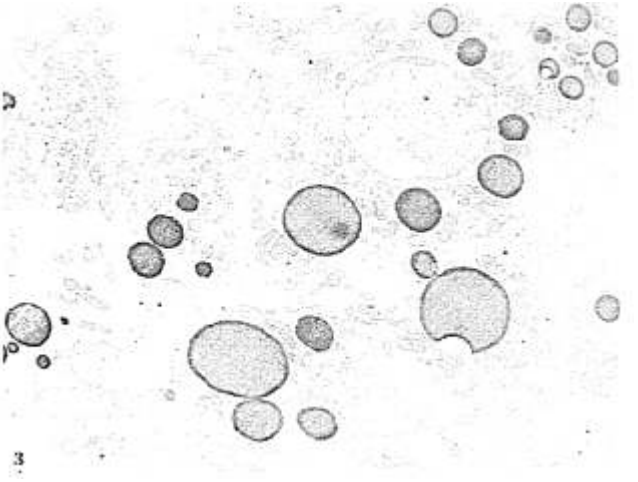

FIG. 3. Liver, neonatal rat, 10 ppm halothane throughout gestation. Extensive accumulation of lipid droplets (fatty change) within some hepatocytes. ×5,000.

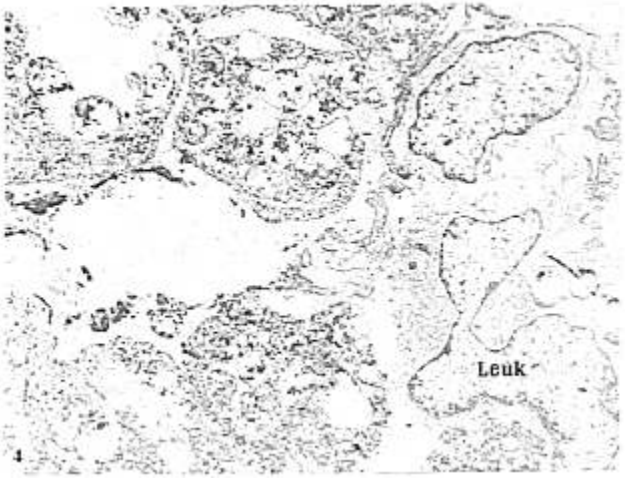

FIG. 4. Liver, neonatal rat, 10 ppm halothane throughout gestation. Large areas of necrosis were observed in the liver. Infiltration of leukocytes (Leuk) at necrotic sites was prominent. ×12,500.

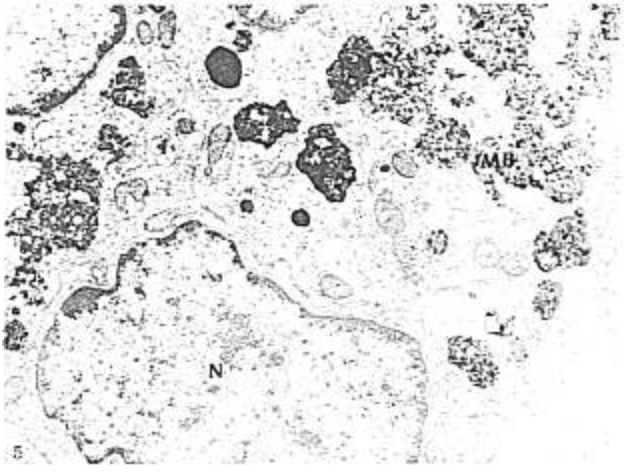

FIG. 5. Proximal convoluted tubule, adult rat kidney, 500 ppm halothane. Accumulation of membranous bodies (MB) within the epithelial cell. The membranous bodies are believed to be derived from degenerative mitochondria. ×14,500.

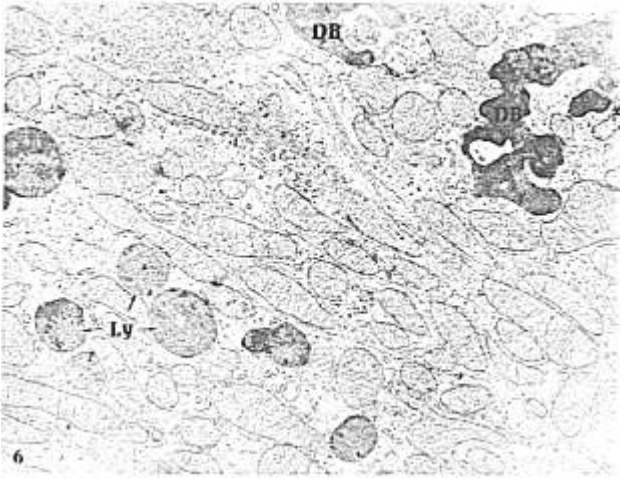

FIG. 6. Proximal convoluted tubules, adult rat kidney, 500 ppm halothane. Fusion of the lysosomes (Ly) to form irregular-shaped dense bodies (DB). ×14,500.

trusion of large cytoplasmic masses into the tubular lumen, aggregation of smooth endoplasmic reticulum, and swirling of the basal plasma membrane were observed in the proximal tubules (fig. 7). The clusters of spherical microparticles within the basement membrane, as well as the extrusion of cytoplasmic material, have been found in both human and animal kidneys affected by disease.[67–70] It is believed that these phenomena represent discharge and extrusion of cellular debris and material from injured cells. The formation of smooth endoplasmic reticulum aggregates and the swirling of basal plasma membrane, however, may represent a compensatory response of the kidney, since the basal plasma membrane is involved in detoxification processes and transport of the end products into the tubular lumen. The swirling found in our animals' basal plasma membranes indicates a probable compensatory response of the membranes to halothane metabolites.[71]

Chang and co-workers also found pathologic changes in neonatal kidneys of rats subjected to intrauterine exposure to low levels of halothane (10 ppm).[72] General degenerative changes such as mitochondrial swelling (fig. 8), accumulation of lysosomes, and enlargement of the apical vacuoles (fig. 9) were observed. These degenerative changes were found to be confined to the proximal convoluted tubules. Massive cellular casts and cytoplasmic material were also found within the tubular lumen, indicating tubular injury (fig. 10).

The clear-cut nature of the morphologic alterations found in our laboratory following chronic exposure suggests that, at least in one species, halothane acts as a cellular toxin to the kidney. Whether such changes occur in man has not been determined.

Pathologic Effects on the Brain

Apparently no pathologic effect on the brain of acute exposure to clinical concentrations of anesthetics has been reported. However, there are suggestions in the literature that chronic exposure to subanesthetic concentrations may be deleterious to central nervous system function. Several reports from the European literature suggest that headaches and irritability in operating room personnel and patients were caused by direct action of general anesthetics on the brain or cerebral vessels.[5,6,73] Functional disturbances of the CNS, such as headaches and depression, were reported to occur in Russian anesthetists following prolonged exposure in poorly ventilated operating rooms.[5] Many investigators have shown that acute exposure to subanesthetic concentrations produces temporary deficits in a variety of human behavioral functions, including memory, mood, and psychomotor actions.[75–79]

One of the authors showed a deterioration in psychological function of anesthesiology residents from the start of their residency to the end of one year (Katz, unpublished observation). In a part of that study, the Reitan-Halstead test, a well-known measure of organic brain disorders, was marginally positive in several of the residents. Because of the many variables in that study, conclusions concerning cause and effect could not be drawn.

Our laboratory has repeated studies in a more controlled situation using the rat as a model.[80] We have shown that there was indeed a learning deficit in animals exposed *in utero* to 10 ppm halothane throughout gestation. The deficit continued many months past weaning and after the rats were out of the halothane environment, indicating that it was permanent.

We believe that the work done in this laboratory is the first to demonstrate morphologic changes in the brain as a result of exposure to low concentrations of halothane. In adult rats after four to eight weeks in an environment of 10 to 500 ppm halothane, degenerative changes such as severe vacuolation of the Golgi complex (fig. 11) and collapse of the rough endoplasmic reticulum (fig. 12) could be observed in some cortical neurons.[81] We have also found degenerative changes in the cortical neurons of neonatal rats exposed to halothane *in utero* at a level of 10 ppm in the ambient air throughout gestation.[82] Vacuolation of the Golgi complex was again a prominent pathologic feature. Weakening and focal disruption of the neuronal nuclear membrane (fig. 13) was a frequent finding. Such changes in the nuclear membrane are precursors of cell death. Accumulation of cytoplasmic debris and lysosomes could still be observed within

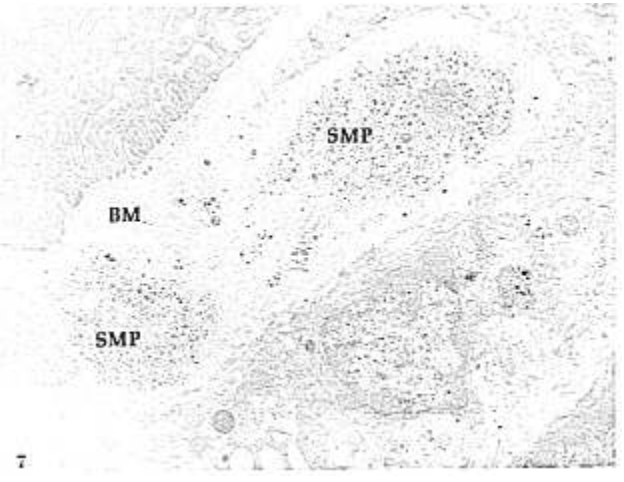

FIG. 7. Kidney, adult rat, 500 ppm halothane. Accumulation of spherical microparticles (SMP) in a pocket of the basement membrane (BM). The SMP's are probably cellular debris being extruded into the basement membrane. ×10,500.

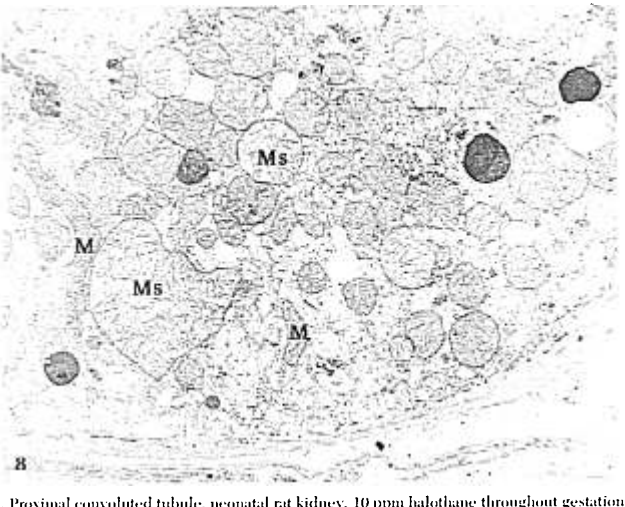

FIG. 8. Proximal convoluted tubule, neonatal rat kidney, 10 ppm halothane throughout gestation. Severe swelling of some of the mitochondria (Ms) in the renal epithelial cells, indicating cellular injury. Some mitochondria (M) still appeared normal. ×10,500.

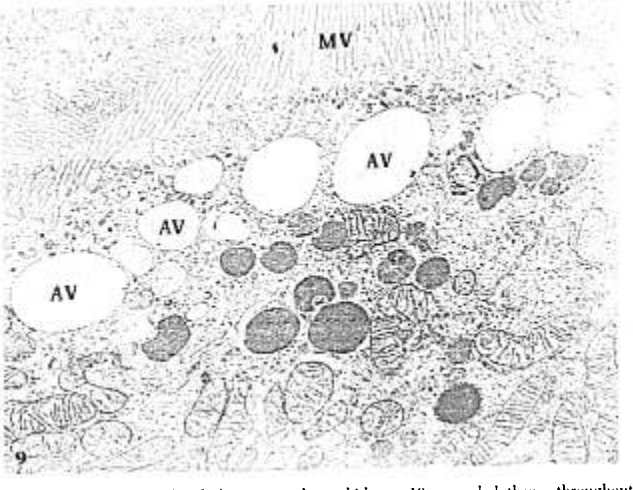

FIG. 9. Proximal convoluted tubule, neonatal rat kidney, 10 ppm halothane throughout gestation. Enlargement of the apical vacuoles (AV) forming membrane-limited vacuolations. Microvilli (MV). ×14,500.

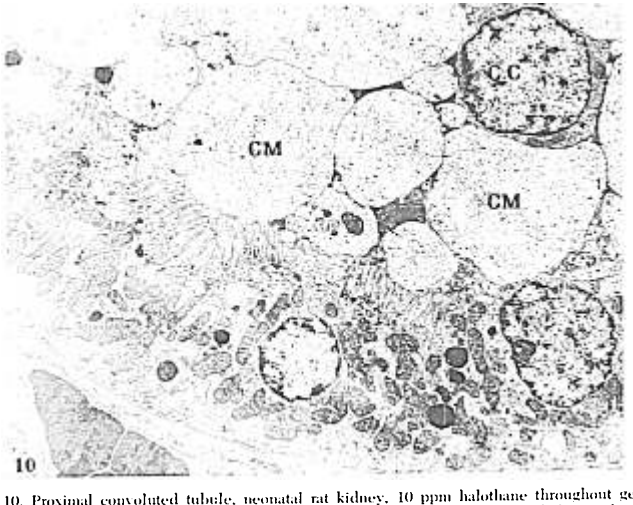

FIG. 10. Proximal convoluted tubule, neonatal rat kidney, 10 ppm halothane throughout gestation. Degenerated cellular cast (CC) and cytoplasmic masses (CM) were being extruded into the tubular lumen. ×5,000.

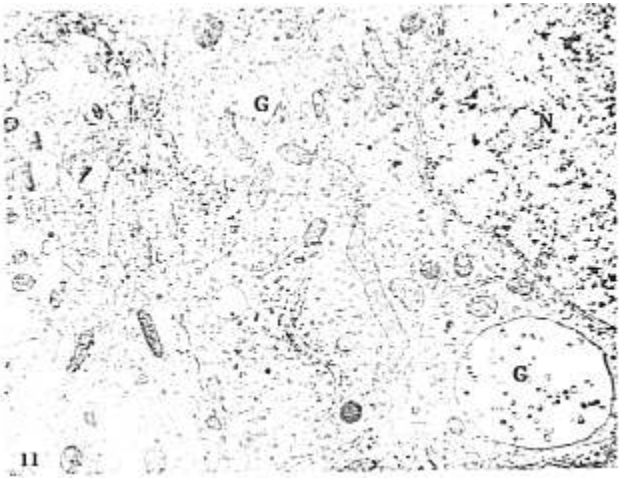

FIG. 11. Cortical neuron, adult rat, 500 ppm halothane. Degeneration and vacuolation of the Golgi complex (G). Nucleus (N). ×22,000.

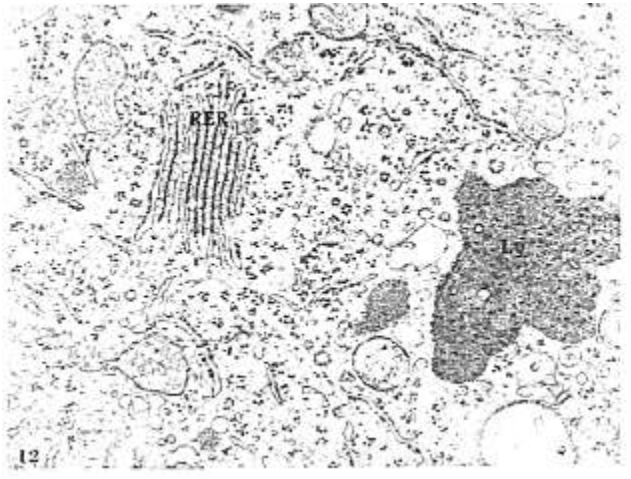

FIG. 12. Cerebral cortex, adult rat, 10 ppm halothane. Collapse of the rough endoplasmic reticulum (RER) was observed within some neurons. A dense matrical material was found between the stacks of collapsed reticular membranes, which became devoid of ribosomes. A giant lysosome (Ly) is also evident. ×41,000.

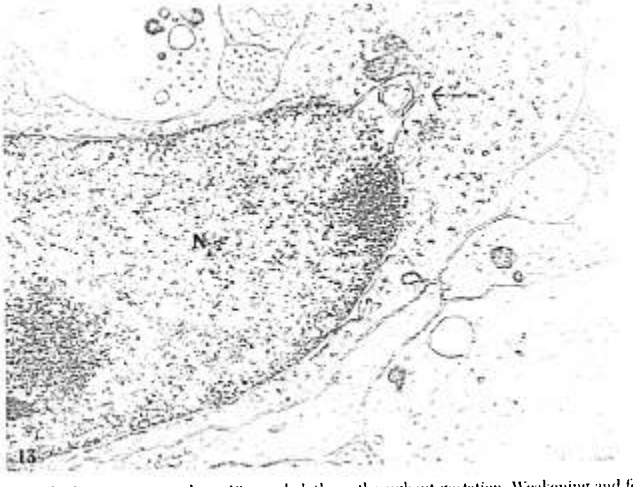

FIG. 13. Cerebral cortex, neonatal rat, 10 ppm halothane throughout gestation. Weakening and focal outpouching of the nuclear envelope (- - ->) could be observed in many neurons (N). ×30,500.

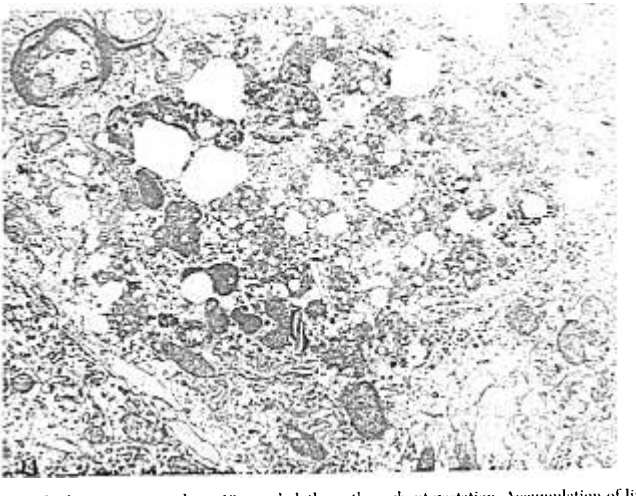

FIG. 14. Cerebral cortex, neonatal rat, 10 ppm halothane throughout gestation. Accumulation of lipids, lysosomes, and cellular debris within a neuronal process. ×20,000.

some neuronal processes and macrophages (fig. 14) in 100-day-old rats that had been subjected to prenatal exposure to halothane, indicating that the damage to the nerve cells in these animals by halothane or its metabolite is an enduring one.[2] These findings support the concept that halothane may have an undesirable effect on the developing nervous system of the rat. Whether such occurs in other species, including man, has not been determined.

Concluding Remarks

We have reviewed both clinical and laboratory data suggesting that acute or chronic exposure to general anesthetics, primarily halothane, has deleterious effects on at least three organs—the liver, kidney, and brain. The present review represents only a general overview and an up-to-date summary of the morphologic and pathologic changes in the rat following exposure to halothane.

Since the pathologic effects of halothane have been revealed by electron microscopy only recently, the preciese "pathogenic mechanism" of halothane or its metabolites still needs to be investigated and cannot be determined at the present time. However, in view of the pathologic involvement of the cytomembrane systems (plasma membrane, mitochondria, nuclear membrane, endoplasmic reticulum, and Golgi complex) after exposure to halothane, it is not unreasonable to postulate that the prime toxic effect of halothane (or its metabolites) is on the biological membranes.

Most of the information in the present review concerning the pathologic effects of halothane is derived from studies in our laboratories. The experimental animals were exposed to 10 and 500 ppm halothane for four to eight weeks in carefully monitored chambers, while the control animals were housed in halothane-free chambers. All the animals were sacrificed by intracardial perfusion with glutaraldehyde to ensure proper and immediate preservation of the tissue and cellular morphology. Tissue samples from the cerebral cortex, renal cortex, and liver were then carefully obtained with a sharp blade and further fixed in proper fixatives for light and electron microscopy. Lesions we have found in specimens of brain, liver and kidney represent very subtle pathologic changes in the tissues, because most of them are observable only with electron microscopy and not with light microscopy. However, we are confident that our findings are valid because they are readily observable and are consistent more than in 85 per cent of the tissue samples examined. None of these abnormalities was observed in the tissues of the control animals. Moreover, we have reproduced our findings consistently in subsequent experiments, some performed under a "double-blind" system to ensure total objectivity.

There is no doubt that many of the findings reviewed in the present paper are still subject to critical debate. Nevertheless, from all the data and information obtained to date, indications that halothane or its metabolites may have a direct toxic effect on the biological system are strong. However, since all these observations were obtained from laboratory animals subjected to experimental conditions, direct extrapolation of these findings to man is nor warranted.

Since the pathologic effects of other anesthetic agents were not comparatively studied, it cannot be assumed that the lesions obtained in response to halothane exposure are "specific" for halothane. The demonstration of a relationship between structural and functional changes in animals following exposure to halothane is still lacking, and this relationship needs to be investigated in future studies.

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Cerebral Blood Flow and Metabolism

HYPOTENSION WITH TRIMETHAPHAN AND NITROPRUSSIDE In 14 unpremedicated dogs anesthesia was induced with thiopental (5 mg/kg) and maintained with ketamine (2 mg/kg). Muscular paralysis was achieved with pancuronium, the trachea intubated, and pulmonary ventilation maintained to keep Pa_{CO_2} normal. Cerebral perfusion pressure (CPP) was reduced with either trimethaphan or sodium nitroprusside, and the effects of these drugs upon cerebral blood flow (CBF) and oxygen uptake (CMR_{O_2}) compared. Anesthesia alone altered neither CBF nor CMR_{O_2}. When nitroprusside decreased CPP to levels as low as 30 torr, cerebral autoregulation remained nearly intact and CBF was lowered by no more than 10–15 per cent. However, during administration of trimethaphan autoregulation was lost when CPP decreased below 60 torr. With values below this level, CBF progressively diminished as CPP decreased. The response of CMR_{O_2} was similar. A rate of infusion of trimethaphan sufficient to lower CPP below 50 torr resulted in decreased CMR_{O_2}; when CPP was 30 torr, CMR_{O_2} was 35 per cent below normal. On the other hand, sodium nitroprusside produced no change in cerebral metabolism even when CPP was as low as 30 torr. The authors conclude that these differences in drug action may be of clinical significance. (*Stoyka WW, Schutz H: The Cerebral Response to Sodium Nitroprusside and Trimethaphan Controlled Hypotension. Canad Anaesth Soc J 22: 275–283, 1975.*) ABSTRACTER'S COMMENT: Although major differences in the circulatory and metabolic effects of these drugs were seen at extremely low CPP, their effects were much more similar at the usual clinical ranges of induced hypotension.