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Halothane and hepatic necrosis

Shirley A. Simmons
University of Nebraska Medical Center

HALOTHANE AND HEPATIC NECROSIS

Shirley Ann Simmons

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College of Medicine, University of Nebraska
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INTRODUCTION

General anesthetics have been in use for over 100 years since the first public administration of general anesthesia with ether was made by William T.G. Morton at the Massachusetts General Hospital in Boston on October 16, 1846. To date here is no absolutely established mechanism of action of any drug producing general anesthesia. Certain correlations between physical, chemical or biochemical properties and their narcotic potencies have been found for a limited series of compounds.

Theoretical mechanisms of action include: Overton-Meyer lipoid-solubility theory, surface tension and absorption theory, cell permeability theory, oxidative metabolism depression theory, and decreased utilized energy through depressed function.

In developing new drugs for use as general anesthetic agents certain chemical and physical properties are sought in relation to the molecular structure of the drug.

The physical state of the agent is an important consideration. A gas is more accurately metered than a volatile agent. Modern anesthetic liquid vaporizers deliver concentrations of an agent which can be controlled within limits. Transportation of gas in tanks is more difficult than transportation of bottles of volatile liquids.

Dr. Joseph F. Artusio, Jr. and Dr. Van Poznak[23] have found in their investigations that a compound of the hydrocarbon series, other than a single carbon compound, must have some hydrogen present in the molecule to have sufficiently depressing properties on the central nervous system to make it a useful clinical anesthetic agent. This may not be true of single carbon compounds such as the methane series of drugs. Among the halogenated hydrocarbons and ethers, individual

agents will show mixed excitation and depression, and by regulating the amount of hydrogen, the quantity and quality of halogen, basic carbon chain drugs can be produced which have more depressing properties or more central nervous system exciting properties, so much so that some compounds produce so much excitation that any of their depressant properties are masked.

Nonflammability is an important prerequisite for a new anesthetic agent. No new anesthetic agent, regardless of its excellence, would be likely to gain widespread use if it were flammable.

There are two general classifications of potency of anesthetic agents: first, the absolute potency and second, the drug's biologic potency. Absolute potency is defined as that concentration of the drug which produces the desired clinical effect, and, when exceeded, produces no greater effect as long as the subject is receiving adequate tissue oxygenation for metabolic processes. Biologic potency of an anesthetic refers to its ability to produce varying degrees of depression of physiologic function. For example, a drug of high biologic potency would produce complete depression of the organism to eventual paralysis of the most resistant cells of the central nervous system which control respiration and circulation. Continued administration of full concentrations of an anesthetic agent of 100 per cent biologic potency produces death. Therefore, a new anesthetic agent should be a drug of limited biologic potency and have a specific absolute potency.

A drug with limited biologic potency would have the advantage that the biologic limit would prevent anesthetic overdose. Thus, inadvertent death of the organism by administration of too high concen-

trations of the agent, or the accumulation in the tissues of a large quantity of the agent to the point of tissue toxicity, resulting from assisted or controlled ventilation would be prevented. The ideal anesthetic agent would have these limiting factors as an inherent property of the molecule itself, eliminating the danger of anesthetic overdose.

Anesthetic safety can also be related to the saturated vapor pressure of a liquid agent, as there is an inverse relationship between saturated vapor pressure and boiling point, and the boiling point of a compound and its anesthetic potency vary in direct proportion. Thus, compounds with higher points and low saturated vapor pressures would combine the properties of anesthetic potency and safety. The anesthetic safety factor of compounds with low saturated vapor pressures is associated with the few molecules of the anesthetic vapor on the surface of the liquid at any one time. With the few number of molecules of the vapor available it is almost impossible to introduce a sufficient quantity of agent into the inspired mixture during the initial phase of anesthesia. Anesthetic agents with high saturated vapor pressures have large numbers of molecules of vapor over the surface of the liquid which makes possible sudden anesthetic overdose, either by deep inhalation or by assisted or controlled ventilation. Agents with low saturated vapor pressure decrease the speed of anesthetic induction when used as the sole anesthetic agent. The disadvantages of a long induction time are far outweighed by the elimination of the danger of rapid initial anesthetic overdose.

Halogens are elements of a closely related chemical family, all of which form similar compounds in combination with sodium. These

compounds resemble salt (NaCL). The elements comprising the halogen series are chlorine, bromine, iodine and fluorine. The addition of chlorine and bromine to hydrocarbons or ethers confer various degrees of biologic potency on them, and the anesthetic potency can, within limits, be adjusted readily by the choice of the number and position of chlorines and bromines on the basic molecular structure.

The abundance of hydrogen in the molecules of hydrocarbons and ether makes them flammable in air or oxygen, within certain limits. The addition of fluorine atoms to the compound readily changes the flammability characteristics of these molecules. Sufficient flourine in the molecule negates the hydrogen, and the compound will not burn in air or oxygen. The fluorine atom does confer some degree of anesthetic potency on the hydrocarbon, but it does not do so the extent that bromine and chlorine do. Hence, within limits, fluorine, without significantley affecting anesthetic potency, can be added to the hydrocarbon until the molecule has a considerably reduced flammable range.

Newly developed inhalation anesthetic agents should have the following desirable characteristics: no biotransformation within the body, molecular stability in the presence of alkali absorbents, and solubility parameters such that it is not preferentially partitioned to the aqueous phase of the body.

When new agents have been developed, drug testing and species choice for testing in animals is most important. Many authorities believe that the cat is the best animal to use, as dose-response data found in the cat can frequently be transferred to man on a milligram-kilogram basis. Others believe the monkey to be the experimental animal of choice in which the dose-response of the drug most nearly resembles

the dose response found in man. Dogs are readily available in most instances and usually the data are readily transferable to man. However, great care must be taken in the early stages of clinical investigation lest the drug behave entirely differently in the human being than it behaved in the experimental animals.

Most halogenated anesthetic agents in clincal trials seem to have the following advantages: 1) minimal irritant quality on upper respiratory passages, 2) relatively less nausea and vomiting in the postanesthetic period than drugs previously used, and 3) only mild irritation of the upper airway with few pharyngeal or tracheobronchial secretions. Clinically tested halogenated anesthetics available at present include chloroform, trichlorethylene, fluroxene, halothane, mexthoxy flurane, tribromethanol (avertin) and ethyl chloride. Among these agents halothane is the most widely used in clinical practice today.

II. CLINICAL CHARACTERISTICS OF HALOTHANE.

Halothane was first synthesized by Suckling in 1956. Its anesthetic properties were discovered by Raventos and clinical trials were made by Johnstone in the same year. Its chemical formula is CF_3-CHCLBr. The physical characteristics of halothane are compared with other widely used agents in Table I.

J. Raventos tested the agent on rabbits, dogs, rats, monkeys, mice, and isolated tortoise atrium[2]. A summary of his conclusions are:

1. The therapeutic ratio of halothane is approximately twice that of ether. Induction of anesthesia and recovery are both rapid and free from excitement. Muscular relax-

Table 1

PHYSICAL CHARACTERISTICS OF SOME INHALATION ANESTHETICS

	Mol. Wt.	Boiling Point (C.)	Specific Gravity: Gas or Vapour (Air =1)	Specific Gravity: Liquid (Water =1)	Solubility in 100 Parts Water	Oil Water Solubility	Oil Blood Solubility	Inflammability Limits (%): Air	Inflammability Limits (%): Oxygen	Vapour Tension at 20 C. (mm Hg)
Chloroform	119.39	61.26	4.12	1.49	0.822	100				160.5
Cyclopropane	42.08	-34.4	1.42	1.42	33ml.	34.3	15.3	2.4-10.3	15.3	
Ether	74.12	34.6	2.6	0.713	7.5	15.46 3.2	15.08 3.3	1.85-36.5	2.10-82.0	439
Nitrous Oxide	44.2	-181.0	1.527	1.226	150ml.	3.2	3.0			49.4
Halothane	197.39	50.2		1.86	0.345	330		Not inflammable in oxygen 0.5 to 50.0		243

ation produced is good and it does not cause salivation or vomiting.

2. No serious functional disturbances with the exception of hypotension are produced. The agent itself does not produce cardiac irregularities, but it increases the sensitivity of the heart to epinephrine. Capillary bleeding is not increased.

3. Inhalation of high concentrations (3.5%) stops respiration, but this apnea is readily reversible.

4. The most consistent histopathological change in animal tissues is a dilatation of proximal convoluted tubules of the kidney. This lesion is not associated with alteration of renal function.

The potency of halothane is such that a specially devised vaporizer must be used for its administration. Accurate metering of the vapor concentration is necessary at all times. Several specially designed vaporizers are available for this purpose. This vaporizer must be placed outside the "circle" system so commonly employed in anesthesia. The Fluotec vaporizer compensates for varying rates of gas flow, the the amount of vapor produced being dependent upon the amount of gas passing through the vaporizer. With the vaporizer in the "circle", the flow rate varies from moment to moment and the amount of vapor would also vary. Overdosage would be a real hazard. The open drop technique of administration is possible with halothane but most unsafe. Unknown high vapor concentrations may be offered to the patient with extreme rapidity. Accuracy and moment-to-moment control of concentration is necessary with this agent.

The first clinical trials of halothane anesthesia in humans were performed on 500 patients by Michael Johnstone[1]. Many of the patients had cardiovascular, pulmonary, renal hepatic diseases complicating the surgical lesions. Types of surgery performed on these patients were: abdominal surgery, 139 cases; genitourinary surgery, 129 cases; orthopedic surgery, 31 cases; herniorrhaphy, 31 cases; neurosurgery, 29 cases; radical mastectomy, 17 cases; thyroidectomy, 23 cases; gynecology, 4 cases; and, chest surgery, 5 cases. Twenty eight of the abdominal surgery cases were cholecystectomies and seven were cholecystoduodenostomies.

Each patient was premedicated with atropine, either alone or combined with pethidine and anesthesia was induced in most cases with a sleep dose of thiopentone. Anesthesia was maintained in all cases by continuous administration of halothane vapor, using a Boyle's vaporizer and a gas flow of 10 liters per minute with 50% oxygen and nitrous oxide. Anesthesia so produced was smooth and rapidly reversible.

No deaths occurred during halothane anesthesia. Six patients died in the post-operative period, none of them capable of being attributed to toxic effects of the anesthetic.

Eight adult patients with jaundice were anesthetized with halothane for periods up to two hours. In seven of these cases jaundice was due to carcinoma of the head of the pancreas and cholecystoduedenostomies were done in each case. The eighth patient became jaundiced after an attack of acute cholecystitis. Seven made uneventful recoveries, the jaundice disappearing within two or three weeks. One patient with metastatic lesions in the liver died on the 7th post-operative day from bile peritonitis.

The general picture of the cardiovascular system during halothane anesthesia is one of vasodilatation combined with hypotension and bradycardia. Vasodilatation is evidenced by dry, warm, and pink skin with prominent superficial veins and becomes obvious within a few seconds after the start of inhalations. This persists throughout anesthesia, even when minimal vapor concentrations are inhaled. Hypotension suggestive of depression of sympathetic activity was consistently observed. This was modified, to a certain extent, by atropine and the strength of vapor concentration inhaled. The shock syndrome--tachycardia, hypotension, sweating, pallor, and vasoconstriction was completely absent during and immediately following surgical operations.

Vagal type cardiac arrhythmias were observed when the higher vapor concentrations were inhaled. These arrhythmias included sinus bradycardia, atrioventricular nodal rhythms often with interference, dissociation, and an unusual form of sinus arrhythmia with coupling of the sinus beats. Normal sinus rhythms were restored by atropine in these cases.

Ventricular arrhythmias were observed only in the presence of inadequate oxygenation in lightly anesthetized subjects and were mild in degree. Ventricular tachycardia was not observed.

The combined use of d-tubocurarine and controlled respiration on patients anesthetized with halothane was followed by cardiovascular collapse and slow pulse with profound hypotension.

Tachypnea was observed during surgical stimulation in lightly anesthetized patients. This reaction was controlled by pethidine or regional nerve block.

The hypotension associated with the administration of halothane has been ascribed to a ganglionic-blocking action, to a central de-

pression of vasomotor mechanisms,or to a direct depression of the myocaudium. Permanent damage to the cardiovascular system is disproved by the rapid return of blood pressure to normal levels as concentrations of the drug are reduced. When overdosage of drug is purposely produced, respiratory failure always precedes cardiac failure by a recognizable margin.

In early stages of induction with fluothane in air or oxygen, respirations are deep and regular with little airway irritation by vapour. Following loss of consciousness, breathing becomes shallow. This reduction in tidal volume usually persists throughout maintenance of anesthesia. This reduction in depth of respiration is generally associated with an increase in rate. This respiratory depression increases risk of inadequate tissue oxygenation and carbon dioxide retention.

Metabolic effects of fluothane include a moderate elevation of blood glucose and inorganic phosphate levels. Serum lactic acid, pyruvic acid and citric acid levels are slightly less elevated. These changes are considered to be nonspecific and have been noted following administration of other anesthetic agents in several clinical studies.

No specific alterations of renal or hepatic function were noted in any clinical trials of halothane.

III. COMPARISON STUDIES OF HEPATOTOXICITY DUE TO HALOTHANE AND OTHER INHALATION AGENTS

In the preliminary experimentation of Raventos [2] two liver function tests were undertaken. Two batches of 4 rats each were anesthetized with halothane for 5 consecutive days for periods of 1 hour. Hippuric acid excretion tests were carried out before the first and immediately after the last period of anesthesia and were found to be the same both times. Similar results were found when the bromsulphthalein retention

test was carried out in a dog before and after anesthesia.

Virtue, et al[7], performed animal experiments which would tend to accentuate any ill effect that halothane might have on the liver. Previous experiments had shown that fasting and low oxygen concentrations each produce deleterious effects on the liver of dogs receiving chloroform anesthesia. These conditions were used in their experiments. Six dogs stressed by moderate hypoxia and a two day fast indicated that bromsulphthalein retention after four hours of halothane anesthesia in crossover experiments was no greater than that following ether anesthesia in the same dogs unstressed by fasting or hypoxia.

Certain coexisting factors active in the organism may be misleading in the true interpretation of hepatotoxicity. Among variables which may themselves contribute to liver damage are anoxia, nutritional status of the subject, and alterations of hepatic blood flow.

Jones, et al[9], sought a more direct approach to the problem by introducing drugs directly into the esophagus of mice, thereby allowing primary absorption in the portal blood stream from the gastrointestinal tract with concentration of its effect on the liver. Proper instillation of the drug produced onset of narcosis within five to ten minutes. The mice were sacrificed 72 hours after exposure and the livers were fixed and stained for study. Drugs so tested included chloroform, halothane, trichlorethylene, vinyl ether and ethyl ether. Due to its known hepatotoxicity, chloroform was used as a standard of reference. None of the drugs tested failed to produce at least minimal hepatotoxicity. Frank necrosis was observed with chloroform and vinyl ether only. Ethyl ether was found to produce the least toxic changes and chloroform the most. Liver cell injury by halothane was manifested as fatty infil-

tration without necrosis.

Little, et al[10], compared effects of halothane, cyclopropane and ether anesthesia on liver function with a battery of liver function tests. Tests employed included determinations of serum cholinesterase, and per cent cholesterol present as cholesterol ester, serum alkaline phosphatase, total serum bilirubin concentration, and cephalin-cholesterol flocculation. Patients were grouped into 3 series of 10 each, receiving fluothane, ether or cyclopropane as primary anesthetic agent. Tests were performed pre-operatively, on the second post-operative day and on the seventh postoperative day in 30 normal female patients who underwent major pelvic or perineal surgery under halothane, cyclopropane, or ether anesthesia.

A summary of their results revealed postoperative abnormalities occurred in 8 of 10 patients who received ether anesthesia, 4 of 10 patients who received cyclopropane anesthesia and 5 of 10 patients who received halothane anesthesia. The abnormalities noted often occurred in only an isolated test in a single postoperative determination. These were occasionally of such limited deviation from the normal that they were of questionable significance. Hepatic functions tested were not affected more following anesthesia produced by halothane than following that produced by cyclopropane or ether.

Gibson[11] made pathologic studies of mouse liver and kidney following halothane exposure. Thirty experimental mice were anesthetized in a 1 to 2 percent halothane vapor for 45 minutes once and for 45 minutes on 5 consecutive days. Animals were sacrificed 2 days post-anesthesia, 5 days post-anesthesia and 10 days post-anesthesia. Histologic studies

of liver and kidney were made on all animals. In the kidneys no gross or microscopic alterations in renal structure were found. In the liver studies no alteration on gross examination were found. Three changes were noted on microscopic examination: (1) vacuolar formation--fatty change; (2) nuclear change--excessive numbers of binucleated cells, pyknosis of nuclei excessive; (3) zonal areas of cloudy swelling with pallor of cells. In a high percentage of livers (22 out of 30) examined 2 days after exposure to anesthesia evidence of fatty degeneration was noted. This was the usual transient type of fatty degeneration.

Haley and Wyant[13] studied the effect of halothane on the liver of dogs exposed to mild hypoxia. They used four groups of 6 dogs each, each dog receiving 3 hours of inhalation anesthesia. The first group received halothane in 20% oxygen and 80% nitrous oxide. The second group received halothane in 100% oxygen. The third group received halothane in 85% nitrous oxide and 15% oxygen. The fourth group received 85% nitrous oxide and 15% oxygen alone. The mean concentration of halothane in all groups was 0.8%. They found halothane had no effect on liver histology of dogs exposed to it for 3 hrs. while adequately ventilated. Halothane had no adverse effect on cellular structure, liver fat and glycogen, even when administered in an atmosphere slightly deficient in oxygen.

In a comparison study of toxic effects of chloroform and halothane on the liver, Drake[18] reported that chloroform produced metabolic acidosis, jaundice, liver necrosis and frequently death. Swelling of hepatic parenchymal cells interpreted as fatty change was noted in halothane and control groups. This fatty change was considered

to be a reversible process. No significant functional liver impairment was noted in halothane anesthetized dogs.

Morris and Feldman[20] hypothesized that conditions of decreased tidal excursion, tachypnea and hypotension produced by halothane might potentiate any hepatotoxic action of halothane. They undertook a clinical investigation of hepatic function in two groups of patients, one in which patients were subjected to an additional stress of carbon dioxide in the respired atmosphere during halothane administration and one in which patients were subjected to marked hypotension as a consequence of deliberate anesthetic overdosage. These were compared with liver function in patients anesthetized with halothane in whom ventilation was adequate to avoid appreciable carbon dioxide retention and in whom hypotension did not occur. Tests performed included bromsulphthalein retention, thymol turbidity test, total and direct bilirubin determinations and the Quick two stage prothrombin time. Bromsulphthalein retention was found to be the most sensitive test of impaired hepatic function.

These authors found that the only patient in the control group with abnormal bromsulphthalein retention postoperatively had an elevated preoperative level and the increase in retention was minimal. In the control group anesthetized with halothane no patient had a total bilirubin greater than 1.0 mgm% postoperatively. A moderate increase in thymol turbidity was noted in 2 of 5 cases.

Five patients were first stabilized on halothane, then the soda lime canisters were removed and carbon dioxide was added to the inspired atmosphere. Carbon dioxide was administered for 30 to 40 minutes and carbon dioxide concentrations in the expired gases were measured using

a Liston-Baker infra-red canalyzer. This concentration was kept at a level of ten to fifteen per cent and reduced slowly at the end of the procedure to decrease the possibility of ventricular arrhythmias and hypotension associated with sudden diminution of carbon dioxide.

In four of five patients receiving carbon dioxide and halothane there were gross abnormalities of bromsulphthalein retention postopertively. This increased retention was maximal at 24-72 hours postopertively and persisting for four to six days. Smaller, but significiant postoperative increases in total serum bilirubin were also observed in these patients.

Five patients were maintained with a systolic blood pressure level of less than two-thirds of their pre-anesthetic systolic blood pressure for thirty minutes or more under circumstances in which the blood pressure drop could not be easily attributed to blood loss or surgical maneuvers. Ventilation was continuously assisted to prevent hypercarbia or anoxia. These patients also had greatly increased bromsulphthalein dye retention postoperatively and smaller elevations of serum bilirubin.

One additional patient who received carbon dioxide during halothane administration died of peritonitis after a bowel perforation at operation. Post-mortem histologic sections showed diffuse focal necrosis of the liver, not specifically centri-lobular in distribution.

These authors concluded that carbon dioxide retention should be avoided and that the hypotension produced by overdosage with halothane as well as hypotension from all other causes should be avoided during halothane anesthesia.

IV. CASE REPORTS OF HEPATIC NECROSIS FOLLOWING HALOTHANE ANESTHESIA

In August, 1957, Burns et al[4] reported clinical trials with halothane in 245 patients. There were seven deaths in this series. One of these cases is suggestive. A 56 year old man with malignant ulcer on the left side of the tongue was anesthetized with halothane for 40 minutes for total clearance of remaining teeth and diopsy of tongue ulcer. He received fluothane, nitrous oxide and oxygen from a Boyle apparatus. Recovery was satisfactory except for a rise in temperature to 100.8 on the evening of operation. Two days later radium needles were inserted under thiopentone, nitrous oxide and oxygen anesthesia. Radium needles were removed 7 days later. Temperature remained elevated for the next four weeks during which time he complained of nausea and vomited occassionally. He received 25 mgm of chlorpromazine on one occasion. After 4 days on penicillin and 5 days on chloramphenicol he became relatively afebrile and was discharged home. He received telecobalt therapy to the neck as an outpatient on 3 successive days. This was discontinued when he developed attacks of retching. Four days later he was admitted to the hospital, mildly jaundiced. Jaundice rapidly became marked and he developed epistaxis. Gross examination of the liver at autopsy revealed it to be pale and hemorrhagic. On cut section the biliary system was normal and the surface was flabby. Histologic examination revealed diffuse infiltration of the portal tracts by anaplastic neoplastic cells and widespread fatty degeneration of liver cells, many of which were necrotic.

In 1958, Burnap et al[6] reported clinical trials of halothane in 102 patients selected at random from the daily operating schedule.

Two patients developed postoperative hepatic damage.

The first case was a 48 year old man, totally incapacitated with symptoms of heart failure and angina secondary to severe aortic stenosis, left and right heart failure. Preparation for surgery was difficult and evidence of hepatic dysfunction secondary to prolonged heart failure had not entirely cleared preoperatively. Total serum bilirubin was 1.77 mgm % and prothrombin time 46% of normal.

Preoperative medication consisted of 100 mgm pentobarbital and 6 mgm morphine. Anesthesia was induced with nitrous oxide and Fluothane and maintained with Fluothane and oxygen in a closed system. Frequent hypotensive episodes occurred during the first hour of surgery despite extremely light anesthesia. Because of the hypotension Fluothane was discontinued and anesthesia maintained with cyclopropane for the remainder of the three-hour procedure, an aortic valvuloplasty. The patient received 7 transfusions during the procedure and four postoperatively.

Postoperatively anuria and hepatic failure appeared and progressed rapidly until death occurred on the sixth postoperative day. Serum bilirubin level had reached 44.8 mgm %.

Histologic examination of the liver revealed marked central lobular necrosis consistent with severe chronic passive congestion. This was considered similar to the characteristic appearance of carbon tetrachloride or chloroform poisoning. The kidneys revealed hemoglobin casts compatible with lower nephron nephrosis (hemoglobinuric nephrosis).

The second case was a 46 year old Italian man who was healthy except for recurrent acute frontal sinusitis. No history of

alcoholism, jaundice, exposure to hepatic toxins or an illness resembling hepatitis was obtained. He underwent radical frontal sinusotomy under halothane-oxygen anesthesia in a closed system. He developed mild hypotension to 80 mm Hg systolic and respiratory depression requiring controlled respiration. Immediate recovery was uneventful.

The patient was readmitted to the hospital 10 weeks later with fatigue, right lower quadrant abdominal pain and a right upper quadrant mass. There had been no jaundice or acute illness in the intervening period. The mass was found to be an enlarged rubbery liver which was biopsied.

Microscopic examination of the liver revealed marked distortion of architecture by irregular bands of fibrous tissue infiltrated with lymphocytes, distorting groups of liver lobules into irregular nodules compatible with the diagnosis of postnecrotic cirrhosis.

J. D. M. Barton[12] reported 2 cases of jaundice occurring within 48 hours of halothane administration in a letter to the editor of Lancet in May, 1959.

The first occurred in a patient receiving anesthesia for retropubic prostatectomy. Jaundice was so severe that exploratory laparotomy for obstructive jaundice was performed three weeks later. No obstruction was found. Jaundice finally subsided 3 weeks later without treatment.

The second case occurred in an 11-year-old child after anesthesia for a fractured patella and had persisted for a week at the time the letter was written.

In 1958 Drs. Hall, Geisler and Norris[5] presented a case report

on the death of a patien who had received loage doses of Fluothane. The patient was a 21 year old man who had been in good health until age 10 years when he had a febrile illness lasting about two weeks. After this he developed cerebral seizures believed to be bitemporal in origin. After two different hospitalizations he underwent right temporal lobectomy. He had been taking Mysoline, 250 mg., four times a day, for seizure control.

On admission routine laboratory data were normal. Between January 8 and March 29, 1957 he was anesthetized seven times. Four of these made use of Fluothane with nitrous oxide, representing a total of 117 gm. of the drug. This was administered in a partial rebreathing circle filter system at a total flow rate of 7 liters per minute. Total Fluothane exposure was 5 hours. The patient died on March 31, two days after the last anesthesia.

In the last month of life the patient developed an aggressive hostile personality disturbance and frequent seizures. He received large doses of tranquilizers sedatives and antibiotics including meprobamate up to 1600 mg. per day, chlorpromazine up to 200 mg. per day, aspirin, Dilantin, Mysoline, codeine, penicillin, streptomycin and dihydrostreptomycin.

On March 21, 1957 the patient developed microscopic hematuria, gross hematuria on March 27 and on March 29 he bled from injection sites and the most recent surgical wound. Laboratory data include: silicone clotting time; no clot during 24 hours of observation. Prothrombin time control 12.7 seconds; patient: 16 seconds; Fibrinolysin, none; platelets 302,000.

Microscopic sections of liver and kidney showed only slight

congestion of these organs. These authors felt that Fluothane did not contribute to the patient's death in any way.

Dr. Robert W. Virtue and Kathleen W. Payne[8] reported a post-operative death after Fluothane in 1958. The patient was a 39 year old housewife who had had an acute attack of right upper quadrant pain 11 months prior to admission. She had four subsequent attacks during one of which she had jaundice, dark urine and acholic stools. Other historical information included: previous hospitalizations for deliveries only; no past serious illnesses; frequent frontal headaches which sometimes caused her to vomit; no cardiac symptoms and constipation.

Admission physical examination revealed an obese woman who was not jaundiced and presented no abnormal findings other than carious teeth. Preoperative laboratory work: hemoglobin 16.3, with white cell count 9850 with a normal differential; urine normal; blood glucose 88 mg.%; non protein nitrogen 52 mg. percent; prothrombin time 100%.

Cholecystectomy was performed under Fluothane, nitrous oxide and oxygen anesthesia with a total flow rate of 1 liter per min. On three separate occasions blood pressure fell below 80 systolic and spontaneous respiration ceased. Fluothane was discontinued and the breathing bag was flushed with oxygen followed by return of spontaneous respirations shortly. On two of the three occasions blood pressure by auscultation disappeared.

The patient did well during the first few postoperative days receiving penicillin and tetracycline to the fifth postoperative day. A spiking temperature of 40 C appeared on the 6th day. Chest film was normal. White blood count was 12,950 with 87 per cent polymorphonuclear leukocytes. Antibiotic therapy was resumed with

the addition of erythromycin and tetracycline to the previous drugs. On the ninth postoperative day serum amylase was reported as normal and clotting time was found to be more than 30 minutes. Conjunctival hemorrhage was noted on this day, the temperature remained high. The patient died on the eleventh postoperative day.

At autopsy the liver showed severe central, midzonal and peripheral necrosis without focal abscesses. The hepatic vessels appeared normal. The pancreas was not hemorrhagic but almost completely necrotic. The adrenal cortices were depleted of lipid with small focal hemorrhages.

In 1960 Vourc'h et al[14] reported a case of hepatorenal necrosis following Fluothane administration.

The patient was a 35 yr. old man in perfect general condition without a history of alcoholism or residence in a tropical area. The procedure performed was a right inguinal herniorrhaphy with plastic repair of an old appendectomy scar. Total anesthetic time was 1 hour 50 minutes. Total flow rate was 8 liters per minute, with 5 liters nitrous oxide and three liters oxygen. Fluothane concentration varied from 1.5 to 4.0 per cent of the inspired atmosphere.

Postoperatively the patient was slow in coming to and 5 hours after leaving the operating room his temperature was 40 C. He was placed on Vitamin K, penicillin and adrenoxyl. On the first post-operative day he developed jaundice and urine output was 700 ml. In the evening profuse vomiting and abdominal distention appeared necessitating intravenous feeding. On the second postoperative day the patient became more deeply jaundiced with the following laboratory findings: red corpuscle count: 5.9 million; white corpuscles; 37,000; hemoglobin

17.6 gm. per 100 ml.; blood urea 1.92 gm/100 ml.; blood glucose 0.82 gm. per 1000. On the third day urine output was 500 ml. with 1.6 gm. albumin per liter; urea 6 gm. per 1000 and specific gravity 1.017. On the fourth postoperative day blood urea was 2.88 gm. per 1000; blood glucose 1.05 gm. per 1000; chloride, 85 meq. per liter, total bilirubin 30 mg. per 1000. Urine output was 440 ml. with specific gravity 1.014; urea 7 gm. per 1000. The patient died on the fourth day.

Microscopic examination of the liver revealed a typical picture of superacute hepatitis of toxic origin. The kidneys showed sudden, total necrosis of renal parenchyma, both tubular and glomerular.

Drs. Temple, Cole and Gorens[16] also reported a case of fatal hepatorenal failure in a 44-year old male following halothane anesthesia. He was admitted because of chronic ulcer of the left leg. The patient denied past history of fever or chills. He had noted a swelling in the right side of his neck which had gradually increased in size. The patient reported that he drank 2 to 3 bottles of beer daily with no nicotine or narcotic intake. Prior to his operation he denied any allergies but postoperatively, after penicillin had been given he reported that he was allergic to penicillin.

Physical examination revealed a mildly lethargic, obese (300 lb.) male. Multiple areas of superficial ulceration and brawny induration were present on the left leg. Cultures of the area showed S. albus. A soft cystic mass was noted in the right side of the neck, measuring 8 by 10 cm. and underlying the sternocleidomastoid muscle.

Preoperative laboratory findings were: hemoglobin, 16.3 gm. per 100 ml.; white cell count, 6300 with a normal differential; total protein, 8.67 gm.; albumin, 4.07 gm.; phosphorus 4.1 mg.; total choles-

terol, 206 mg.; protein-bound iodine, 5.0 micrograms per 100 ml.; alkaline phosphatase, 5.4 Bodansky units; prothrombin time, 100%; platelet count, 210,000 per $mm.^3$; bleeding time, 30 seconds. Urinalysis was normal.

A split thickness isograft was applied to the left leg four days after admission. General anesthesia consisting of halothane, nitrous oxide, and oxygen with a 4 liter flow rate, 2 liters each of nitrous oxide and oxygen was administered. Halothane concentration was 2.5% for the first 10 minutes, 2.0% for the following 10 minutes and 1.5% for the final 10 minutes. The first postoperative course was uneventful.

Several radioactive uptake studies revealed the patient's condition to be euthyroid. Grafting sites were noted to be cyanotic on the 3d postoperative day. On the 7th postoperative day, cultures were positive for S. aureus, but the grafts appeared to be healing without benefit of antibiotic therapy. Two weeks later a routine urinalysis was 1 plus for bile and contained 2 to 5 white cells per high powered field. Nurses recorded frequent episodes of profuse diaphoresis during this interval.

The patient underwent elective thyroidectomy on the 25th hospital day. Preoperative hemoglobin was 15.1 gm. per 100 ml., with hematocrit of 48. The patient was maintained during the 3 hour surgical procedure on halothane, nitrous oxide and oxygen anesthesia with a 4 liter flow of nitrous oxide and oxygen, 2 liters each, in a semi-closed circle absorption system. The concentration of Fluothane did not exceed 1% on the Fluotec scale at any time. Respirations were assisted thoughout the operation, both manually and by intermittent use of the Bird respirator, with a tidal volume of 600 to 700ml. and normal minute volume. Blood pressure ranged from 120/80 to 140/90 and pulse from 90 to 100. During the procedure 5 tracheobronchial toilets, producing 1 to 2 ml.

of tenacious white mucous per aspiration, were performed. Right thyroid subtotal lobectomy was performed with biopsy of the left lobe. Estimated blood loss was 800 ml. and the patient received one unit of whole blood.

Postoperative hemoglobin was 13.9 gm. per 100 ml., with hematocrit of 46. During the next 18 hours there were four episodes of emesis of greenish fluid. During the initial retching period there was a short period of cyanosis lasting 2 to 3 minutes in the recovery room. Respiration was assisted for the next several hours by means of the Bennett pressure breathing unit. Recovery room medications consisted of: 75 mg. meperidine hydrochloride, 0.5mgm. levallorphan and 500,000 units penicillin given twice intramuscularly.

On the first postoperative day the patient had several episodes of profuse diaphoresis and continued to be nauseated. Temperature was 101 F., blood pressure 146/86, and pulse 96. Chest x-ray taken on the morning of the 2d postoperative day was negative.

At 6:00 PM on the 2d postoperative day the patient was definitely jaundiced and anuric. Treatment for renal shutdown was immediately instituted. Complete retesting of the blood administered during surgery revealed no evidence of incompatibility.

On the 3d postoperative day renal and hepatic failure progressed rapidly. Laboratory findings included: hemoglobin, 15.3 gm./100 ml.; hematocrit, 48; negative blood culture; urea nitrogen, 63 mg.; total bilirubin, 11.9 mg. with 1-minute direct value, 6.7 mg./100ml.; negative direct Coombs test; alkaline phosphatase, 14.3 Bodansky units; transaminase, 244 units; prothrombin time, 10%; sodium, 144 mEq. per

liter; potassium, 6.5 mEq.; carbon dioxide, 15.3 mEq per liter. Urine output for the 24-hour period was 25 ml. with a specific gravity of 1.010 and 4 plus test for albumin. Urine was negative for occult blood and bile.

Steroids were administered without benefit. Renal dialysis could not be undertaken due to the patient's lowered prothrombin time. Late on the 3d postoperative day, the patient became hypertensive, spiked a temperature of 105 F. and expired.

Autopsy performed 2 hours postmortem revealed that the heart weighed 625 gm., with old healed aortic valvulitis and atherosclerosis. Coronary arteries were adequately patent and normal in distribution. The myocardium was soft, flabby and tan with petechiae on the posterior epicardial surface and revealed an inflammatory reaction on microscopic examination. The lungs were heavy and wet revealing acute congestion and edema with generalized intraalveolar hemorrhage.

The liver was very soft, tan to grayish-tan, flabby and putty-like weighing 1830 gm.. Extra- and intrahepatic circulation was patent throughout. All lobular pattern had disappeared grossly. Microscopic examination confirmed loss of lobular pattern and showed complete lysis of all cells. Necrosis was also present in the pancreas to a lesser degree. Right and left kidneys weighed 150 and 275 gm., respectively, and were large, pale and swollen. The microscopic appearance showed early extensive necrosis of glomeruli and more advanced necrosis of tubular epithelium. Proximal tubules were completely autolyzed and showed desquamation of pink amorphous masses of epithelial cells, with only occasional nuclei remaining. The lower nephrons also showed desquamated cells and tubulorhexis; some of these cells showing peripheral calcification. Right adrenal gland weighed 15 gm. and was anatomi-

cally normal; the left contained a large central myelolipoma and weighed 170 gm.

The vessels in all organs examined revealed no microscopic evidence of hypersensitivity angiitis. Tissue analysis for heavy metals and halothane and its breakdown products was negative.

The surgically removed thyroid tissue revealed a microfollicular adenoma wit capsular infiltration but no definite vascular invasion.

Brody and Sweet[19] reported four cases of massive hepatic necrosis following halothane anesthesia in1963.

The first case was a 70-year old woman with presenting complaints of flatulence, fatty food intolerance, occasional bouts of nausea and vomiting and right upper quadrant abdominal pain. Cholelithiasis was demonstrated with oral cholangiograms. Hypertension (170/80 mm. Hg) and arteriosclerotic heart disease were present.

Preoperative laboratory findings were: prothrombin time, 61%; bromsulphthalein retention, 12%; alkaline phosphatase, 6.0 King-Armstrong units; thymol turbidity, 2.0 units; total bilirubin, 0.3 mg. per 100 ml., 1-minute direct, 0.1 mg./100 ml.; and normal levels of total protein and albumin/globulin ratio.

Cholecystectomy and incidental liver biopsy were performed under halothane, nitrous oxide and oxygen anesthesia. Total flow rate was 6 liters per minute, 3 liters each of nitrous oxide and oxygen. Halothane concentration varied from 0.4 to 0.8% of inspired gases. Six mg. of d-tubocurarine was administered intravenously just prior to opening of the peritoneal cavity. Assisted and controlled respirations were used throughout the entire procedure. Total anesthetic time was 2 hours and 50 minutes with an uneventful course.

Histologic examination of the gall bladder revealed chronic inflammation; liver showed only minimal lipidic infiltrate. Postoperative course was afebrile and uneventful and the patient was discharged on the 7th postoperative day.

The patient was readmitted on the seventeenth postoperative day in coma. She had been jaundiced for two days with nausea and vomiting for five days, becoming comatose en route to the hospital and responding only to pain on admission. There was abdominal distention and guarding on the right side. Bowel sounds were absent. Blood pressure was 140/70 mm. Hg. Laboratory findings were as follows: white cell count, 16000 on first day and 24000 on the next; alkaline phosphatase, 5.9 King-Armstrong units; total bilirubin level, 11.8 mg./100 ml. with 1-minute direct, 5.4 mg./100 ml. and on the next day total bilirubin 19 mg./100 ml., 1-mimute direct, 9.4 mg./100 ml.; serum transaminase, 1100 units. Her condition deteriorated, the patient became hypotensive, required blood transfusions, and during the last 2 days of life she was oliguric. The patient expired on the 20th postoperative day.

At autopsy the liver weighed 600 gm. and presented the typical gross appearance of acute yellow atrophy. The histologic sections revealed severe centrolobular and midzonal necrosis which had extended in many areas to involve entire hepatic lobules. Surviving hepatic cells at the periphery of the lobules showed vacuolar degeneration of the cytoplasm. There was fresh hemorrhage in the center of the lobules and abundant lipochrome pigment in reticuloendothelial cells. The portal spaces contained leukocytes but there was no suggestion of ascending cholangitis. No hepatic endophlebitis was seen. The hepatic artery was dissected and was patent throughout. In addition to the hepatic findings, there was evidence of multiple hemorrhages and massive melena from

an acute gastric ulcer.

The second case reported by Body and Sweet occurred in a 74-year-old woman who had had recurrentattacks of right upper quadrant pain with occasional light-colored stools and dark urine during the past 30 years. Cholecystograms revealed gallstones. Cholecystectomy, common bile duct exploration and incidental liver biopsy were performed without preoperative laboratory examinations.

General anesthesia was maintained with a semi-closed, circle, carbon dioxide absorbing system with nitrous oxide, oxygen and halothane. Halothane concentration varied from 0.4 to 1.0 per cent from a "copper-kettle" vaporizer. Oxygen concentration, as determined by flow rates, varied from 33% to 50% with a total flow rate varying from 2 to 8 liters per minute. Anesthetic time was 3 hours, and the patient's anesthetic course was deemed satisfactory. No blood was given.

Microscopic examination of the specimens revealed a normal liver and chronic cholecystitis with cholelithiasis. Eight days postoperatively a cholangiogram was obtained through the T-tube; no obstruction was seen. The day following this, fever spiked to 103 F. and the patient was believed to have an ascending cholangitis. Coagulase-positive Staphylococcus was isolated from the T-tube drainage. Appropriate antibiotics were given, but the fever continued for seven days, after which the temperature became normal. In the week before death she again had a fever of 101.8 F.. Laboratory findings sixteen days before death included: alkaline phosphatase, 13.7 King-Armstrong units; total bilirubin, 32.4 mg./100 ml., 1-minute direct, 14.8 mg./100 ml.; serum transaminase, 330 units; prothrombin time, 14%; cephalin flocculation, 4 plus at 48 hours; and bromsulphthalein retention, 77%. Two days before death total bilirubin was 52 mg./100 ml. and alkaline phospha-

tase was 26 King-Armstrong units. Her condition remained at first unchanged, but later she developed an asynchronous tremor and became comatose. The patient expired 43 days postoperatively.

At autopsy the liver weighed 780 gm. and presented the clinical of massive necrosis on gross examination; 2700 ml. of cloudy, yellow ascitic fluid were present. No localised abscesses were present in the liver. Hepatic arteries, portal vein, and the common bile duct were carefully examined and found to be normal. Histologic sections revealed large areas of coagulation necrosis, containing many "ghost" cells in areas in which no viable liver tissue could be identified. Where some hepatic parenchyma survived, necrosis was centrolobular and midzonal and surviving cells showed lipidic change.

Their third case involved a 63-year-old man admitted with recurrent left retinal detachment. Previously he had had a cataract removal under local anesthesia and a left retinal imbrication receiving thiopental, nitrous oxide, oxygen and halothane anesthesia with a 0.2% succinylcholine intravenous drip. The concentrations of halothane were not known but operative and postoperative course were uneventful and he was discharged on the seventh postoperative day.

Seven weeks later he developed recurrent retinal detachment and a second scleral imbrication with silicone sponge implantation was performed. Anesthetic agents were endotracheal,halothane,nitrous oxide and oxygen in a semi-closed , carbon dioxide absorbing filter system. Halothane concentrations varied from 0.8 to 1 percent. Total anesthetic time was was two hours and 45 minutes.

On the 3d postoperative day the patient became depressed, anorexic, lethargic, completely tired out and slept frequently. The patient was discharged on the 6th postoperative day. Shortly thereafter jaundice

became apparent and the patient expired later of hepatic failure, 16 days after the last operative procedure.

At necropsy the liver was described as very small with some evidence of necrosis on gross examination. Histologic appearance was described as early cirrhosis of postnecrotic type with prominent regeneration activity, condensation of supporting connective tissue and proliferation of bile ducts. Bile stasis in distended intralobular canaliculi was present. There were additional wide areas of recent necrosis. The portal spaces contained many neutrophils and lymphocytes.

The fourth case in the series of Brody and Sweet was that of a 51-year-old woman whose complaints were painful mass in the left breast of 2 months' duration and intolerance to fatty foods and flatulence for many years.

The mass was excised from the left breast and proved to be a ruptured epidermal cyst. Halothane was administered in a semiclosed circle filter, carbon-dioxide absorbing system with a gas flow of 4 liters per minute of nitrous oxide plus 2 liters per minute of oxygen, and the halothane concentration varied from 0.6 to 1 percent. Anesthetic course and recovery were entirely satisfactory.

On the 2d postoperative day the patient experienced acute onset of right upper quadrant pain, nausea, vomiting, temperature, 100.8 F., and leukocytosis, 15500 per cu. mm.. The diagnosis of acute cholecystitis was made and oral cholecystograms resulted in nonvisualization of the gallbladder. When the symptoms failed to abate after 24 hours, cholecystectomy and common bile duct exploration were carried out. Liver function tests on the morning of the operative procedure were normal.

Anesthesia for the procedure consisted of semiclosed, endotracheal

halothane, nitrous oxide and oxygen with a total gas flow of 6 liters per minute following induction. Oxygen concentration was maintained at at leas 33% and the halothane concentration did not exceed 1%. Blood pressure dropped from the normal 134/90 mm. Hg. to 100/80 mm. Hg on two occasions, but for the most part it was maintained at approximately 129/90. Total anesthetic time was three and one half hours.

The gallbladder was distended, edematous and filled with small stones. The liver appeared normal at operation and was not biopsied.

Immediate postoperative course was satisfactory. Urticaria and fever appeared on the 5th postoperative day. Penicillin therapy was promptly discontinued. Urticaria abated but the fever continued, ranging from 102 F. to 104 F. Operative and postoperative cholangiograms were normal. Scleral icterus developed on the eleventh postoperative day. Laboratory findings included: white cell count, 1700/cu. mm.; total bilirubin level, 3.8 mg./100 ml. Alkaline phosphatase was 18 King-Armstrong units but transaminase had dropped to 618 units. The T-tube continued to drain clear yellow bile, and the patient was anorexic, lethargic and seriously ill. No exact diagnosis was made but coincidental acute viral hepatitis was considered. Ascending cholangitis was ruled out because the liver was not tender. Following gradual recovery the patient was discharged 35 days after the procedure. Liver function has returned to normal.

Morris and Feldman[20] reported a case of massive hepatic necrosis in a patient who received carbon dioxide during a halothane anesthesia. The patient had diffuse abdominal carcinomatosis, not involving the liver,

for which palliative colostomy was performed. He had an unrecognized bowel perforation at operation and subsequently developed peritonitis and died on the 3d postoperative day. Liver function tests on the day before death were grossly abnormal. Necropsy sections of the liver revealed diffuse focal necrosis of the liver, not specifically centrilobular in distribution. It is somewhat equivocal as to whether the liver necrosis was contributed to by the anesthetic or was only a consequence of the peritonitis.

Lindenbaum and Leifer[22] presented a case report of 9 patients in which halothane was at least sus pectas a cause of hepatic dysfunction.

Their 1st case occurred in a 52-year old who had had poliomyelitis at age 7, leaving her with a shortened, atrophic right leg. She underwent complete arthrodesis of the right ankle under halothane, nitrous oxide and oxygen anesthesia in December, 1959. She felt well after the operation until the tenth postoperative day. She complained of chills and malaise. Temperature spikes to 102 to 103 F. were recorded over the next 3 days and she complained of myalgia and weakness. Cephalin flocculation and thymol turbidity were negative. Urine and blood cultures showed no growth and it was believed that she had an obscure viral infection. Temperature dropped to normal on the 14th postoperative day.

She was readmitted in January, 1960, for further reconstructive orthopedic surgery, again performed under halothane and nitrous oxide anesthesia. Eight hours after the procedure, the temperature rose to 102 F. and she complained of myalgia, marked malaise, and weakness. On the 1st postoperative day the temperature rose to 104 F. although physical examination, complete blood count and urinalysis were normal. On the 3d day the temperature had dropped, but on the 4th days she

appeared icteric. Minimal temperature elevation persisted, ranging from 100.2 F. to 100.4 F for the next 2 weeks. Maximum abnormalities of liver function appeared during the 3d postoperative week. Bilirubin rose to 30.8 mg./100ml; alkaline phosphatase, 38 King-Armstrong units ; cephalin flocculation, 2 plus; thymol turbidity, negative; serum glutamic oxalacetic transaminase, 146 units; prothrombin time, 24 seconds. Six months later in the outpatient department, alkaline phosphatase was still 20 King-Armstrong units. Two months later alkaline phosphatase was 20 units and infectous hepatitis was consdered the most likely diagnosis.

In June, 1962, the same nurse was readmitted to the hospital for further orthopedic surgery. Alkaline phosphatase was 13 King-Armstrong units. Serum glutamic oxalacetic transaminase was 19 units. Reconstructive surgery was performed on the right foot under halothane and nitrous oxide anesthesia. Eight hours after the procedure the temperature rose to 100.4 F. and she complained of epigastric discomfort. On the 1st postoperative day epigastric tenderness was noted on physical examination and the liver edge was barely palpable. White-cell count was 3800, with 93% neutrophils and on the following day the white cell count was 3550 with 91% neutrophils and 4% eosinophils. There daily temperature spikes to the range of 100.2 to 100.6 F. over the next 15 days. The urine appeared dark on the 6th postoperative day and the white cell count was 6750, with 50% lymphocytes, many of which were atypical forms similar to those seen in infectious mononucleosis, though the heterophil-antibody agglutination titer was not elevated. On the 7th postoperative day the liver edge was palpable 1 fingerbreadth below the right costal margin. Liver function tests were at the height of abnormality

on this day: serum bilirubin, 1.2 mg./ 100 ml.; alkaline phosphatase, 33 units; cephalin flocculation, negative; thymol turbidity, negative; serum glutamic oxalacetic transaminase, 597 units; serum glutamic pyruvic transaminase, 880 units. Tests of hepatic function showed gradual improvement during the 3d and 4th weeks, and the patient was discharged 30 days after the procedure, feeling well except for mild anorexia and easy fatiguability. The liver was palpable at the right costal margin. Bilirubin was 0.9 mg. per 100 ml., serum glutamic oxalacetic transaminaminase, 213 units, and the alkaline phosphatase was 23 King-Armstrong units.

Three months the patient was asymptomatic, the liver edge was no longer palpable, and serum glutamic oxalacetic transaminase and pyruvic transaminase were normal.

The second case was a 50-year-old housewife admitted for removal of bleeding colonic polyps. Admission white-cell count was 11,900, with a normal differential, and alkaline phosphatase was 12 King-Armstrong units. Exploratory laparotomy and excision of 2 colonic polyps was performed under anesthesia with cyclopropane, halothane and nitrous oxide. No abnormalities of liver and gallbladder were noted at operation. Fever of 100.4 F. and 103.4 F. were present on the 1st and 2d postoperative days respectively. On the 3d postoperative day the temperature spiked to 106.4 F., the patient had a shaking chill, and blood pressure dropped to 60/0. She had generalized erythema with a few urticarial areas although she did not appear very ill. White cell count was 1750, with 63% lymphocytes. Generalized peritonitis was suggested, despite normal abdominal findings, and exploration was carried out 3 days af-

ter the original procedure with cyclopropane anesthesia. No perforation or evidence of peritonitis was found and the patient received 1 unit of blood during the procedure. She was treated with hydrocortisone and tetracycline for an assumed gram-negative septisemia despite negative blood cultures. The temperature dropped to normal and pressor agents were no longer required by the 3d day after the 2nd procedure. Low grade fever from 100 to 101 F. on the 25th day after the first procedure scleral icterus was noted. Hepatic function tests showed: bilirubin, 5.8 mg./100ml.; alkaline phosphatase, 57 units; cephalin flocculation, 2 plus; thymol turbidity, +. Liver function tests gradually returned toward normal in the outpatient department.

The patient was readmitted one year later for repair of an incisional hernia after doing well at home. Physical examination and complete blood count were within normal limits. Ventral incisional herniorrhaphy was performed under halothane and nitrous oxide anesthesia with no blood transfusions. A few hours later the temperature rose to 103.4 F. though the patient felt well and physical examination was unrevealing. Two days later an eosinophil count of 7% was noted. By the 5th postoperative dat the temperature had fallen to the range of 100 to 101 F. and remained at this level until the 24th postoperative day when it became normal. Darkening of the urine became apparent on the 10th postoperative day when the bilirubin was 1.6 mg./100 ml. and cephalin flocculation negative. Liver function tests reached their peak abnormalities two days later: bilirubin, 4.2 mg./100 ml.; alkaline phosphatase, 54 King-Armstrong units; cephalin flocculation and thymol turbidity, negative; serum glutamic oxalacetic transaminase, 1000 units. These gradually returned to normal and 4½ months later

She was asymptomatic, the liver was no longer palpable and oral cholecystography was within normal limits.

The third case, a Puerto Rican housewife, age 62, was admitted for removal of vulvar lesions in July, 1962. Physical examination was normal, except for bilateral, indurated, ulcerated vulvar lesions and blood pressure of 190/100. Serum alkaline phosphatase was 11 King-Armstrong units. She was given a single transfusion when biopsy of a colonic lesion at proctoscopy was followed by rectal bleeding. The biopsy revealed chronic inflammation. A mass lesion in the left kidney was demonstrated by intravenous pyelogram. Radical vulvectomy with bilateral inguinal-lymph-node dissection was performed with halothane and nitrous oxide anesthesia. Total anesthetic time was 9 hours and the patient received 5 transfusions during the procedure. Specimens revealed carcinoma of the vulva without involvement of regional lymph nodes. Postoperatively the temperature rose to 100.6 F. and 100 F. on the 1st and 2nd days, respectively.

Seven days after the first procedure skin grafts were applied to the infuinal areas under halothane and nitrous oxide anesthesia. There was prolonged, intermittent nausea and vomiting for 3 weeks. The temperature rose to a peak of 103.6 F. on the 3d postoperative day. The patient was noted to be markedly lethargic with shock tenderness in the hepatic bed. The urine appeared dark on the 4th day and the serum icteric on the 5th day. Cephalin flocculation was ± and thymol turbidity negative. The peak abnormalities in hepatic function tests were: bilirubin, 4.0 mg./100 ml.; alkaline phosphatase, 55 King-Armstrong units; cephaling flocculation, 2+; thymol turbidity ±. The patient was discharged on the 29th postoperative day when the serum glutamic pyruvic transaminase was 59 units and the remainder of the hepatic function tests were normal.

Eighteen days after her dismissal the patient was admitted for excision of the left kidney mass and physical examination was unremarkable. Serum glutamic oxalacetid transaminase was 30 units and the alkaline phosphatase, 9 King-Armstrong units. A cyst was excised from the left kidney under halothane and nitrous oxide anesthesia in a procedure lasting 1 hour and 20 minutes. The first 5 postoperative days were marked by intermittent nausea and vomiting, with temperature elevations of 102 to 103 F. No hepatomegaly, hepatic tenderness or jaundice were found. On the 5th postoperative day serum glutamic oxalacetic and pyruvic transaminases were both 340 units and the alkaline phosphatase was 14 King-Armstrong units. The patient was discharged on the 10th postoperative day after the temperature fell to normal and the patient remained asymptomatic. At this time alkaline phosphatase was 18 King-Armstrong units. Ten days later in the outpatient department the patient felt well: serum glutamic oxalacetie transaminase was 75 units; serum glutamic pyruvid transaminase 30 units; and alkaline phosphatase 16 King-Armstrong units.

The fourth case was a 60-year-old Puerto Rican woman admitted for biopsy of a vulvar lesion in August, 1962. Alkaline phosphatase was 9 King-Armstrong units. The patient was anesthetized for 10 hours with nitrous oxide and halothane while radical vulvectomy and bilateral inguinal lymph node dissection were performed. The patient was afebrile except for the second postoperative day when the temperature reached 100.2 F. by mouth. The patient did well except for intermittent moderate nausea lasting for several weeks. The patient had old, inactive but never adequately treated tuberculosis so long term treatment with streptomycin and isoniazid was begun. On the 12th postoperative day and on subsequent days a generalized urticarial rash developed. The

patient complained of right upper quadrant pain, nausea and vomiting one week later. On the 21st day the liver edge was tender and palpable 5 fingerbreadths below the right costal margin. Two days later slight splenomegaly was noted. At that time the only abnormal hepatic function tests were: thymol turbidity +; serum glutamic oxalacetic transaminase, 480 units; and serum glutamic pyruvid transaminase, 340 units. By the 25th day the patient felt well, appetite was excellent and the liver was no longer tender. Oral cholecystography showed multiple radiolucent gallstones while cystic and common bile ducts appeared normal. The patient was discharged on the 46th day although the liver was still palpable and serum glutamic oxalacetic transaminase was 440 units.

The fifth case discussed was a 59 year old man with a past history of diverticulitis and chronic gastric ulcer. Physical exami ation revealed a mass palpable on rectal examination. Liver function studies were normal. Cystoscopy and rectal biopsy were performed in February, 1962, under halothane and nitrous oxide anesthesia. Postopertive course was normal. Six days after the first procedure he developed severe abdominal pain and signs of generalized peritonitis without hypotension developed. Laparotomy and partial gastrectomy for perforated gastric ulcer was performed under nitrous oxide and halothane anesthesia. He was given 1 unit of blood during the procedure. Postoperative course was uneventful except for a transient deep thrombophlebitis of the right calf.

In March, 1962, he underwent sigmoid colectomy and cecostomy for diverticulitis with surrounding abscess formation with halothane and nitrous oxide anesthesia. Immediately after the procedure, the temperature began to rise, reaching a peak of 101.8 F. on the 1st postoperative day. On the 2nd day the temperature became normal and appeared

appeared icteric. Marked hepatic functional disturbances were present during the first 3 postoperative weeks: serum bilirubin, 20.8 mg./100 ml.; alkaline phosphatase, 42 King-Armstrong units; cephalin flocculation ±; thymol turbidity, ±; serum glutamic oxalacetic transaminase, 800 units; serum glutamic pyruvic transaminase, 1500 units. The patient remained asymptomatic, ate well and derived his usual satisfaction from cigarettes. Janudice slowly cleared and there was no hepatosplenomegaly. Bilirubin had dropped to 3.0 mg./100 ml. on the 28th day after the colectomy and just before discharge. On readmission for reeraluation 6 months af ter operation, hepatic function studies revealed no remaining abnormalities.

The sixth case presentation was that of a 72-year-old woman, admitted in July, 1962, for evaluation of a breast mass. There was a 4 by 5 cm. mass in the right breast on physical examination. Alkaline phosphatase was 9 King-Armstrong units. Breast biopsy under halothane and nitrous oxide anesthesia revealed papillary adenocarcinoma. Temperature ranged from 100 to 101 F. immediately and on the first two postoperative days. Four days later simple mastectomy was performed under nitrous oxide and halothane anesthesia. A few hours later temperature rose to 102.6 F.. Daily temperature spikes to 101 F. continued. On the 5th day the tmperature rose to 103.8 F. and the patient complained of weakness. On the 6th day she had several shaking chills and white cell count was 6300, with 6% eosinophils. The liver edge was palpable 2 fingerbreadths below the right costal margin on the 12th day. One day later the patient became jaundiced and continued to become more jaundiced through the 2nd week at which time the liver became tender. Peak liver function abnormalities were observed during the 3d postoperative week:

serum bilirubin, 18.0 mg./100 ml.; alkaline phosphatase, 45 King-Armstrong units; cephalin flocculation, negative; thymol turbidity, negative; serum glutamic oxalacetic transaminase, 2800 units; prothrombin time, 21 seconds. Exploration was performed on the 20th postoperative day, with a preoperative diagnosis of common duct obstruction under cyclopropane and nitrous oxide anesthesia. The gallbladder, biliary tree and pancreas as well as the operative cholangiogram appeared normal. Liver biopsy revealed extensive areas of necrosis most prominent in the central zones. Inflammatory mononuclear infiltrate was seen in the triads. Bile stasis, though present, was not conspicuous. The excised gallbladder was histologically normal. The postoperative course was benign and the patient was discharged 37 days after the mastectomy though the temperature still rose daily to 100.4 F. and bilirubin was 4.0 mg./100 ml.. Two weeks later as an outpatient she felt well although the liver edge was palpable 2 finger-breadths below the right costal margin. Three months after the operation liver-function tests revealed no abnormality.

The seventh reported case was that of a 16-year-old schoolboy who was admitted a few hours after a right knee injury in August, 1962. Physical examination was within normal limits except for a temperature of 100.4 F. and tender soft-tissue swelling on the medial aspect of the right knee. Examination of the right knee and aspiration of 50 ml. of blood were performed under halothane and nitrous oxide anesthesia on the day following admission. The swelling recurred after operation and there were continued fever spikes of temperature to the range of 101 to 102 F. Six days after admission he underwent arthrotomy of the right knee and repair of a muscle tear with halothane and nitrous oxide anesthesia. The patient felt well after operation

despite the fever. On the 5th postoperative day he complained of headache, anorexia, lethargy, fatigue and malaise. Physical examination revealed minimal, nontender, generalized adenopathy and slight shock tenderness in the hepatic bed. The spleen was palpable 4 cm. below the left costal margin; firm and slightly tender. Peripheral blood smear appeared normal and heterophil-antibody agglutination titer was normal. Liver function tests showed significant abnormalities: bilirubin, 1.0 mg./100 ml.; alkaline phosphatase, 34 King-Armstrong units; cephalin flocculation and thymol turbidity, negative; serum glutamic oxalacetic transaminase, 540 units; and prothrombin time, 19 seconds.

A 34-year-old physician admitted in May, 1962, with complaints of nausea, and abdominal pain of 5 hours' duration was presented as the eighth case report. Physical examination revealed mild tenderness in the upper quadrant localizing to the right lower quadrant that evening. White cell count was 11,850 with a normal differential. Appendectomy for acute appendicitis was performed under halothane and nitrous oxide anesthesia. The temperature rose to 101.8 F. fourteen hours later. He remained febrile, but asymptomatic for the first 4 days. He was discharged on the 6th day, feeling well. He was readmitted 6 days later after having noted anorexia, weakness, darkening of the urine, and a temperature of 100 F. the day before. Physical examination revealed the liver edge to be tender and palpable 2 fingerbreadths below the right costal margin. The tip of the spleen was also palpable. Temperature was 102.2 F. and a stool appeared to be light colored. Hepatic function tests revealed the following findings: serum bilirubin, 8.2 mg./100 ml.; alkaline phosphatase, 33 King-Armstrong units; cephalin flocculation and thymol turbidity, 3+; serum glutamic oxala-

acetic transaminase, 1730 units; serum glutamic pyruvic transaminase, 1270 units; prothrombin time, 15 seconds. White cell count was 4300 with a normal differential. Temperature returned to normal on the 15th postoperative day, but the jaundice had deepened. During the next 3 months icterus and hepatosplenomegaly gradually disappeared, though all hepatic function tests did not return to normal until the 16th postoperative week.

The ninth reported case in the series was that of a 49-year-old man admitted for treatment of sudden severe abdominal pain. He had had recurrent epigastric pain for 5 years, with a recent exacerbation. There was also a history of chronic alcoholism. Significant physical findings were: boardlike rigidity on the right side of the abdomen and absent bowel sounds. Plication of a perforated duodenal ulcer was performed shortly after admission with halothane and nitrous oxide anesthesia. At laparotomy the liver appeared normal and the patient was not transfused. The patient did well until the temperature rose to 102 F. on the afternoon of the 1st postoperative day and to 102.6 F. on the 3d postoperative day. The urine appeared dark on the 4th postoperative day and a urine test for bile was reported "trace positive". Bromsulphthalein retention was 35% in 30 minutes. The temperature returned to normal on the 7th day and he was discharged on the 12th postoperative day.

One month later he was readmitted for elective gastrectomy and physical examination was within normal limits. Partial gastrectomy and vagectomy were performed under methoxyflurane and nitrous oxide anesthesia. The temperature rose to 100.6 F. on the 1st postoperative day and on the 2d day he appeared lethargic and scleral icterus was observed. Abnormalities of hepatic function tests gradually in-

creased to these peaks: serum bilirubin, 29.5 mg./100 ml.; alkaline phosphatase, 17 King-Armstrong units; cephalin flocculation, 2 ; thymol turbidity, 1 ; serum glutamic oxalacetic transaminase, 720 units; serum glutamic pyruvic transaminase, 600 units; prothrombin time, 44 seconds. By the 5th day a flapping tremor was noted and fetor hepaticus and intermittent coma had appeared on the 7th day. Treatment with intravenous hydrocortisone, vi amin K and neomycin was administered. Coma developed on the following day as well as pneumonia in the left upper lobe. Antibiotics were administered. The occurrence of upper gastrointestinal bleeding was controlled with transfusions and gastric hypothermia. The patien died on the 11th postoperative day with oliguria, hypotension and shock despite massive doses of intravenous nor-epinephrine.

The principal autopsy findings were in the liver which weighed 1050 gm. Grossly the parenchymal architecture was obliterated with areas of softening, extensive hemorrhage and necrosis. There was complete loss of normal architecture with collapse of hepatic plates on microscopic examination. Collections of acute and chronic inflammatory cells were present in portal connective tissue and fatty changes in the few remaining hepatic cells in addition to considerable cholestasis.

Two cases of liver necrosis following halothane anesthesia were reported by Bunker and Blumenfeld.[22]

The first occurred in a 16-year-old girl admitted for repair of a deep laceration of the right wrist which she sustained when she fell through the glass window of a door. There was nothing remarkable in the routine history and physical. Five hours after admission surgical repair was performed with halothane and nitrous oxide anesthesia for maintenance following induction. Total anesthetic time was 4

hours. No periods of hypotension occurred while respirations were controlled or assisted initially but were spontaneous throughout most of the procedure. The postoperative course was not unusual until the 6th day. Then the temperature rose to 100 F., and pulse to 100. The pulse rose to 160 or higher and the temperature to 104.5 F. in the next 2 days. On the 8th postoperative day temperature was 104.4 F. and subsequently fell to below normal. White counts on the 7th and 8th postoperative days were 8450 and 3610, respectively, but rose to 21,800 on the 12th day with a marked neutrophilic leukocytosis and shift to the left. A tendency to bleed was noted on the 12th day and prothrombin determination at that time was less than 10% of normal. Severe nosebleed, originating in the left anterior nasal septum, was controlled by cauterization on the 13th day. During the last few days of life, cerebral symptoms ranging from listlessness to yelling and screaming appeared and the patient expired 13 days after surgery.

Postmortem findings were limited to the liver and kidney. Histologic sections of the liver showed profound necrosis, estimated to have destroyed more than 4/5 of the liver. Liver cells near the portal canals, still showing stainable nuclei, were generally altered by marked marginal vacuolization of the cytoplasm. Tyrosine crystals were present in abundance. Small plugs of bile were occasionally observed in bile canaliculi. An infiltrate of lymphocytes, occasional eosinophils and rare neutrophils were seen in the portal canals.

Microscopic kidney sections showed degenerative changes primarily involving the proximal convoluted collecting tubules, commonly associated with liver necrosis. Further changes included acute hyperemia of the spleen, slight focal myocarditis and aspirated blood and vegetable matter in the respiratory tree.

The second case reported was that of a 67 year old man who was admitted to the hospital January 23, and died on February 11, 1962. Chief complaint on admission was severe upper abdominal pain of 4 hours' duration. The illness began 2 weeks prior to admission with intermittent pain in the upper abdomen. Past history of duodenal ulcer and rectal polyps was obtained. There was also a history of alcoholism, although not during the past few years. Admission physical findings included: ashen color; dyspnea; cyanosis; temperature varying between 97.6 and 99 F. by mouth; pulse varying between 60 and 90; respirations 20; blood pressure varying between 90/60 and 130/80; emphysematous chest; chest described as clear by one physician and by another to have dullness and diminished breath sounds over the left lower lobe with a few rales; boardlike abdomen with absent bowel sounds; prostate twice normal size. Laboratory findings were reported as follows: hemoglobin, 17.9 gm./100 ml.; hematocrit, 53%; white cell count, 9700; Lee-White coagulation time, 13 minutes; bleeding time 2 minutes. Eight hours after admission, laparotomy was performed with nitrous oxide, oxygen and halothane anesthesia following induction with methohexital with succinylcholine for relaxation. Total anesthetic time was 1 hour 25 minutes. A perforated ulcer on the anterior wall of the duodenum was found and repaired. The liver was described as normal in appearance and size. Postoperatively there was progressive improvement except for some continued respiratory difficulty. Gross melena and hematemesis occurred on the 10th postoperative day. Second laparotomy was performed after a transfusion. Anesthesia was induced with thiopental and maintained with endotracheal halothane, nitrous oxide, and oxygen, with succinylcholine for muscular relaxation. Total anesthetic time was 4 hours 45 minutes. A hypotension of 80/60 was

sustained during the first ½ hour of surgery but blood pressure subsequently rose to 120/80 as additional blood transfusions were administered throughout the procedure. An ulcer of the posterior duodenal wall with an eroded large artery in its base was found. Suture ligature was placed in the artery and gastric resection was done. The liver again appeared normal. Postoperatively the course was uneventful and fluids were being taken orally 4 days later. That evening the temperature rose to 101.2 F. and to 103 F. on the following day. Rectal temperature was 104.4 on the 6th day, pulse 108 and respiration 25. Jaundice became apparent and was verified by an elevated serum bilirubin. Renal output decreased and blood urea nitrogen rose to 96 mg./100 ml. On the 9th day renal output ceased and serum bilirubin rose to 10 mg./100 ml.. The patient expired that evening.

The most significant postmortem findings were again located in the liver and kidney. Renal changes were that of degeneration of cells lining the proximal convoluted tubules. Microscopic evidence of preexisting liver disease or interstitial hepatitis was absent. Severe acute necrosis of the liver was present with small islands of still recognizable liver cells present around the portal canals. These demonstrated considerable damage, characterized by dense, granular cytoplasm, marked variation in nuclear size and hyperchromatism of many nuclei. Occasional liver cells were recognized somewhat more within the interior portion of a lobule, but in the majority of places coarsely granular necrotic debris and hemorrhage were all that was left of the remainder of each lobule. In addition there was marked coronary artery sclerosis, evidence of recent coronary occlusion with infarction probably 2 or 3 weeks old and bilateral bronchopneumonia.

V. DISCUSSION OF CASE REPORTS

A total of 24 cases have been reported in the literature in which halothane was considered a possible cause of deranged liver function with jaundice or massive hepatic necrosis resulting in death.

A total of 10 cases resulted in death with death occurring in a range from 2 to 43 days postoperatively, the median being somewhere between 9 and 11 days. Fourteen of the reported cases survived with hepatic function tests gradually returning to normal values within a period lasting from days to months.

Cholecystectomy was the major procedure performed in 4 of the cases, 3 of which resulted in the patient's death.

In all of the cases discussed in any detail the patient received several drugs in addition to halothane. (Two of the cases included in the tabulation were merely reported as jaundice occurring after administration of halothane without any other information concerning the patient's course.) There are at least 70 drugs known to produce jaundice as a side effect in man. Evidence for halothane as the etiologic agent was somewhat more convincing in those cases receiving repeated halothane anesthesia with deranged hepatic function more prominent after each halothane administration.

Two of the patients admitted to chronic alcholism in the admission history. Infectious mononucleosis was considered as a possible diagnosis in at least two cases although heterophil-antibody agglutination titers were normal at the time they were measured. Infectious hepatitis was also considered in the differential diagnosis of several of the cases without being completely ruled out.

Factors present in the organixm which may contribute to hepatotoxicity of any drug have been previously discussed. These include

hypoxia, poor nutritional status, hypercarbia, and impaired blood supply to the liver. Details pertaining to these factors are surprisingly lacking in many of the case descriptions, particularly those regarding adequacy or inadequacy of ventilation during the anesthetic procedure. Batteries of liver function tests were rarely performed preoperatively so that impaired hepatic function could be detected prior to anesthetic administration. A few patients also received anesthetic agents other than halothane during their hospitalizations.

VI. HEPATIC NECROSIS IN GENERAL

The liver's response to injury is somewhat stereotyped, beginning in the central zone of the lobule with fatty infiltration and coagulation necrosis, followed by breakdown, scavenger activity and ultimately regeneration of the liver cells. This makes it virtually impossible to distinguish among the various causes of hepatic necrosis on a morphologic basis.

Some of the etiologic agents producing massive hepatic necrosis are: viral hepatitis, caused by Virus A (infectious) and Virus B (serum); drugs and chemicals; endogenous toxins; eclampsia and toxemia of pregnancy; experimental dietary agents (in rats); circulatory disturbances with anoxia.

Drugs and chemicals producing massive hepatic necrosis may be divided into two groups: (1) those in which the amount of hepatic damage is related to the dose of drug or chemical; (2) those in which there is no relationship between dose of drug or chemical and the amount of hepatic damage. Examples of the first group of drugs and chemicals are carbon tetrachloride, chloroform, arsenical compounds, lead, etc.. Included in the second group are iproniazid, certain sulfonamides, para-aminosalicylic acid and a host of others.

Endogenous toxins include those produced by bacteria and tissue necrosis in other body regions. Best known bacterial toxins include those produced by Corynebacterium diphtheriae, clostridial infections, pneumococcal infections and possibly tuberculosis. Tissue toxins are generally associated with severe burns.

The increasing incidence of cases of unexplained liver necrosis was called to attention by Brunson, et al[3], in 1957. They presented a review of 3229 autopsy protocols of patients examined at the Minnesota University Hospitals from 1946 through 1955. All of these patients died prior to the introduction of Fluothane for general use. The greatest percentage of these cases presented hepatic necrosis for all practical purposes indistinguishable from that described in these cases.

Caravati and Wootton[17] discussed 9 cases of acute massive hepatic necrosis occurring in 662,252 hospital admissions at 3 hospitals in Richmond, Virginia area in a 15 year period. Four of these cases were attributed to acute viral hepatitis and 5 to drugs and chemicals other than halothane.

VII. SUMMARY AND CONCLUSIONS

A complete review of published literature concerning halothane covering the years from 1956 to 1963 is presented. Physical, physiological and pharmacological properties of halothane as an anesthetic agent have been discussed as well as its effect on organ systems in humans and animals. Certain limited comparisons with other anesthetic agents have been made.

Details of 24 cases of deranged hepatic function and massive hepatic necrosis following halothane anesthesia have been presented and discussed.

In view of the fact that there are multiple etiologic factors which may produce massive hepatic necrosis ant that massive necrosis produced by other causes cannot be distinguished from that attributed to halothane, it is considered unwise and unnecessary to remove halothane from the anesthesiologist's armamentarium.

Prior to its release for general use halothane was probably the most thoroughly investigated and tested agent for use in clinical anesthesia. It has been administered to literally tens of thousands of patients without adverse effects.

Halothane is an extremely potent agent and careful attention to detail in its administration is paramount. Inadequate ventilation and hypotension should be meticulously avoided. Clinical advantages and reasons for preference of halothane have been discussed.

For the present time an agent other than halothane should probably be selected for general anesthesia in patients with a history of jaundice or with deranged hepatic function by history or laboratory findings.

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