HALOTHANE ANESTHESIA

AND

LIVER DAMAGE

PARKLAND MEMORIAL HOSPITAL

MEDICAL GRAND ROUNDS

October 17, 1968

Case 1. [redacted]

The patient, a 29 year old woman of [redacted] descent, was referred to the hospital on [redacted]/65 because of fever, nausea, vomiting, restlessness progressing to semi-coma, petechial rash and abdominal distention. She was said to have been in excellent health except for a perforated ear drum. On [redacted]/65, a left tympanoplasty was performed at another hospital under general anesthesia which included halothane. The procedure was uncomplicated, the patient awoke promptly and was felt to be well enough for discharge on [redacted]. Subsequent history is fragmentary. On 5/18, she experienced back ache, a shaking chill, felt feverish, was seen at a local clinic and given tetracycline for possible urinary tract infection. Fever persisted, unsteadiness of gait developed and the patient was admitted to the local clinic on [redacted]. Temperature peaked at 105 on 5/20, and ranged from 101-103 on [redacted] and [redacted].

Diagnostic studies revealed an SGOT of 216 and 2000 and serum bilirubin of 1.6 and 0.8 on [redacted] and [redacted] respectively. Therapy included penicillin, Gantrisin and Colistin

Physical examination at [redacted] on [redacted] revealed an acutely ill, disoriented young woman who was hallucinating, T-102. The left tympanic membrane was scarred but no evidence of infection was noted. Scleral hemorrhages were seen but no icterus was noted. The abdomen was minimally distended and shifting dullness was demonstrable. Liver and spleen were not palpable. A petechial rash was present over the lower arms and anterior and posterior trunk. Neurologic exam was negative save for disorientation.

With a history of exposure to fleas and ticks (a tick had been removed from the patient a week previously) and with her clinical findings a provisional diagnosis of endemic typhus was made and the patient was started on chloramphenicol 1.5 gm/day I.V. On [redacted] the patient appeared better. She was now oriented but still febrile. Fever disappeared by [redacted] and chloramphenicol was changed to 3 gm/day by mouth. Chemical evidence of acute hepatocellular disease was now clearly present. On [redacted] increasing abdominal distention was apparent, and scleral icterus was more prominent. The markedly prolonged prothrombin time indicated severe hepatic damage. On [redacted] she developed asterixis and became semiconscious. Her condition deteriorated thereafter. She lapsed into coma, developed a metabolic acidosis, evidence of impaired renal function and became hypotensive prior to death on [redacted]. Her therapy in the last few days of life included neomycin, glucose, prednisolone 100 mg/day, occasional injections of aquamephyton, and fresh blood. Serologic studies drawn on [redacted] and [redacted] were non reactive for Proteus OX_{19}, and complement fixation tests for various rickettsial diseases were negative.

Autopsy (A65-198) revealed Massive Hepatic Necrosis.

LABORATORY DATA FOR CASE I

	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hgb	11.8			9.3		8.9		7.9	7.4	12.6
WBC	6,600			7,500	10,000	11,500		11,600		29,800
Platelets			100,000		200,000					275,000
Bilirubin - D/T			2.7/4.4		6.4/12.0	9.0/17.0	20.0	17.5/25.0		15.2/27.6
SGOT			2796		2233	1297	2110	1460	990	511
Thymol Turbidity									14.3	10.5
Cephalin flocculation			4+		4+					
Alkaline Phosphatase (Bodansky Units)			6.3				6.6			5.9
Prothrombin time-seconds Patient/Control						34/12.5		36/12.5	42/12.5	

ETIOLOGY OF FULMINANT HEPATIC NECROSIS

1. Infectious (viral) hepatitis.
2. Serum hepatitis
3. Hepatotoxins
    a. Carbon tetrachloride
    b. Chlorinated naphthalenes and diphenyls (insulation for wires; condenser material - no longer used commercially because of toxicity)
    c. Dimethylnitrosamine (formerly used to inhibit corrosion)
    d. Amanitotoxin (Amanita phalloides)
    e. Tetrachlorethane (solvent for cellulose acetate, used in "dope" - latter use abandoned; impregnating clothing with materials capable of neutralizing poisonous gasses).
    f. Trinitrotoluene (munitions workers) - ? sensitivity reaction rather than direct hepatotoxin.
    g. Chloroform
4. Drugs (Produce hepatitis-like injury)
    a. Hydrazine derivatives - Iproniazid (Marsilid); Pyrazinamide; Pheniprazine (Catron, Cavodil); Phenelzine (Nardil); Phenoxypropazine (Drazine); Isocarboxazid (Marplan); Isoniazid
    b. Metahexamid (Euglycin, Melanex).
    c. Zoxazolamine (Flexin)
    d. Cincophen
    e. Others
5. Halothane
6. Methoxyflurane (Penthrane)
7. Prolonged Shock
8. Acute fatty metamorphosis of pregnancy.

HALOTHANE AS A CAUSE OF LIVER DAMAGE AND FULMINANT HEPATIC NECROSIS

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Lancet 2: 1466, 1966

Approximately 400 cases of liver injury following halothane reported in literature by 1967. There were 144 deaths, a mortality rate of 35.6 percent.

Age distribution in cases of liver injury following halothane
(194 patients)

Age in Years	Per Cent
0-10	2.7
11-20	6.7
21-30	11.7
31-40	12.6
41-50	21.9
51-60	27.3
61-70	8.3
71-80	7.7
81-90	1.1

Sex distribution reported in 266 cases, 68 per cent men, 32 per cent women.

Almost half of the patients had received two or more exposures to the anesthetic agent.

Many papers report fever or a normal convalescence after a first exposure to anesthesia. Subsequent exposure followed by obvious development of liver injury.

Site of operation in 191 instances of reported liver injury

Site	Per Cent
Intracranial	6.3
Head and neck	6.3
Intrathoracic	4.2
Cardiac	1.0
Upper abdominal	31.4
Lower abdominal	23.6
Trunk	10.5
Genitourinary and perineal	9.4
Extremities	7.3

Onset of symptoms or signs postoperatively

Days	Per Cent
0- 2	30.1
3- 7	41.2
8-14	16.6
15-21	5.1
Over 21	7.0

Presenting findings usually include fever. Shaking chills were reported commonly. Chills might be delayed till the second week after exposure to anesthesia. Symptoms include malaise, anorexia, nausea, vomiting, lethargy, cerebral symptoms (agitation or drowsiness), abdominal pain. Jaundice appears approximately 4 to 7 days after the most recent exposure to the anesthetic but may be delayed for 2 to 3 weeks, a time at which many patients have already been discharged from hospital.

Physical findings and laboratory tests resemble those found in patients with any type of acute hepatocellular disease, with viral hepatitis the prototype.

Duration of the disease ranged from 2 to 36 days in those who died. Death occurred within 10 days or less in 55 per cent of the patients. It tended to be a fulminant disease, therefore, in those who died. In survivors, the disease ranged from a few to 121 days and persisted more than 10 days in approximately 57 per cent. Symptoms and particularly signs were apt to persist for a long time and convalescence was slow.

Pathologic diagnosis (Autopsy or biopsy in reported cases of liver injury following anesthesia)

Diagnosis	Per Cent
Massive necrosis	69
Focal necrosis	10
Fatty infiltration and cell necrosis	5
Toxic hepatitis	4
Centrolobular necrosis	2
Acute hepatitis	1
Cholangitis causing hepatocellular damage	1
Advanced cirrhosis	1
Postnecrotic cirrhosis	1
Subacute hepatic necrosis	1
Obstructive biliary cirrhosis	1
Liver stasis	1
Viral hepatitis	1

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Halothane: The first five years.
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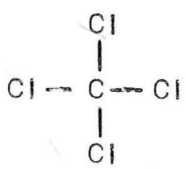
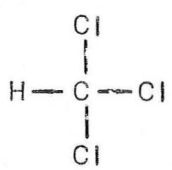
Halothane (fluothane) is a halogenated hydrocarbon anesthetic, CF_3 - CHClBr, 2-bromo-2 chloro-1, 1, 1-trifluoroethane. It is nonexplosive and noninflammable when mixed in all proportions with air or oxygen. Laboratory studies in experimental animals demonstrated some depression of hepatic function in a number of instances, fatty metamorphosis developed occasionally. The liver was resistant however, to prolonged and repetitive anesthetic exposures.

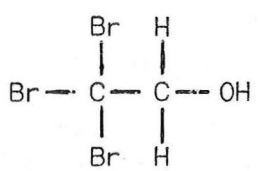
When administered in a hypoxic atmosphere, halothane had no more effect on dog liver than inhalation of an oxygen deficient mixture alone. Toxic necrosis as observed with carbon tetrachloride or chloroform was not a feature of the agent.



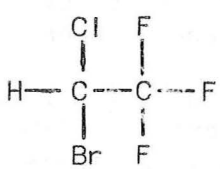
Carbon tetrachloride



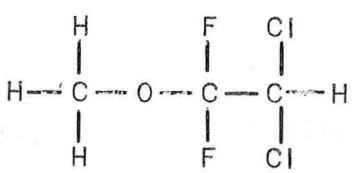
Chloroform



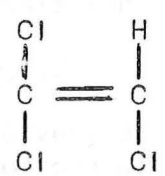
Tribromethanol



Halothane



Methoxy flurane



Trichlorethylene

HEPATIC FUNCTION IN MAN AFTER ANESTHESIA AND SURGERY

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Pathological and functional changes in the liver following upper abdominal operations.
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Abnormalities in results of liver tests are relatively common after anesthesia-surgery. In general the more peripheral and minor the surgery (saphenous vein stripping, inguinal herniorrhaphy, dilatation and curettage), the lower the incidence, extent and duration of abnormality of the test. Abdominal surgery such as subtotal gastrectomy and particularly cholecystectomy followed by an even higher incidence and extent of abnormalities. Jaundice is uncommon postoperatively. Abnormalities involve tests such as BSP, cephalin-cholesterol flocculation, thymol turbidity, alkaline phosphatase. BSP retention noted most frequently. Recent studies indicate that abnormal BSP retention is common and develops rapidly after fasting alone. Fasting undoubtedly contributes to postoperative BSP retention. Surprisingly, there is little information available about results of SGOT and SGPT in the entire postoperative period. Modest increases, usually less than 100 units, but occasionally higher, are recorded. For any comparable operation, patients with underlying liver disease can be expected to have a higher incidence of abnormalities, of greater extent and longer duration, than patients without liver disease.

There appears to be no evidence that any of the anesthetic agents in common usage (halothane, cyclopropane, ether, thiopental, nitrous oxide-oxygen) account for hepatic dysfunction more commonly than any other.

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RETROSPECTIVE HALOTHANE STUDIES

50. Summary of the National Halothane Study. Possible association between halothane anesthesia and postoperative hepatic necrosis. J.A.M.A. 197: 775, 1966.

A retrospective survey of the incidence of fatal massive hepatic necrosis and overall death rate following general anesthesia in 34 hospitals for the four-year period from 1959 through 1962 was undertaken. The study was based on data from 856,500 patients undergoing surgery and general anesthesia in 34 institutions in the four-year period before the appearance of reports of liver damage. Special attention was paid to a comparison of halothane and other commonly used anesthetics with respect to hepatic necrosis and post-operative death generally. The main conclusions are:

1. Fatal postoperative massive hepatic necrosis was a rare occurrence. It could usually be explained on the basis of circulatory shock, sepsis, or previous hepatic disease. The possible rare occurrence of halothane-induced hepatic necrosis following single or multiple administrations could not be ruled out.

2. Halothane, rather than being a dangerous anesthetic, had a record of safety as reflected in an overall mortality of 1.87%, compared to an average for all anesthetic practices of 1.93%. This overall parity of halothane holds up when imbalances in patient populations are taken into account by detailed statistical adjustments. No evidence was found to support the imputed risk of halothane in operations performed on the gall-bladder or bile ducts, or in craniotomies.

3. In the middle-death-rate operations cyclopropane and "other" were associated with reliably higher mortality than were halothane and nitrous oxide-barbiturate; in terms of crude death rates there was a nearly twofold contrast. After statistical adjustment to compensate for differences in the populations exposed to the various agents, cyclopropane and "other" had death rates 2.5% or more, compared to approximately 2% for halothane and nitrous oxide-barbiturate, roughly 25% greater.

4. Ether deserves more systematic study; although the death rate following ether administration was lowest of all, the result is unreliable because so few hospitals in the study used it extensively, and so no further conclusions can now be drawn.

Death Rates Standardized for Physical Status, Age, and Sex, Percentage Dying Within Six Weeks

Mortality Level of Surgical Procedure	Halothane	N-B*	Cyclopropane	Ether	Other	Total
Low	0.23	0.16	0.26	0.18	0.34	0.22
Middle	1.92	1.97	2.77	1.85	2.58	2.21
High	8.54	9.23	12.58	8.30	10.84	9.33

*N-B - nitrous oxide-barbiturate.

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Postanaesthetic liver complications in a general hospital: A statistical study.
Can. Anaes. Soc. J. 10: 531, 1963

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Anesth. and Analg. 42: 759, 1963.

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A search for halothane liver complications.
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New Eng. J. Med. 270: 983, 1964.

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Halothane and liver dysfunction: a retrospective study
Brit. Med. J. 2: 329-341, 1964.

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The incidence of postoperative jaundice with special reference to halothane.
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Prospective and retrospective searches for liver necrosis following halothane anesthesia
J. A. M. A. 195: 157, 1966

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Postoperative massive liver necrosis: A clinical and pathological study
New Eng. J. Med. 276: 645, 1967

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An evaluation of the effect of halothane on liver function and disease.
Am. J. Surgery 114: 658, 1967.

Acute massive hepatic necrosis is uncommon after anesthesia-surgery. Moreover, the studies indicate that the incidence of massive necrosis is no greater after exposure to halothane than to other anesthetic agents. Most reports suggest an incidence of massive necrosis after halothane anesthesia of 1/4000 to as infrequent as 1/700,000. Some have concluded that the entity of halothane hepatic necrosis does not exist.

FACTORS CONTRIBUTING TO LIVER INJURY DURING SURGERY AND ANESTHESIA AND IN POSTOPERATIVE PERIOD

Decreased Perfusion of the Liver

Anesthesia *per se* results in a fall in hepatic blood flow of approximately 30 percent. Cyclopropane induces an increase in, whereas halothane and spinal anesthesia do not alter splanchnic vascular resistance. Premedication, and thiopental-nitrous oxide anesthesia produce no change in splanchnic blood flow unless accompanied by hypercapnia, when blood flow falls and splanchnic vascular resistance increases. Splanchnic oxygen consumption was not altered in the above studies.

Virtually no good data are available on hepatic blood flow and oxygen consumption during anesthesia and surgery.

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Circulation 6: 894, 1952.

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The effect of hypercapnia on estimated hepatic blood flow, circulating splanchnic blood volume and hepatic sulfobromophthalein clearance during general anesthesia in man.
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Anesthesiology 27: 24, 1966.

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Hemodynamic and metabolic effects of hemorrhage in man with particular reference to the splanchnic circulation.
Circulation Res. 18: 469, 1966.

Hypoxia and ischemia result in impaired hepatic function and eventually in tissue destruction. Hypoxia must be severe before functional impairment ensues.

79. Brauer, R. W.
Liver circulation and functions.
Physiol. Rev. 43: 115, 1963.

80. Shorey, J., Schenker, S. and Combes, B.
Hepatic transport in hypoxia.
Clin. Res. 16: 292, 1968

81. Ellenberg, M. and Osserman, K. E.
The role of shock in the production of central liver cell necrosis.
Am. J. Med. 11: 170, 1951.

Duration of shock important

Hours of Shock	Central Necrosis	No Central Necrosis
0 - 10	2	41
11 - 24	5	18
> 24	25	2

Causes of shock:

Myocardial infarction	9
Pulmonary emboli	4
Acute heart failure	4
Hemorrhage	6
Operation, sepsis, pleural aspiration, peritonitis	9

Hypoxia and hypercarbia accentuate hepatic dysfunction observed with anesthesia and surgery.

82. Goldschmidt, S., Ravdin, I. S., and Lucke, B.
Anesthesia and liver damage. I. The protective action of oxygen against the necrotizing effect of certain anesthetics on the liver.
Jour. of Pharm. & Exper. Therap. 59: 1, 1936.

83. Sims, J. L., Morris, L. E., Orth, O. S., Waters, R. M.
The influence of oxygen and carbon dioxide levels during anesthesia upon postsurgical hepatic damage
J. Lab. Clin. Med. 38: 388, 1950.

84. Holmes, E. L., and Barnhart, M. I.
Effect of increased carbon dioxide retention on liver function in the dog.
J. Appl. Physiol. 13(2): 184-188, 1958.

85. Morris, L. E. and Feldman, S. A.
Influence of hypercarbia and hypotension upon liver damage following halothane anaesthesia.
Anaesthesia 18: 32, 1963

86. Morris, L. E.
Liver function with various anesthetic agents.
Pac. Med. and Drug 73: 60, 1965

87. Brunson, J. G., Eckman, P. L. and Campbell, J. B.
Increasing prevalence of unexplained liver necrosis.
New Eng. J. Med. 257: 52, 1957.

Pale infarcts and confluent, diffuse areas of ischemic and hemorrhagic necrosis not accounted for by usual causes of hepatic necrosis found in 51 patients in a review of 3229 autopsies during period 1946-1955. Majority occurred in 1953-1955. High correlation between administration of sympathomimetic amines and development of lesions.

Preexisting Liver Damage, known or unsuspected, at the time of surgery

88. Harville, D. D., Summerskill, H. J.
Surgery in acute hepatitis: Causes and effects
J.A.M.A. 184 257, 1963

58 patients with known hepatocellular disease underwent laporotomy.
42 viral hepatitis - 4 died (mortality 9.5%)
- 5 major but non lethal complications
16 drug-induced hepatitis - no deaths and no serious complications.

89. Stauber, R.
The problem of the postcholecystectomy syndrome with reference to damaged liver tissue.
J. Internat. Coll. Surg. 41: 7, 1964

90. Dykes, M. H. M., and Walzer, S. G.
Preoperative and postoperative hepatic dysfunction.
Surgery, Gyn. & Obstet. 124: 747-751, 1967

91. Marx, G. F., Nagayoshi, M., Shoukas, J. A. and Wollman, S. B.
Unsuspected infectious hepatitis in surgical patients
J.A.M.A. 205: 169, 1968

INFECTIONS

Systemic infections occasionally may be accompanied by jaundice not accounted for by hemolysis, therapy of the infection, shock, anoxia, etc. The jaundice frequently has cholestatic features.

92. Klatskin, G.
Hepatitis associated with systemic infections. In Diseases of the Liver, Edited by Schiff, L., Second edition, J. B. Lippincott Co., 1963.

93. Fahrlander, H., Huber, F., and Glon, F.
Intrahepatic retention of bile in severe bacterial infections.
Gastroenterology 47: 590, 1964.

94. Eley, A., Hargreaves, T., Lambert, H. P.
Jaundice in severe infections.
Brit. Med. J. 2: 75, 1965.

Jaundice, frequently "cholestatic", may develop in patients with major surgery who receive many transfusions. Tentatively considered to be due to increased pigment load (transfusion, blood in tissues) in patient with impairment of hepatic secretory function acquired in some way as a result of extensive surgery.

95. Geller, W., and Tagnon, H. J.
Liver dysfunction following abdominal operations. The significance of postoperative hyperbilirubinemia
Arch. Int. Med. 86: 908, 1950

96. Schmid, M., Hefti, M. L., Gattiker, R., Kistler, H. J., and Senning, A.
Benign postoperative intrahepatic cholestasis
New Eng. J. Med. 272: 545, 1965

97. Kantrowitz, P. A., Jones, W. A., Greenberger, N. J., and Isselbacher, K. J.
Severe postoperative hyperbilirubinemia simulating obstructive jaundice.
New Eng. J. Med. 276: 591, 1967.

98. Sanderson, R. G., Ellison, J. H., Benson, J. A. Jr., and Starr, A.
Jaundice following open-heart surgery
Ann. Surgery 165: 217, 1967.

99. Lester, R.
Causes of postoperative jaundice.
Am. J. Surgery 116: 342, 1968

DRUG-INDUCED HEPATIC INJURY

100. Klatskin, G.
Symposium on toxic hepatitis.
Gastroenterology 38: 789, 1960

101. Popper, H. and Schaffner, F.
Drug-induced hepatic injury.
Ann. Int. Med. 51: 1230, 1959.

CHARACTERISTICS OF DIRECT HEPATOTOXINS

1. Invariably provoke hepatic injury in all individuals if administered in sufficient doses.
2. Severity of the lesion directly related to dose.
3. Lesion produced in most, if not all, experimental animals.
4. Lesions have a characteristic histologic pattern.
5. Latent period between exposure and appearance of hepatic injury is constant and almost always relatively brief.

CHARACTERISTICS OF DRUG-INDUCED HEPATIC INJURY OF THE HYPERSENSITIVITY TYPE (Allergy or Idiocyncracy)

1. Hepatic lesion cannot be induced with regularity; only a small proportion of exposed individuals are affected.
2. Injury is not related to dose.
3. Morphology of lesions variable.
4. Latent period highly variable.
5. Clinical manifestations of hypersensitivity, such as fever, skin rash, arthralgia, eosinophilia, often accompany the hepatic lesions.

EVIDENCE THAT HALOTHANE IS A CAUSE OF LIVER INJURY

A. Reference 25
Klatskin, G., Sherlock, S. - Personal communications.

Three anesthetists with recurrent acute hepatocellular damage. Test exposure to halothane for brief period results in chills, fever, abnormalities in laboratory tests.

B. At least eight instances of recurrent episodes of jaundice after separate exposures to halothane.

Case 2 - [redacted] (Local Hospital)

This 65 year old woman underwent a right radical mastectomy on [redacted]/67 under anesthesia that included halothane. No blood was given. Fever (Temp > 100) was present on the day of operation and for the next 7 days postoperatively. This was attributed to pulmonary infection and the patient received ampicillin, then chloramphenicol. The patient had a long history of asthmatic bronchitis. A cholecystectomy had been performed in 1963 (details not available). She was discharged from hospital on [redacted].

Low grade fever persisted at home. Nausea and occasional vomiting appeared and she was readmitted on [redacted] when jaundice was noted. She felt poorly for several days then gradually improved symptomatically.

	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Temperature	> 100	> 100	> 100				
Bilirubin Direct/ Total		7.2/ 9.7		9.3/ 12.8	10.7/ 14.8	9.0/ 13.9	8.9/ 14.6
Thymol Turbidity		17		22.8			22.4
Cephalin Flocculation		4+		4+			4+
Alkaline Phosphatase (Bodansky Units)		18.6		17.4	20.2		26
SGOT		1270	1280	1100	650	420	
Prothrombin time Patient/ Control		13/ 13					
WBC/eos		9700/5	8500/4				

The patient was discharged on [redacted], continued to improve although jaundice was slow in clearing. In [redacted] bilirubin was 0.2, SGOT 9, Cehp. Floc 3+ and Alkaline phosphatase 15.

On [redacted]/67 the patient underwent repair of a ventral hernia with anesthesia that included halothane. Temperature rose to 102 on the day of surgery, to 103.6 the next day and exceeded 100 on 6 of the next 8 days. Jaundice was detected on [redacted].

	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
			Coffee-ground Vomitus		Tarry Stools		Coffee-Ground Vomitus	
Bilirubin D/T		8.9/13.9	10.2/16.8	12.1/21.6		14.4/22.2		13.4/21.0
SGOT		2200	2960	3800		3800		4470
Thymol. Turb.		14.2						
Ceph. Floc.		4+	4+					
Alk. Phos.		8.4	10.8					
Pro. Time			18/13	17/2		22/13		
Proteins/ Albumin			6.3/ 2.9					
Hgb.	16		12	8.4	(Transfusions)			9.4
WBC	10,900				16,700			
Eos	0				11			

The course was characterized by deepening jaundice, coffee ground vomitus on [redacted], tarry stools on [redacted] and continued GI bleeding thereafter. Obvious ascites was apparent on [redacted]. The patient became comatose on [redacted] and died on [redacted]. An autopsy was not obtained.

C. Some patients with presumed halothane-induced liver injury have an anticytoplasmic (antimitochondrial) antibody in their serum whereas such a substance is uncommon in patients with viral hepatitis.

102. Doniach, D., Roitt, I. M., Walker, J. G., and Sherlock, S. Tissue antibodies in primary biliary cirrhosis, active chronic (lupoid) hepatitis, cryptogenic cirrhosis and other liver diseases and their clinical implications. Clin. exp. Immunol. 1: 237, 1966.

103. Goudie, R. B., MacSween, R. N. M., and Goldberg, D. M. Serological and histological diagnosis of primary biliary cirrhosis. J. Clin. Path. 19: 527, 1966.

104. Paronetto, F., Schaffner, F., and Popper, H. Antibodies to cytoplasmic antigens in primary biliary cirrhosis and chronic active hepatitis. J. of Lab. & Clin. Med. 69: 979, 1967

105. Kantor, F. S., and Klatskin, G. Unpublished observations.

"FLUOTHANE" AND IMPURITIES"

106. Cohen, E. N., Bellville, J. W., Budzikiewica, H. and Williams, D.H. Impurity in Halothane Anesthetic. Science 141: 899, 1963.

107. Cohen, E. N., Brewer, H. W., Bellville, J. W. and Sher, R. The Chemistry and toxicology of dichloro-hexafluorobutene. Anesthesiology 26: 140, 1965

108. Raventos, J. and Lemon, P. G. The impurities in Fluothane: Their biological properties. Brit. J. Anaesth. 37: 716, 1965.

109. Nagel, E. L., Moya, F., Burg, S. P., Vestal, B. and Jalowayski, A. Dichlorohexafluorobutene concentration in clinical vaporizers. Anesthesiology 27: 673, 1966.

RESULTS OF ANTICYTOPLASMIC FLUORESCENT ANTIBODY TEST

Diagnosis	Goudie et al		Doniach et al		Kantor & Klatskin		Paronetto et al		PMH		Overall Total	
	No +	Total	No +	Total	No +	Total	No +	Total	No +	Total	No +	Total
Obstructive Jaundice												
Primary Biliary Cirrhosis	26	30	40	41	25	30	45	53	3	3	139	157
Extrahepatic Obstruction	0	72	2	28	0	88	0	11	0	3	2	202
Secondary Biliary Cirrhosis	0	5			0	14					0	19
Cholestatic Jaundice with chronic ulcerative colitis			0	5	0	3			0	1	0	9
Cholestatic Drug Jaundice			0	7					0	1	0	8
Hepatocellular Diseases												
Viral hepatitis	0	25	1	25			1	6	1	11	3	67
Chronic Active Hepatitis			12	43			12	15	0	2	24	60
Postnecrotic (cryptogenic) cirrhosis	3	42	10	32	5	231						
Alcoholic Cirrhosis			0	14			0	8	0	3		
Drug Hepatitis	0	10	3	5[a]			3[b]	4	4[c]	14[c]	8	Halothane
Collagen Diseases												
Rheumatoid arthritis			7	71	0	27					7	98
SLE	0	18	5	17	0	11					5	46
Other			16	44	0	3					16	47
Controls (Healthy; mixed hospital patients)	1	184	2	466			0	25			3	650

(a) 2 halothane, 1 chlordiazepoxide.
(b) 2 halothane, 1 chlorpromazine
(c) All suspected of having halothane liver damage.

ETIOLOGY OF FULMINANT HEPATIC FAILURE

A. FULMINANT HEPATIC FAILURE SURVEILLANCE STUDY

Combined Study - 150 patients

Jan. 1, 1966 - May, 1968

Age	No. Pts.	IH	SH	Halothane	Drugs	Others or Unknown
0-18	23	14	3	1	1	4
19-44	53	13	15	7	7	11
45-64	59	14	13	23	4	5
65 +	15	5	3	5	0	2
		46	34	36	12	22

B. PARKLAND MEMORIAL HOSPITAL 1958-1968; Partial list of cases from other Dallas Hospitals (9)

Age	No. Pts.	IH	SH	Halothane	CCl_4
16-20	7	6	--	1	-
21-40	10	3	4	3	-
41-60	14	4	3	6	1
61-80	5	1	3	1	-
		14	10	11	1

MULTIPLE EXPOSURES TO HALOTHANE

Data support concept that hepatotoxicity represents hypersensitivity (allergy or idiocyncracy) rather than direct toxic effect of the anesthetic.

110. Samrah, M. E.
Liver damage after halothane
Brit. Med. J. 1: 1736, 1963

111. Dawson, B., Jones, R. R., Schnelle, N., Hartridge, V. B., Paulson, J. A., Adson, M. A. and Summerskill, W. H. J.
Halothane and ether anesthesia in gallbladder and bile duct surgery. A retrospective study into mortality and hepatobiliary complications.
Anesth. Analg. 42: 759, 1963

112. Wilson, R. D., Tarrow, A. B. and Garvin, S.
Hepatic effects of halothane. A clinical and laboratory evaluation of 10,129 administrations.
Anesth. Analg. 43: 40, 1964

113. Gronert, G. A., Schaner, P. J., and Gunther, R. C.
Multiple halothane anesthesia in the burn patient.
J.A.M.A. 205: 170, 1968

METHOXYFLURANE (PENTHRANE)

Hepatotoxicity has been reported after this agent. Appears to represent hypersensitivity. Cross sensitivity with halothane reported in literature. Both types of hepatotoxicity have been seen by us in Dallas.

114. Klein, N. C. and Jeffries, G. H.
Hepatotoxicity after methoxyflurane administration.
J.A.M.A. 197: 207, 1966

115. Durkin, M. G., Brick, I. B. and Schreiner, G. E.
Total hepatic necrosis following penthrane.
Gastroenterology 50: 420, 1966.

DALLAS CASES WE ARE AWARE OF SINCE 1965

No. Cases	Died	Survived
21	12	9

CASE NO: 3

[redacted] - 52, [redacted] man (Local Hospital)

[redacted] 1962 - Right inguinal herniorrhaphy under spinal anesthesia. Temperature elevations to 101 for 3 days post-operatively.

[redacted] 1965 - Cholecystostomy for acute cholecystitis, cholelithiasis and pancreatitis. Anesthesia and post-op course unknown.

[redacted], 1965 - Cholecystectomy, common duct exploration. Anesthesia included halothane. Temperature 100 or greater for 12 days starting on day of surgery with peak temperature of 102 on post-operative days 10 and 11. Patchy atelectasis detected on chest X-ray, and wound edges separated during this period. Liver tests prior to surgery were normal. SGOT 12, bilirubin 0.4 total, alkaline phosphatase 7 KA units. Thymol turbidity 1.1. No liver tests performed post-operatively.

[redacted] 1967 - Repair incisional hernia. Anesthesia included halothane. Temperature 100 or greater for 10 days starting on day of surgery with peak temperature 102.4, 102, 102, 102.2 on post-operative days 1, 3, 4, 5 respectively. No liver tests before or after surgery.

[redacted] 1967 - Interim workup for recurrent right inguinal hernia. SGOT 22; bilirubin 1.55; alkaline phosphatase 14 KA units; total protein 8.2, albumin 4.3.

[redacted] 1967 - Right inguinal herniorrhophy under spinal anesthesia supplemented by general anesthesia. Anesthetist's records do not indicate administration of general anesthesia although surgical resident's note immediately post-op lists general anesthesia. General anesthesia was added because of ineffectiveness of spinal. Discussion with anesthetist indicates that any such general anesthesia was likely to have included halothane.

Temperature rose to 100 or greater on day 2 post-op and remained elevated for 10 days. Nausea was experienced from post-op days 3 to 7 and jaundice was noted on day 6.

	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SGOT	20		250	620		680	85
Bilirubin D/T	0.95		5.4	1.4/4.0		3.1	0.8/1.8
Alkaline Phosphatase King Armstrong	11	DAY OF SURGERY	13	17	LIVER BIOPSY	16	13.5
Proteins-Total	7.8		6.8	8.5		9.0	7.6
Albumin	4.5		3.3	3.4		3.5	3.6
Prothrombin time Patient/Control			17.5/14	15/13		15/13	14/14
Percent			69%	76%		76%	100%

Course thereafter was characterized by progressive improvement. Liver biopsy 2 weeks after surgery revealed cirrhosis plus relatively acute hepatocellular process. Patient never received blood transfusions; did not drink alcohol, and had never been jaundiced prior to the most recent hospitalization.

CHOICE OF ANESTHESIA FOR PATIENTS WITH LIVER DISEASE

Anesthetist rather than anesthetic is the important factor.

116. Bunker, J. P.
Choice of anesthesia for patients with liver disease.
Amer. J. Gastroenterology 29: 604, 1958

117. Mackby, M. J.
Recent concepts in the treatment of portal hypertension.
J. Internat. Coll. Surgeons 38: 27, 1962.

118. Jones, R. R., Dawson, B., Adson, M. A., and Summerskill, W. H. J.
Halothane and nonhalogenated anesthetic agents in patients with cirrhosis of the liver: Mortality and morbidity following portal-systemic venous anastomoses.
S. Clin. North Amer. 45: 983, 1965.

CONCLUSIONS

1. Halothane does induce hepatic damage in some patients.

2. Liver injury appears to represent a hypersensitivity rather than a direct hepatotoxic reaction.

3. Recognized liver disease appears more frequently after reexposure to the anesthetic.

4. Unexplained fever or jaundice after exposure to halothane would lead me to use a different, nonhalogenated anesthetic in the future. All instances of fever should be carefully explained, with liver tests an integral part of the diagnostic workup.

5. Fatalities attributable to the anesthetic appear to be low, and on the basis of present retrospective evidence not much different from that noted after other anesthetics. Halothane is a good anesthetic and apparently the agent of choice for many anesthesiologists.

UNANSWERED QUESTIONS

1. The incidence of hepatotoxicity after halothane is unknown. It is undoubtedly higher than published mortality figures indicate. It is unknown whether a considerable increase in incidence will be observed as more of the population reappears for additional exposures to this anesthetic.

2. Attention has focused on massive hepatic necrosis. The fate of the liver in survivors needs to be examined carefully for evidence of development of cirrhosis with its sequelae.

3. The underlying basis of the suspected hypersensitivity reaction and whether it is genetically determined are unknown. (We are aware of 2 members of a family dying a year apart with massive hepatic necrosis after halothane anesthesia). No information is available on the incidence of hepatotoxicity in patients deemed "allergic", or in patients with various diseases considered to be "immunologic".

4. The expected febrile course and alterations in modern hepatic function tests for each type of surgery are documented poorly. Such information needs to be obtained in order to anticipate complications of anesthesia and surgery.