PAPERS AND ORIGINALS

Jaundice after Repeated Exposure to Halothane: An Analysis of Reports to the Committee on Safety of Medicines

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Summary

Analysis of data derived from 130 reports of jaundice occurring after anaesthesia with halothane showed a significant relation between the number of exposures to this anaesthetic and the rapidity with which jaundice develops after exposure. This is considered to provide strong evidence of a cause-effect relationship between the use of halothane and jaundice. Out of 114 patients with complete anaesthetic histories 94 (82%) had been exposed more than once; of those so exposed 80% had been anaesthetized with halothane more than once within 28 days. Altogether 66 (51%) of the 130 patients died.

Introduction

Though the incidence of jaundice after exposure to halothane is believed to be low, concern remains for the safety of patients who may be exposed to halothane several times within a short period. Apart from nitrous oxide and possibly thiopentone, halothane is the most widely used of all the anaesthetics, and an increasing number of patients have been exposed to it more than once. Of some 850,000 patients included in the American National Halothane Study (National Research Council, 1969) 9% were estimated to have been exposed to it more than once within a 28-day period. Mushin *et al.* (1971), in a study of 558 unselected surgical patients in three South Wales hospitals, found that 7% had been similarly exposed. In this paper we attempt to identify at least one of the many possible factors associated with jaundice after exposure to halothane or other anaesthetic vapours. Since thiopentone and nitrous oxide are commonplace as adjuncts to anaesthesia with other agents no separate analysis for them is possible.

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Material and Methods

The study was based on 130 reports of jaundice attributed to halothane received by the Committee on Safety of Medicines* during January 1964 to December 1972. About half of the patients were included in the earlier analysis by Mushin *et al.* (1971). In 17 of these reports other anaesthetics apart from thiopentone and nitrous oxide had also been used. In one, for example, a patient was noted to have received at various times propanidid, trichloroethylene, and methoxyflurane in addition to halothane. Another patient had been anaesthetized with methohexitone on six occasions for electric convulsion therapy. In the nine-year period, however, no report attributed jaundice to any other anaesthetic agent.

We grouped the reports according to the number of exposures to halothane (table I). With the exception of 1964, when reports were received during only part of the year, the number of adverse reactions reported each year had been fairly consistent, suggesting that the reporting rate had not been influenced to any large extent by publications on the potential toxicity of halothane (table II).

Results

ONE EXPOSURE

Altogether 20 patients were reported to have developed jaundice after a single exposure to halothane (table III). Their ages ranged from 13 to 76 years (mean $49.2 \pm \text{S.D. } 18.1$ years). Seven (35%) died from hepatic failure. One patient (case 4) gave a history of alcoholism, and another (case 15) had been started on rifampicin three days after exposure to halothane. In this case the jaundice soon cleared and she was subsequently anaesthetized a second time with halothane without incident. One patient (case 18) had been anaesthetized with trichloroethylene six months previously and developed jaundice two days after the use of halothane.

Jaundice occurred within 28 days of exposure to halothane in all 20 cases. The exact interval between exposure and onset was recorded in 17 (mean interval 11.7 days). The three remain-

*Formerly the Committee on Safety of Drugs.

TABLE I—Details from Reports of Jaundice in Patients exposed to Halothane during 1964-72

No. of Exposures	No. of Cases of Jaundice	Mean Age of Patients $\pm$ S.D. (Years)	% of Patients Exposed Twice or More within 28 Days	Mean Interval between Last Exposure and Onset of Jaundice (Days)	Proportion of Deaths (Attributed to Jaundice)		Exposure to Other Anaesthetics†	
					No.	%	Agent	No. of Patients
1	20	49.2 $\pm$ 18.1		11.7	7	35	Trichloroethylene	1
2	49	60.0 $\pm$ 13.2	80	6.7	26	53	Methoxyflurane	1
3	29	55.7 $\pm$ 16.0	86	4.6	17	59	Methohexitone	4
4-6	16	65.2 $\pm$ 9.6	79	5.3	10 (+ 1†)	63	Propanidid	3
Unspecified	16	64.6 $\pm$ 18.5	100*	4.5	6	38	Methohexitone	1
All cases	130	56.9 $\pm$ 15.5		6.7	66 (+ 1†)	51	Propanidid	1
							Propanidid, trichloroethylene, methohexitone, methoxyflurane	3
								17

*Based on only 8 out of 16 patients where dates of administration of halothane were known with certainty.

†Death attributed to coronary thrombosis.

‡Nitrous oxide and thiopentone not included.

TABLE II—Reports of Patients developing Jaundice after Exposure to Halothane. Numbers of Deaths are given in Parentheses

No. of Exposures	1964	1965	1966	1967	1968	1969	1970	1971	1972	Total
1	1	2 (1)	1	4 (3)	5 (2)	1 (1)	2	1	3	20 (7)
2	2 (1)	4 (2)	3 (2)	2 (1)	4 (2)	3	8 (4)	12 (7)	11 (7)	49 (26)
3	3 (1)	0	5 (3)	5 (3)	5 (4)	7 (4)	2	1 (1)	1 (1)	29 (17)
4-6	0	2 (1)	1 (1)	1	1 (1)	3 (3)	3 (1)	3 (1)	2 (2)	16 (10)
Unspecified	0	2 (1)	2 (2)	4	0	0	2	3 (1)	3 (2)	16 (6)
Total	6 (2)	10 (5)	12 (8)	16 (7)	15 (9)	14 (8)	17 (5)	20 (10)	20 (12)	130 (66)

TABLE III—Details of Patients in whom Jaundice occurred after Single Exposure to Halothane

Case No.	Sex	Age (Years)	Operation or Condition	Interval between Exposure and Onset of Jaundice (Days)	Outcome
1	M.	60	Herniorrhaphy	5	Recovered
2	F.	29	Cholecystectomy	?	Died on 4th day
3	F.	34	Haemorrhoidectomy	12	Recovered
4	F.	55	Minor operation on hand	5	Recovered
5	F.	41	Hysterectomy	7	Recovered
6	M.	76	Angiography	?	Died on 21st day
7	M.	52	Herniorrhaphy	3	Died
8	M.	74	Prostatectomy	16	Died
9	M.	69	Cystoscopy	16	Recovered
10	M.	66	Herniorrhaphy	27	Recovered
11	F.	65	Cataract	14	Died in 2nd month
12	M.	13	Appendicectomy	3	Recovered
13	M.	58	Intestinal obstruction	4	Died
14	F.	38	Cerebral aneurysm	?	Died on 25th day
15	F.	60	Gland biopsy	12	Recovered
16	M.	50	Not reported	17	Recovered
17	F.	46	Incision of abscess	28	Recovered
18	F.	42	Fracture	2	Recovered
19	F.	24	Dental extractions	15	Recovered
20	M.	21	Eye injury	13	Recovered

ing patients died on the 4th, 21st, and 25th postoperative days respectively, but the exact date on which jaundice had developed was not reported.

TWO EXPOSURES

A total of 49 patients were exposed twice to halothane (table IV). Their ages ranged from 24 to 82 years (mean 60.0 $\pm$ 13.2 years). One patient (case 26) was given two halothane anaesthetics on the same day and this was regarded as a single exposure for the purposes of this analysis. There were 26 deaths from jaundice in this group (53%). One patient (case 42) had been anaesthetized for a cholecystectomy six years previously and the possible presence of liver damage before the second anaesthetic cannot be excluded. Another patient (case 33) was an anaesthetist who became jaundiced 47 days after a minor operation for which he had been anaesthetized with halothane. He returned to work five months later and became jaundiced again the day after an anaesthetic session in which he had used halothane. Two other patients (cases 24 and 31) became jaundiced after both exposures to halothane and in each case the interval between the second

exposure and the appearance of jaundice was shorter than the interval after the first exposure.

Several patients in this group had been exposed to anaesthetic agents other than thiopentone and nitrous oxide. One (case 22) was anaesthetized with methoxyflurane 10 days after a halothane anaesthetic without incident. Six days later she had a further halothane anaesthetic and after three days became jaundiced. Four patients (cases 30, 36, 51, and 58) were induced with methohexitone, and three (cases 25, 32, and 57) with propanidid.

The interval between halothane exposures was 28 days or less in 39 patients (80%). The interval between the second exposure and the onset of jaundice ranged from 1 to 20 days (excluding three patients who died and for whom this interval was not specified precisely). The mean interval was 6.7 days.

THREE EXPOSURES

Twenty-nine patients became jaundiced after three exposures to halothane (table V). Their ages ranged from 19 to 77 years (mean 55.7 $\pm$ 16.0 years). There were 17 deaths (59%).

One patient (case 72) gave a history of jaundice more than 20

TABLE IV—Details of Patients exposed to Two Halothane Anaesthetics

Case No.	Sex	Age (Years)	Operation or Condition	Interval between Halothane Exposures (Days)	Interval between 2nd Exposure and Onset of Jaundice (Days)	Outcome dated from 2nd Exposure
21	F.	68	Dilatation and curettage, thyroidectomy	57	20	Died on 27th day
22	F.	41	Dilatation and curettage, radium	16	3	Recovered
23	F.	39	Varicose veins	43	20	Died on 29th day
24	M.	82	Appendectomy, resuture	28	1	Recovered
25	F.	69	Cataract, retinal detachment	14	17	Died on 29th day
26	F.	41	Gastrectomy, laparotomy	13	2	Recovered
27	F.	63	Not reported	25	?	Died on 5th day
28	F.	68	Dilatation and curettage, radium	23	3	Died on 6th day
29	M.	53	Not reported	5	3	Recovered
30	F.	68	Excision ganglia	11	16	Died on 49th day
31	M.	66	Prostatectomy, cystoscopy	29	5	Died on 27th day
32	F.	60	Cystoscopy, radiotherapy	15	4	Recovered
33	M.	27	Occupational exposure	5 Months	1	Recovered
34	F.	43	Vulvectomy, block dissection	25	5	Recovered
35	M.	32	Gastrectomy, subphrenic abscess	11	3	Died on 3rd day
36	F.	32	Air encephalograms	3	9	Recovered
37	M.	65	Arthrodesis, manipulation	7	3	Recovered
38	M.	38	Perforated duodenal ulcer	18	2	Recovered
39	F.	63	Dilatation and curettage, hysterectomy	21	7	Recovered
40	F.	48	Dilatation and curettage, hysterectomy	5	12	Recovered
41	F.	50	Varicose veins	14	5	Died on 45th day
42	F.	34	Cholecystectomy, laparotomy	6 Years	2	Died
43	M.	38	Perforated duodenal ulcer	7	1	Recovered
44	F.	74	Laryngectomy after biopsy	21	3	Died on 5th day
45	F.	70	Mastectomy, wound resuture	21	?	Died
46	F.	55	Oesophagoscopy	21	14	Recovered
47	F.	70	Radiotherapy	14	14	Recovered
48	F.	—	Cataracts	9	4	Recovered
49	F.	56	Arthrodesis, removal of wire	23	2	Recovered
50	F.	24	Parotid biopsy, sterilization	54	4	Recovered
51	F.	44	Gingivectomies	42	11	Died on 25th day
52	F.	61	Cataracts	7	7	Died on 14th day
53	F.	63	Fracture, plaster change	18	3	Died on 9th day
54	F.	60	Eye operations	14	4	Died on 6th day
55	M.	74	Cataracts	21	5	Died on 4th day
56	M.	63	Fracture, internal fixation	16	7	Recovered
57	F.	74	Herniorrhaphy, resuture	22	5	Died on 10th day
58	F.	57	Plastic surgery to hand	18	6	Died
59	M.	71	Cystotomy, cystoscopy	3	17	Died on 39th day
60	F.	47	Hysterectomy, laparotomy	4	10	Died on 20th day
61	F.	43	Laparotomies	10	3	Died on 13th day
62	F.	53	Two dilatation and curettage operations	19	8	Recovered
63	M.	51	Fracture, internal fixation	6	10	Recovered
64	M.	70	Hiatus hernia	8	6	Recovered
65	M.	65	Fractures	5 Years	13	Died on 2nd day
66	F.	52	Not reported	14	4	Recovered
67	F.	61	Vulvectomy and block dissection	29	3	Died on 15th day
68	F.	49	Varicose veins and dental surgery	31	?	Died on 6th day
69	M.	59	Colostomy, resection	18	4	Died on 8th day

TABLE V—Details of Patients exposed to Three Halothane Anaesthetics

Case No.	Sex	Age (Years)	Operation or Condition	Interval between 1st and 3rd Exposure (Days)	Interval between 3rd and Exposure Onset of Jaundice (Days)	Outcome dated from Last Exposure
70	F.	73	Manipulations	21	?	Died on 7th day
71	M.	53	Plastic surgery	28	3	Recovered
72	M.	50	Cystoscopy, prostatectomy, orchidectomy	21	1	Recovered
73	F.	38	Not reported	?	3	Died
74	F.	68	Dilatation and curettage, hysterectomy, resuture	16	?	Recovered
75	F.	68	Not reported	23	?	Died on 29th day
76	F.	63	Not reported	27	5	Died on 17th day
77	F.	?	Rectal carcinoma	21	10	Recovered
78	F.	?	Epithelioma of tongue	5 Years	3	Recovered
79	F.	39	Cannulation of artery, grafting	18	3	Died on 5th day
80	M.	75	Excision of melanoma, grafting	14	1	Died on 3rd day
81	F.	41	Operations on foot	18	4	Died on 11th day
82	F.	56	Carcinoma cervix, radium	28	12	Recovered
83	M.	30	Occupational exposures	69*	1	Recovered
84	F.	63	Biopsy, resection, closure of colostomy	24	3	Died on 7th day
85	F.	65	Burns	17	?	Died on 10th day
86	F.	76	Glaucoma, cataracts	25	?	Died on 4th day
87	F.	67	Cystoscopies	35*	?	Died
88	F.	44	Fracture, aspiration, Kunstcher nail	21	3	Died on 6th day
89	F.	57	Arteriogram, craniotomy, closure of flap	33*	1	Died on 5th day
90	F.	42	Dilatation and curettage, radium insertions	3 Months*	4	Recovered
91	F.	66	Fracture, manipulation, replastering	28	5	Recovered
92	M.	52	Operations for retinal detachment	60	?	Died on 39th day
93	F.	45	Operations for retinal detachment	91	25	Died on 41st day
94	M.	22	Closed reductions fracture	17	3	Recovered
95	F.	64	Carcinoma cervix, radium	28	1	Recovered
96	M.	19	Cystoscopy, aortogram, nephrolithotomy	14	6	Recovered
97	M.	76	Dorsal slit, amputation of penis, prostatectomy	25	2	Died on 6th day
98	F.	57	Arteriogram, two osteotomies	27	4	Died on 13th day

*Patients whose second and third exposures were 28 days or less apart.

years previously (he was the only patient in the whole series with a history of jaundice not associated with previous anaesthesia). In case 77 the patient had been induced with propanidid on at least one occasion, and one man (case 97) was induced with methohexitone at the time of all three halothane exposures. In case 80 the patient became jaundiced three days after the first, one day after the second, and one day after the third exposure, dying three days after the third exposure. An anaesthe-

tist (case 83) became jaundiced on three separate occasions after occupational exposures to halothane.

The interval between the first and third exposures to halothane was recorded for 28 patients and ranged from 14 days to five years. In 21 of the 28 cases (75%) the interval was 28 days or less. In four others (cases 83, 87, 89, and 90) the two most recent halothane anaesthetics were, respectively, 18, 28, 26, and 14 days apart, and thus a total of 25 of the 28 patients (89%)

had actually been exposed more than once within a 28-day period. The interval between the third exposure and the onset of jaundice was recorded for 25 patients and ranged from 1 to 25 days the mean interval was 4.6 days.

FOUR OR MORE EXPOSURES

Sixteen patients were anaesthetized with halothane on four to six occasions (table VI). Thirteen had four exposures, one had five, and two had six exposures. Their ages ranged from 51 to 84 years (mean 65.2 ± 9.6 years). Ten patients (63%) were reported to have died from liver failure and one (case 110) was believed to have died from coronary thrombosis.

One patient (case 102) had been induced with propanidid on four occasions. Another (case 112) had been induced with methohexitone at the first of four exposures to halothane. One woman (case 113) had had two episodes of jaundice. The first occurring 14 days after a fifth exposure and the other five days after a sixth exposure to halothane. Her anaesthetic history was complicated by the fact that several inductions had been with propanidid and that between the fifth and sixth halothane exposures she had been anaesthetized with trichloroethylene. A further complication was that methoxyflurane had been given in addition to halothane at the time of the sixth exposure. She finally died seven days after the last of a total of seven general anaesthetics given over three-and-a-half years. In case 111 the patient became jaundiced after all but the first of four halothane exposures.

The interval between the first and last exposures was recorded in 14 of the 16 reports and ranged from 16 days to three-and-a-half years. In six (43%) it was 28 days or less. In five other patients

(cases 100, 103, 104, 105, and 111) the interval between the two most recent exposures was, respectively, 8, 12, 12, 25, and 14 days; thus of the 14 patients 11 (79%) had been exposed at least twice within a 28-day period. The interval between the last exposure and the onset of jaundice was recorded in only 12 reports and ranged from 3 to 12 days the mean interval was 5.3 days.

UNSPECIFIED NUMBER OF EXPOSURES

Sixteen patients received halothane on one or more occasions but had incomplete anaesthetic histories. Six (38%) died (table VII). Three of the six radiotherapy cases (cases 120, 121, and 122) were reported by the same doctor and had been induced with propanidid. One patient (case 130) developed jaundice two days after the fourth or possibly the fifth exposure over a period of six years. He recovered and was anaesthetized again two and four months later without incident, but halothane was not used on these occasions.

In this group we could not establish with certainty all the dates of various anaesthetic procedures. These dates were known, however, for eight of the nine patients exposed to halothane at least twice, and all eight had been exposed within 28 days or less.

INTERVALS BETWEEN EXPOSURE AND ONSET

The mean interval between the last exposure to halothane and the onset of jaundice was very significantly shorter for patients exposed two or more times than for those exposed only once.

TABLE VI—Details of Patients exposed to Four, Five, or Six Halothane Anaesthetics

Case No.	Sex	Age (Years)	Operation or Condition	No. of Exposures to Halothane	Interval between 1st and Last Exposure (Days)	Interval between Last Exposure and Onset of Jaundice (Days)	Outcome dated from Last Exposure
99	M.	62	Cystoscopies, laparotomy, resuture	4	16	7	Recovered
100	M.	77	Arteriograms, popliteal aneurism	4	38*	3	Died on 7th day
101	F.	56	Biopsy, radium, examination under anaesthesia	4	17	3	Died on 6th day
102	F.	52	Cystoscopy, radium	4	28	3	Recovered
103	M.	55	Retinal detachment	4	85*	4	Died on 15th day
104	F.	51	Examination under anaesthesia, hysterectomy, radium	4	53*	3	Died on 6th day
105	F.	63	Examination under anaesthesia, hysterectomy, radium laparotomy	5	49*	4	Died on 37th day
106	F.	73	Carcinoma uterus	4	28	?	Died
107	F.	67	Angiogram, biopsy, surgery to orbit	4	?	12	Recovered
108	M.	84	Carcinoma penis	4	?	?	Died
109	F.	62	Examinations under anaesthesia, and biopsy, radiotherapy	4	28	4	Recovered
110	M.	68	Not reported	4	28	?	Died†
111	F.	67	Carcinoma cervix	4	39*	?	Died
112	F.	54	Amputation toe, sympathectomies	4	10 Months	12	Recovered
113	F.	71	Cystoscopies	6	3½ Years	2	Died on 11th day
114	F.	73	Cystoscopies	6	7 Months	6	Died on 36th day

*Interval between penultimate and last halothane exposure less than 28 days.

†Died later from coronary thrombosis.

TABLE VII—Details of Patients with Incomplete Anaesthetic Histories

Case No.	Sex	Age (Years)	Operation or Condition	No. of Halothane Anaesthetics Known	No. of Halothane Anaesthetics Possible	Interval between Last Exposure and Onset of Jaundice (Days)	Outcome dated from Last Known Exposure to Halothane
115	F.	58	Biopsy, laryngectomy	2	3*	4	Recovered
116	F.	?	Not reported	2	3	10	Recovered
117	F.	?	Carcinoma of eyelids and other operations	1	Many	?	Recovered
118	F.	?	Carcinoma uterus	1	2	4	Died on 31st day
119	F.	46	Examinations under anaesthesia dilatation and curettage, radium	1	3	11	Recovered
120	F.	60	Dilatation and curettage, radium	1	2	1	Died on 9th day
121	F.	72	Examination under anaesthesia, radium	2	3*	3	Recovered
122	F.	33	Examination under anaesthesia, radium	1	2	12	Recovered
123	M.	57	Duodenal ulcer, fistula	1	2	?	Died
124	F.	80	Dilatation and curettage, radium	3	4*	1	Recovered
125	F.	59	Not reported	2	3*	1	Died on 2nd day
126	M.	66	Carcinoma of bladder	2	4*	1	Recovered
127	F.	76	Dilatation and curettage, radium	2	3*	4	Recovered
128	M.	69	Retinal detachment and other operations	3	6*	5	Died
129	M.	99	Orthopaedic operations	1	2	?	Died on 7th day
130	M.	61	Cholecystectomy, two bowel bypass operations, two cystoscopies	4	5*	2	Recovered

*Interval between penultimate and final exposure to halothane known to be 28 days or less.

The differences between patients exposed twice, three times, and four or more times were not statistically significant.

In multiple-exposure cases the interval between the most recent exposure and the onset of jaundice did not appear to depend on the length of the period between exposures. The mean interval in 22 patients exposed two to six times over a period of more than 28 days was 6.1 days. In 59 patients exposed over a period of less than 28 days the mean interval was 5.8 days.

Discussion

There have been many reports of a suspected association between the use of halothane and hepatic damage, often derived from studies of necropsy material or patients admitted to specialized units treating liver disease. Trey *et al.* (1968), for example, collected 150 cases of fulminating hepatic failure from 73 centres in the United States. Forty-one patients had had recent surgery and 36 of these died. In 35 cases liver necrosis developed within three weeks of halothane anaesthesia, and 27 patients had been exposed more than once. Sharpstone *et al.* (1971) described 11 patients with a history of multiple exposure to halothane seen in two hospitals over a period of four years and reported six deaths. They pointed out that 10 of these cases could have been averted if unexplained fever after earlier exposures or a history of previous jaundice had been regarded as a contraindication to the further use of halothane.

Studies of this type, however, do not allow the incidence of this complication to be measured, and the material is often selected because of referral of patients to centres known to be especially interested in this problem. Prospective studies of rare events are often impracticable, and none has so far been published that provides an accurate estimate of the incidence of jaundice after the use of halothane or other anaesthetics. No technique is available which will with certainty distinguish viral hepatitis from postanaesthetic jaundice.

A number of attempts have, however, been made to estimate the incidence in retrospective studies, and the results have been conflicting. Keeri-Szántó and Laffeur (1963) studied 50,000 anaesthetic procedures and found that 35,000 (70%) had included the use of halothane. They estimated the possible death rate from post-halothane jaundice to be 1 in 8,000 otherwise uncomplicated anaesthetic procedures. Slater *et al.* (1964) and Mushin *et al.* (1964) failed to incriminate halothane in large retrospective studies in the United States and the United Kingdom. In the American National Halothane Study (National Research Council, 1969) in the U.S.A. halothane had been used in some 30% of 850,000 procedures. There were 82 necropsy diagnoses of acute hepatic failure and a panel of experts attributed 73 of these to postoperative complications, leaving only nine deaths unexplained. Seven of the nine patients had received halothane but the mortality from all causes of death after halothane anaesthesia of 1.87% did not differ from the mortality of 1.93% associated with other anaesthetic agents. Mushin *et al.* (1971) estimated that the risk of jaundice among patients exposed to halothane more than once within a four-week period seemed to lie between 1 in 6,000 and 1 in 20,000.

There is now fairly general agreement that out of several possible factors multiple exposure to halothane has been a common one. In view of the frequent accounts of jaundice occurring after two or more exposures to halothane it appears to be undesirable to rechallenge any patient who has recently been exposed to halothane unless there is an overriding clinical indication.

In this paper the main objective has been to study the time relationship of anaesthetic procedures in patients reported to have developed jaundice after exposure to halothane or other agents and to search for trends which could not be explained by selective or biased reporting to the Committee on Safety of Medicines. The available data are drawn from voluntary reports to the committee's Register of Adverse Reactions.

The principal findings based on 114 patients in this study

who had complete anaesthetic histories (tables III-VI) were as follows: (a) 94 (82%) of the reports described patients who had been exposed to halothane more than once; (b) of these 94 patients, for whom the interval between exposures was known, 75 (80%) had received halothane more than once within a 28-day period; (c) the proportion of reports in which the outcome was fatal increased with age and the number of exposures (see table I); (d) the interval between the second or subsequent exposure and the onset of jaundice was significantly shorter than the interval after a single exposure; and (e) the reports to the committee do not attribute a causal connexion with any anaesthetic agent other than halothane.

It is likely that the reports are highly selected. Many anaesthetists are aware of the possibility that jaundice is more likely to occur after repeated exposures to halothane at short intervals, and reporting bias could influence the first and second of the above findings. Doctors may also have reported fatal events more completely than non-fatal ones. It is difficult, however, to understand how reporting bias could have accounted for the fourth finding—that the interval between exposure to halothane and the onset of jaundice is shorter when there has been more than one exposure. This strongly suggests that earlier exposure to halothane predisposes to some form of sensitivity in certain patients. When jaundice develops late the patient is more likely to have been discharged from hospital and the event is thus perhaps less likely to be reported, because the doctor to whose care the patient has been transferred may not be aware that halothane has been used. This could lead to relative under-reporting of jaundice after single exposure (where the interval has been shown to be longer) but could not account for the significant difference that has been observed in those cases that are reported.

In patients exposed several times there is no evidence that several exposures over a short period are associated with jaundice of more rapid onset than when the patients are exposed over a long period. Unless reports of the latter are seriously under-represented, however, the fact that 80% described jaundice after multiple exposure within a period of less than 28 days suggests that the risk of jaundice may be greater in these circumstances. Analysis of an apparent relation between the ages of patients and the intervals between their last exposure to halothane and the onset of jaundice (table I) showed, in fact, no correlation between them.

Seven doctors each reported two cases of jaundice, one reported three cases, and one seven cases. Five of this cluster of seven patients were concentrated in one group (cases 119-123, table VII), and these five and other patients with incomplete anaesthetic histories were not included in the analysis of time relationships which led to the fourth principal finding outlined above. Reporting by certain individual doctors is not thought to have influenced these findings to any important degree.

Other drugs used during the month preceding the last exposure to halothane or during the interval between that exposure and the onset of jaundice were considered. Phenothiazines had been used in 12 non-fatal cases and 12 fatal cases and blood transfusions had been used in seven non-fatal cases (including two in which phenothiazines were also used) and eight fatal cases. Other drugs not commonly associated with jaundice had been used less often and no consistent pattern of drug use was found. Of particular importance was that in 11 of the 15 patients to whom blood had been given the onset of jaundice was within the incubation period for viral hepatitis. In seven cases blood had been given less than 14 days before the onset of jaundice, and in four cases between 15 and 28 days, while in four cases the patient had been transfused one to three months before the onset of jaundice.

There was nothing to suggest that the proportion of lengthy procedures was greater among patients showing more rapid onset of jaundice or a higher death rate (tables III and VI). Roughly one-third of the procedures appeared to be relatively minor and the distribution of patients with serious diseases such as cancer was fairly even throughout the various groups.

TABLE VIII—Deaths in England and Wales during 1964-72 attributed to Infectious Hepatitis and Acute and Subacute Necrosis of Liver

	1964	1965	1966	1967	1968	1969	1970	1971	1972*	Mean
Deaths from infectious hepatitis (I.C.D. 070)	196	232	207	211	254	208	186	160	144	200
Deaths from acute and subacute necrosis of liver (I.C.D. 570)	113	109	102	103	105	96	79	69	66	94
Total	309	341	309	314	359	304	265	229	210	294
Death rate per 100,000 population	0.7	0.7	0.6	0.7	0.7	0.6	0.5	0.5	0.4	0.6

*Provisional figures for 1972.
Source: Registrar General (1966-73).

The death rate is correlated with age, and it cannot be concluded with certainty that the apparent increase in death rate with increasing numbers of exposures is not due simply to the greater ages of patients so exposed.

In this series nine patients had had more than one episode of jaundice and invariably the onset of jaundice occurred at progressively shorter intervals after the second or subsequent exposure. One patient (case 115), however, was atypical. Jaundice occurred after the second (or possibly the third) exposure to halothane but did not recur after a subsequent exposure. The reappearance of an adverse reaction after rechallenge with a drug is often regarded as providing the strongest possible evidence of causal relationship, and there is no reason why this should not be true also of halothane. Simpson *et al.* (1971) stated that the various stigmata of hypersensitivity have not commonly been observed. In this series most of the reports were received in the form of simple case summaries abstracted, usually in very few words, on one of the committee's yellow reporting cards. In more than half of the cases followed up, however, the doctor volunteered the information that there had been pyrexial reactions to earlier anaesthetics for which quite often no cause could be found. Rash or eosinophilia was also mentioned in a few cases.

During the period under review (1964-72) an average of seven or eight* deaths were reported to the committee each year. Mushin *et al.* (1971) estimated that about 1,500,000 patients are anaesthetized with halothane each year in England and Wales. This accounts for over 80% of all general anaesthetics, a proportion which must indicate a very high level of clinical acceptability. They also estimated that 7% (about 100,000) of them were exposed more than once within a month. Six or seven of the reported deaths occurred after exposure to more than one halothane anaesthetic within a month, and the reported death rate in these circumstances would thus be between six and seven deaths per 100,000. Deaths from infectious hepatitis (I.C.D. 070) and acute or subacute necrosis of the liver (I.C.D. 570) in England and Wales in the years 1964-72 are shown in table VIII together with an estimate for the combined risk of death from these causes in the general population. The average death rate in these years was 0.6 per 100,000. Thus the reported deaths after multiple exposures within a period of one month are equivalent to about 10 times the risk of death in any one year from infectious hepatitis and acute or subacute hepatic necrosis in the general population.

Since many of the reports were not followed up it is possible that some deaths, occurring after a report had been submitted to the committee, are not included in this analysis. It is also highly likely that the reports represent only a small proportion of the events that actually occur. The reporting of "clusters" of cases by individual doctors, mentioned above, suggests that similar clusters of cases occurring elsewhere may not have been reported. This series does not, for example, include any of the 11 cases (with six deaths) reported by Sharpstone *et al.* (1971) to have been seen in two centres in the United Kingdom between 1967 and 1970. It has been the general experience of the committee that even fatal or much publicized adverse reactions are seriously under-reported. Inman and Vessey (1968), for ex-

ample, found that in spite of much publicity about the risk of thromboembolic disease among women using oral contraceptives only 15% of women known to have been taking them when they died from thromboembolism during 1966 were notified to the Committee on Safety of Drugs.

The almost invariable use of nitrous oxide and thiopentone and the frequent use of other agents as an adjunct to anaesthesia with halothane raises the possibility that they too, when administered repeatedly without halothane, might be responsible for cases of jaundice. If this is so it is surprising that no reports have been received. It is impossible to investigate this hypothesis since every doctor reporting jaundice after anaesthesia included halothane in the list of anaesthetic agents used.

The main result of this analysis is the demonstration that the interval between the last of a series of halothane anaesthetics and the onset of jaundice is significantly shorter than the corresponding interval following a single exposure, suggesting that some form of sensitivity may have been induced in certain patients who had been exposed to this agent previously. Only the anaesthetist is in a position to balance this risk against other possibly more common risks which may attend the use of an alternative to halothane. In planning a series of anaesthetics it may be prudent to reserve halothane for the one operation where its advantages may be greatest, but only if the alternative agents are as safe and effective as halothane has proved to be.

It may be concluded that while factors other than exposure to halothane may account for some of the reports there is strong evidence that repeated exposure, especially within a short period, increases the incidence of jaundice, and this in turn may be fatal.

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*Only three deaths in Scotland were reported during the nine-year period covered by this analysis.