The History of Anesthesiology

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Daedalus and Icarus

Antique bas-relief in the Villa Albani, Rome
Alinair - Art Resources/EB Inc.

Daedalus and Icarus

The analogy in the use of this figure derives from Daedalus (Greek: "Cunningly Wrought"), mythical Greek architect and sculptor whose fanciful idea failed. He fashioned wings of wax and feathers for himself and for his son Icarus and attempted to fly to the sun. However, Icarus flew too near the sun. His wings melted so that he fell into the sea and was drowned. The island on which his body was washed ashore was later named Icaria.

(Figure and description adapted from the Encyclopaedia Britannica)

IDEAS THAT FAILED

Introduction

Under this rubric we present a collection of articles whose well-founded intentions and hopes were falsified with the passage of time. And so has it been with inhaled anesthetics. After the advent of ether anesthesia, reports of vapor-related fires, and explosions accumulated over the course of a century. When cyclopropane was introduced, the devastation wreaked by such accidents became more frightful because this agent was breathed in high oxygen mixtures in a closed system. Thus, following a cyclopropane explosion (in which a patient died) at the Lahey Clinic in Boston, a series of attempts to prevent such happenings was inaugurated.

Initially, B. A. Greene (1) described the etiology of such catastrophies. It appeared that static electricity was by far the most frequent incitant. In response, Woodbridge, et al (2) offered a device, an intercoupler, which would prevent static sparking during contacts between personnel in the operating room. There followed a series of other preventive measures: installations of conductive flooring, use of conductive footwear, incorporation of conductive materials in the anesthesia machine and installation of electrical outlets out of the range of anesthetic vapors. Costly they were, but infrequent anesthetic explosions nevertheless persisted.

The most reliable measure, however, was the abandonment of flammable gases and vapors initiated with the advent of fluothane, a potent halogenated agent relatively insoluble in blood (3). This seemed to bear fruit until the spectre of anesthetic induced hepatotoxicity arose (4). Cumulative incidents eventuated in the National Halothane Study (5) which seemed to substantiate the concern. During this same interval, Van Dyke and Chenowith (6) found that all of the inhalants underwent bio-transformation, to some extent, often with the production of toxic metabolites as in the case of fluothane.

Methoxyflurane followed a similar pattern after initial use (7) with nephrotoxicity developing (8) owing to the fluorine atom. The French had long before described this as "diabetes insipidus fluorique".

So we can discern that in the long run progress in prevention of the anesthetic-related fires and explosions has occurred — in spite of detours on the way — initial hopes, then despair, finally elation of a kind.

Leroy D. Vandam, M.D. and B. Raymond Fink, M.D.

IDEAS THAT FAILED

Selected Papers

1. Greene BA. The hazards of fire and explosion in anesthesia: Report of a clinical investigation in 230 cases. *Anesthesiology* 1941; 2:144-160.
2. Woodbridge PD, Horton JW, Connell K. Prevention of ignition of anesthetic gases by static spark. *J Am Med Assoc* 1939; 113: 740-744.
3. Suckling CW. Some chemical and physical factors in the development of fluothane. *Brit J Anaesth* 1957; 29: 466-472.
4. Brody GL, Sweet RB. Halothane anesthesia as a possible cause of hepatic necrosis. *Anesthesiology* 1963; 24: 29-37.
5. National Academy of Sciences-National Research Council. Committee on Anesthesia. Subcommittee on the National Halothane Study. Summary of the National Halothane Study; possible association between halothane anesthesia and postoperative hepatic necrosis. *J Am Med Assoc* 1966; 197: 775-788.
6. Van Dyke RA, Chenowith MB. Metabolism of volatile anesthetic agents. *Anesthesiology* 1965; 26: 348-357.
7. Artusio JF, Van Poznak A, Hunt RE. A clinical examination of methoxyflurane. *Anesthesiology* 1960; 21: 512-517.
8. Crandell WB, Pappas SG, MacDonald A. Nephrotoxicity associated with methoxyflurane. *Anesthesiology* 1966; 27:591-607.

THE HAZARD OF FIRE AND EXPLOSION IN ANESTHESIA: REPORT OF A CLINICAL INVESTIGATION OF 230 CASES

Barnett A. Greene

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THE HAZARD OF FIRE AND EXPLOSION IN ANESTHESIA: *

Report of a Clinical Investigation of 230 Cases

Barnett A. Greene, M.D.

In 1937 the American Society of Anesthetists, Inc. appointed a committee for the study of the hazard of fire and explosion. This is the first comprehensive report of the case findings of this committee. We wish to emphasize here the fact that the American Society of Anesthetists, Inc., by its official action in giving great publicity to the hazard of explosion and by fostering a nationwide inquiry among its members, is to be credited with providing the inspiration and incentive which have led to the recent advances in our knowledge. Furthermore, I wish to secure your recognition of the great encouragement given by Dr. Paul M. Wood and the very helpful advice and cooperation of the many members of our society, especially Drs. Everett A. Tyler and Huberta M. Livingstone.

We have secured information concerning 230 fires and explosions involving anesthetic agents. The distribution of the occurrences is shown in Table 1.

TABLE 1

Fires and Explosions Grouped as to Etiology

1. X-ray apparatus	10	cases
2. Cautery apparatus	57	"
3. Diathermy apparatus	20	"
4. Suction-pressure machines	59	"
5. Endoscopic apparatus	5	"
6. High pressure explosions	10	"
7. Static electricity	63	"
8. Miscellaneous	6	"
	230	

The distribution of injuries is shown in Table 2. It is apparent from this tabulation that at least 152 (or 70 per cent.) of the explosions, and 23 (or 60 per cent.) of the deaths were due to those causes about which effective prophylactic information has long been available and repeated cautions have been urged. For example, despite the authoritative advice issued by the National Board of Fire Underwriters in 1929, against the use of combustible mixtures in the presence of x-ray, cautery and diathermy, we find that more than half of such ignitions

* Read at the Meeting of the American Society of Anesthetists, Inc. in New York City, Dec. 18, 1940. Chairman, Committee on Anesthetic Hazards, American Society of Anesthetists, Inc.; Prospect Heights Hospital, Brooklyn, N. Y.

TABLE 2

ANESTHETIC FIRES AND EXPLOSIONS (EXCL. O_2 THERAPY AND HIGH PRESS.)

Agent	Due to All Causes			Due to Static		
	Total	Deaths	Injuries	Total	Deaths	Injuries
Ether-air	81	1	19	2	0	0
Ether-O_2 (c̄ or s̄ N_2O)	52	12	31	21	4	15
Ethylene-air	0			0		
Ethylene-N_2O	1	1	1			
Ethylene-O_2 (c̄ or s̄ ether)	37	9	16	25	3	8
Cyclopropane-air	1	0	0			
Cyclopropane-O_2 (c̄ or s̄ N_2O or ether)	21	8	13	15	7	12
Ethyl chloride-O_2	•1	0	1			
Ether-air or O_2	8	2	1			
Ethyl chloride-air	3	0	2			
Acetylene-O_2	3	0	2			
Alcohol	4	1	2			
Ether or ethylene	1	1	0			
N_2O-O_2 plus unknown	1	0	1			
Field ether	1	1	0			
Total	215	36	89	63	14	35

have occurred since 1930. We will consider separately each category in the etiology of anesthetic fires and explosions.

X-RAY APPARATUS

In 1929 the National Board of Fire Underwriters stated that "safe practice dictates the absence of such apparatus (x-ray fluoroscopic equipment) in the presence of combustible anesthetics." The International X-ray and Radium Protection Commission in 1937 unequivocally stated "Low flash-point anesthetics should never be used in conjunction with x-rays."

TABLE 3

X-RAY APPARATUS

10 explosions and fires are known.
(8—ether, 1—ethyl chloride, 1—cyclopropane)
The 3 ether-air accidents caused no injuries.
2 patients died and 2 more were seriously injured in those cases involving ether-nitrous-oxide-oxygen.
1 cyclopropane-oxygen explosion caused a slight burn to the patient's cheek and a serious injury to the anesthetist.

In spite of these warnings, explosions and fires due to x-ray equipment are still recurring, and hazardous technics are still widely recommended and used, even in some of our largest hospitals.

It is apropos to point out here that static electricity probably is a greater hazard in the x-ray room than in the operating room because of the greater frequency of movement of the patient, staff and anesthesia equipment over the insulated flooring material in the x-ray room.

The possible sources of a spark in the x-ray rooms are so many that the mere listing of them should be impressive. (See Table 4.)

TABLE 4

POSSIBLE SOURCES OF SPARKS IN X-RAY DEPARTMENTS

A. Under normal operating conditions:
1. Arcing switches, if not sealed or removed from the x-ray room.
   Main switch
   X-ray switch
      Hand switch; foot switch; magnetic contactor; timer contacts
   Overload circuit breaker
   Auto-transformer control
   Rotary rectifier switch
   Open interrupter
   Auxiliary equipment control switches
      Bucky, plate changer and stereo tube shift—if electrically operated and controlled
      Room light switches
2. Charged conductor (which may spark to a person or another conductor).
   Any unshielded part of the high tension system, e.g., reel cord, tube terminal
   Any ungrounded or poorly grounded metallic part of the equipment or metal utensil or metal furniture near the equipment charged by induction. Sometimes a person may be charged sufficiently to cause a spark to ground. Induced charges may be retained even after the equipment has been shut off.
3. High tension arcs.
   Any point in the high tension system where there is a poor contact or friction contact. Because of the nature of the high voltages and low currents used, it is common practice to have such conditions in any x-ray machine, e.g., anode tube connection by means of a ring and hook.

B. Under abnormal operating conditions:
1. Any defect causing arcs.
   Insulation breakdown
   Insufficient clearance between high tension conductors and ground
2. Application of excessive voltage on high tension circuit causing corona or arcing, e.g., by error in setting controls, by excessively gassy tube, by failure of x-ray tube filament or of valve tube.

Some physicians feel safe in using a combustible anesthetic mixture if the x-ray equipment is of the modern shockproof type. For example, Dr. Warren P. Morrill of the American Hospital Association has recently stated that "the manufacturers of the modern self-contained shockproof x-ray machines feel that they carry no hazard of ignition." Shockproof apparatus in general use today diminishes the hazard but does not completely eliminate all sources of igniting sparks. To determine whether further technical improvement of x-ray equipment could entirely eliminate the hazard created by sparking, we solicited the written opinions of the engineering departments of the leading manufacturers of x-ray apparatus. Five companies displayed an excellent comprehension of the hazard and their reports came to approximately the same conclusions, namely,

1. It is possible to develop equipment that would be spark-proof under all circumstances.

2. Very few, if any, of the modern shockproof diagnostic x-ray outfits used today are completely spark-proof.

3. The cost of manufacturing and servicing of completely spark-

proof apparatus would be significantly higher than that of the conventional shockproof apparatus.

4. A completely spark-proof equipment could be secured by following the recommendations in Table 5.

TABLE 5

a. The x-ray tube should be oil-immersed and in a grounded metal container.
b. The transformer and rectifying tube, if any is used, should be oil-immersed or be located outside the x-ray room.
c. The connecting cables and cable sockets should be of shockproof construction.
d. The control panel should be located outside the x-ray room.
e. The foot switch should be vaporproof or enclosed in a bag.
f. The filament control switch should be spark-proof.
g. No part of the high tension wires in the x-ray room should be exposed or ungrounded.
h. All low-voltage connecting wires in the x-ray room should be specially treated, regularly inspected and replaced as they deteriorate.
i. Electric light switches in the x-ray room should be vaporproof.

We know of no institution in which the x-ray equipment, even when of the most modern type, conforms to the outline of necessary safeguards for the complete elimination of sparks. (See Table 5.) This is confirmed by the very wide experience of Mr. I. H. Blatz, x-ray physicist with the Department of Hospitals of New York City and consulting physicist to many private hospitals and roentgenologists.

None of the known explosions and fires has occurred in the presence of shockproof equipment. The use of the conventional shockproof x-ray apparatus only decreases but does not eliminate the hazard of combustion.

The closed method of administration of a combustible anesthetic agent does not make the anesthesia completely safe from ignition by sparks generated during the use of x-ray equipment.

CAUTERY APPARATUS

We report here, in one group, those anesthetic fires and explosions started by the cautery, gas flame, match light or cigarette because they all present obvious and identical features determining the occurrence of an explosion. We also present here, because it is most appropriate, the group of fires caused by the application of the cautery to surgical fields prepared with a spray containing ethyl chloride or with skin cleansers such as ether and alcohol or with skin antiseptics such as the various tinctures.

We have recorded 57 cases ignited by a cautery, flame or similar hot object. This group includes many concrete and forceful examples of ignorance, carelessness and indifference.

In at least 28 cases the cautery or flame was present in or near the head, neck, chest and respiratory tract; in all of the other 29 cases the cautery or flame was incorrectly or inadequately protected from contact with a combustible agent. The general belief exists that there is

TABLE 6

Agent	Total No. of Cases	Cautery or Flame Used Near Head, Neck, Chest, Etc.			Cautery or Flame Used in Abdomen or Elsewhere		
		Cases*	Deaths†	Injuries†	Cases*	Deaths†	Injuries†
Ether-air	14	5	1	3	2	0	0
Ether-O_2 (c or s N_2O)	17	7	4	5	5	0	2
Ether-air or O_2	6	(one patient died—classification not possible for want of details of explosion.)					
Ethylene	9	6	5	4	2	0	3
Ether or Ethylene or both	1	1	1				
Ethyl chloride	3				3	0	2
Acetylene	3				2	0	2
Cyclopropane	2	(one patient died—classification not possible for want of details of explosion.)					
Alcohol	2	1	0	1	1	0	1
	57						

* The cases counted in this group are only those in which the presence or absence of injury is known.

† The total number of persons injured or killed is stated; some cases had more than one person injured. In no case was more than one person killed.

no danger from combustion of ethylene, cyclopropane or ether beyond a 12 inch zone about the mask or expiratory valve during a partial or complete rebreathing administration. While this is generally true, we have found at least 10 cases in which all three of these agents have been ignited at points more distant than 12 inches from the mask or spill valve or point of possible leakage during partial or supposedly closed circuit administrations.

In no instance was there a true closed method of administration, although in several instances there were attempts to secure complete rebreathing for cauterization about the head, and the anesthetists involved believed the circuits to be tightly closed.

Tabulation of the 55 cases presented in this report clearly shows the truth of the following statements:

a) Explosions and fires of all combustible anesthetic agents and mixtures, even ether-air, are capable of causing death.

b) Ether-air mixtures, however, have a relatively small tendency toward propagating a wave of flame or pressure into and down the respiratory tract.

c) Ether-O_2, with or without nitrous oxide, has the same great tendency toward propagating a wave of flame or pressure through the respiratory tract, as have ethylene-oxygen and cyclopropane-oxygen when compared under similar clinical circumstances; i.e., the location of the point of ignition with reference to the respiratory tract of the patient.

d) In no case has anyone been killed when the cautery or flame was present beyond a 12 inch zone surrounding the upper respiratory tract. This is just as true of ethylene as it is of ether. The large admixture

of air (79 per cent. nitrogen) which is inevitable when the inhalant anesthetic is ignited at a distance of 12 inches or more greatly diminishes the explosive force and propagation tendency of combustible mixtures containing high percentages of oxygen.

e) All deaths—and all were patients—have been the result of a flame or cautery employed within a 12 inch danger zone surrounding the upper respiratory tract.

Every tyro of the operating room staff knows that a cautery, flame or hot object should not be permitted to come into contact with any inflammable mixture. Yet there have been at least 57 known and wholly preventable anesthetic fires and explosions ignited by a cautery, flame or other hot object. We think the explanation is to be found in the following reasons:

1. Ignorance of an elementary knowledge of anesthetic combustion. Our personal survey has found an astonishingly large number of surgeons and anesthetists who lack basic and even rudimentary information on this subject.
2. Indifference toward the hazard because of past good fortune while using set-ups which we consider dangerous in the operating room.
3. A paucity and inflexibility of anesthetic methods available to many surgeons who must use the cautery. This is the usual reason for the use of hazardous technics.

In short, the cause is almost always ignorance. The cure must be education, and elevation of the standards of anesthetic training and practice.

DIATHERMY APPARATUS

The hazard of using diathermy in the operating room is discussed separately here because there are many features of the behavior of high frequency electricity which are not seen in the use of the cautery. Nevertheless, it is advisable to recall now that the active electrode of the surgical diathermy machine presents the very same hazard as the hot cautery tip.

We have found published warnings against the use of diathermy apparatus in the presence of inflammable agents as early as 1924. Nevertheless, explosions and deaths have been caused recently by this hazardous practice. We have recorded 19 cases of fires and explosions ignited by diathermy apparatus, as shown in Table 7.

In our detailed written report we have carefully considered the electrical basis of all sparking or arcing during the use of high frequency apparatus. The prevention of all sparks is impossible. No matter how far from the mask the electrodes are placed, there is serious danger of ignition of spark of a combustible inhalation anesthetic mixture. Because of the relatively narrow field of use of surgical diathermy and

TABLE 7

Agent	No. of Cases	Injuries
Ether-air	3	No injuries
Ether-O_2 (c or s N_2O)	9	2 patients died.
		1 patient and 3 bystanders seriously injured.
		1 patient and 2 bystanders slightly injured.
Nitrous oxide-oxygen mixed with an unknown combustible agent seriously injured a patient.		
Ethylene-oxygen	2	1 patient died.
		1 patient suffered a ruptured bladder but recovered.
Cyclopropane-oxygen	2	1 patient died.
Surgical field fires:		
alcohol	2	1 patient died.
ether	1	Patient died.
	20	6 patients died

because of the practical impossibility of the prevention of sparks during diathermy, we have reached the conclusion that combustible anesthesia is contraindicated by the need for diathermy in any part of the head, body or extremities.

In our extended report we have also recorded many instances of the other hazards of surgical diathermy in the operating room, namely, surgical field fires, explosions of hydrogen produced by fulguration in the urinary bladder, and electric shock and sparking resulting from short circuits in defective apparatus.

We have found that there is a marked variation and lack of uniformity in anesthetic practices with regard to diathermy. Our study forces us to conclude with the bold statement: anesthetic fires and explosions ignited by diathermy, like those due to x-ray apparatus, are completely preventable only by the use of non-combustible anesthetic methods.

SUCTION-PRESSURE APPARATUS

We have learned of 59 cases ignited by an electrical spark produced by the use of a suction or vaporizing machine. Forty-eight of these instances were personally reported to us by members of the Society. All manufacturers have denied knowledge of any report involving their machines. Yet oddly enough, a large number of the companies have with effort and expense made some of their models explosion-proof.

Our records show that there have been explosions or fires (more often the latter) ignited by suction and vaporizing machines in the cities shown in Table 8.

This record is a striking tribute, not to the safety of ether but to the retarding influence of air on the force and propagation of the pressure and flame waves of ether combustions with air, as compared with ether-oxygen and ether-nitrous-oxide-oxygen mixtures. The long period of toleration of the hazard has been due largely to this feature of relative harmlessness which is associated with the combustion of any anesthetic mixed with air.

TABLE 8

Brooklyn, N. Y.	3	Philadelphia, Pa.	1
Chicago, Ill.	3	Providence, R. I.	2
London, Eng.	3	Reading, Pa.	1
Harrisburg, Pa.	2	San Antonio, Texas	1
Louisville, Ky.	1	Santiago, Chile	1
Madison, Wis.	3	St. Johns, N. B.	1
Minneapolis, Minn.	2	Syracuse, N. Y.	1
Montreal, Quebec	6	Toronto, Ont.	5
New Rochelle, N. Y.	3	Washington, D. C.	4
New York, N. Y.	13	Winnipeg	3

TOTAL NUMBER—59 cases

Ether-air—58 cases.
Cyclopropane-air—1 case.
No injuries in 47 of the cases (46 ether-air and 1 cyclopropane-air).
1 patient slightly burned and 1 patient seriously burned about the head.
2 surgeons, 1 nurse and 4 anesthetists were seriously burned.
5 surgeons, 1 nurse and 1 anesthetist were slightly burned.

The use of mercury switches, a sealed motor, grounding of the metal cabinet, locking wall sockets placed 4 feet above the floor—all these safety devices have long been available to anesthetists and hospital authorities. Ignorance of the hazards and lack of demand by anesthetists and surgeons have permitted the growth of the presenc dangerous situation wherein most anesthesias by insufflation today are still being administered in the presence of serious, obvious and preventable sources of ignition.

ENDOSCOPIC APPARATUS

The use of electrically lighted instruments in the body cavities during anesthesia, especially in the mouth and larynx, has caused five anesthetic combustions and the death of one patient and a serious injury to another. (See Table 9.)

TABLE 9

1—ether-air—bronchoscope—patient's pharynx burned but he recovered.
1—ether with air or oxygen—pencil light—patient died of lung injury and surgeon's face was burned.
1—ether-oxygen—laryngoscope—no injuries.
1—cyclopropane-oxygen—laryngoscope—no injuries.
1—ethylene-oxygen—no details obtainable.

Such accidents have been started by:

a) Accidental short-circuiting of exposed terminals.
b) Unsuspected failure of insulation.
c) Faulty contacts in the endoscope proper or at the various switches or rheostats.
d) Accidental exposure of a hot filament by the breaking of a bulb.

There are other types of hazard associated with endoscopic instruments and of special interest to the anesthetist, namely, electric shock and electric burn. One patient was fatally electrocuted during cys-

toscopy; another was severely shocked as the result of faulty insulation in an examination light, and a third patient had his urethra severely burned during cystoscopy as the result of a faulty rheostat. Those conditions which permit the patient to be electrically shocked or burned present serious potential hazards of explosion in the presence of inflammable anesthetics.

The desirable features of endoscopic apparatus from the point of view of prophylaxis of accidents are:

1. Solid glass, rather than thin bulbs should be used.
2. Lamp bulb contact should be so arranged in the socket that no sparking can occur between the bulb and socket.
3. The bulb should not become excessively hot during prolonged use.
4. The lamps should be supplied with low voltage currents in the range of 3–4½ volts.
5. The insulation, rheostats and switches should be free of short-circuiting faults and non-sparking.
6. The lamp circuit, if fed by a house current, should conform to those types demonstrated by electrical engineers to be entirely free of the hazard of electrical burn and shock.

MISCELLANEOUS CATEGORY

A. High Pressure Explosions and Fires

The fact that anesthetic gases are under high pressure introduces hazards which are entirely absent in the handling of liquid anesthetics. Consequently we have found, as would be expected, several instances where the presence of highly compressed agents have caused explosions of two types. The first is that due to the sudden release of a highly compressed gas into portions of the anesthetic apparatus inadequately protected against a high pressure wave of oxygen, carbon dioxide, or nitrous oxide.

TABLE 10

EXPLOSIONS FROM PRESSURE

Agent	No. of Cases	Injuries
Oxygen	5	1 patient possibly killed. 1 anesthetist 1 patient 1 bystander
Nitrous oxide	1	None
Carbogen	1	Anesthetist

All of these explosions from pressure, with the exception of one, occurred during the use of a single type of apparatus which, until recently, was without a safety valve. This is now present on the newer models of this make of machine. One explosion occurred during the use of an

emergency oxygen valve on a McKesson machine with endotracheal anesthesia and may have contributed to the patient's death.

The second type of high pressure accident resulted from the passage of oxygen at high speed over combustible material, such as oil or a leather washer, in the anesthetic circuit. Two such accidents have been recorded.

A third type of anesthetic combustion due to high pressure resulted from the inadvertent intermixing of nitrous oxide and ethylene under high pressure. One such case is known and the anesthetist was killed and an orderly seriously injured.

The prevention of explosions under high pressure is easy if the anesthetic apparatus is properly constructed and maintained so that a safety release valve is present on the low pressure side of the apparatus: intermingling of anesthetic gases under high pressure is made impossible and oily contamination and oil-containing leather washers are avoided.

B. Fires in Oxygen Therapy Equipment

There have been five serious or fatal fires due to the violation by the patient of the rule that flames are to be avoided in the presence of high concentrations of oxygen, as in an oxygen tent. While in each case the patient violated the rule, we should realize that the responsibility for the strict observance of this rule should be repeatedly impressed upon those supervising the patient under oxygen therapy.

C. Miscellaneous Types

We have no record of any anesthetic fire or explosion ignited by electrical sparks originating in overhead lighting fixtures in the operating room. We mention this negative fact because two manufacturers of such lighting equipment have recently developed and secured the approval of the Underwriters Laboratories for explosion-proof overhead surgical lamps.

There have been anesthetic explosions caused by igniting agents not classified under any of the groups listed above. For instance, one ether-air or oxygen anesthetic mixture was ignited by a short circuit spark in an electrical apparatus used to heat the ether. The patient died in a few hours.

STATIC ELECTRICITY

This final category of causes of anesthetic explosions and fires has received more attention than any other group because of the supposed mystery surrounding the occurrence of an anesthetic explosion in the absence of any apparent or obvious electrical hazard. Furthermore, the controversy of humidification versus grounding has served to confuse many anesthetists and hospital executives with a consequent delay

in the application of known prophylactic measures. Finally, the high incidence of fatalities among electrostatically ignited combustions has led to a great deal of unfavorable publicity.

We have secured knowledge of the occurrence of 63 static explosions and fires. (See Table 11.)

TABLE 11

Agent	No. of Cases
Ether-air	2
Ether-O_2 (c or s N_2O)	21
Ethylene-O_2 (ether also present in 4 cases)	25
Cyclopropane-O_2 (ether also present in 4 cases)	15
TOTAL	63

As a result of these explosions and fires the injuries shown in Table 12 have occurred.

TABLE 12

Agent	No. of Cases	Injuries	Deaths
Ether-air	2	None	None
Ether-O_2 (c or s N_2O)	21	1 patient—ruptured lung with recovery 7 patients injured 7 other persons	3 patients 1 anesthetist
Ethylene-O_2	25	2 patients 6 other persons	3 patients
Cyclopropane-O_2	15	4 patients—2 recovered from ruptured lungs 7 other persons	7 patients

From Table 12 we may reasonably conclude that any combustible anesthetic agent, when mixed with a high concentration of oxygen or nitrous oxide, may explode to produce the injury typical of a violent blast, namely, rupture of the lung. The fact that 9 of the 11 patients injured in the 15 explosions from cyclopropane experienced rupture of the lung might indicate that explosions from cyclopropane are more likely seriously or fatally to injure the patient than are explosions from ethylene or ether. This may be true, but we have only 15 cases on which to base such a conclusion, and this is too small a number. Furthermore, we should remember that this table shows that explosions of ether-oxygen also injured 11 patients out of 21 cases although only 4 suffered ruptured lungs. This difference in incidence of the fatality may be entirely accidental and may be found to be absent with an increased number of static explosions. Animal experiments are needed to settle the question.

If we consider showing the number of cases of static explosions with each agent, in which the explosion occurred at a time when the

anesthesia was not in progress and the patient was not in the anesthetic circuit, we come to a very interesting conclusion. (See Table 13.)

TABLE 13

PATIENT NOT IN ANESTHETIC CIRCUIT AT TIME OF EXPLOSION

Agent	No. of Cases
Ether-air	2
Ether-O_2	10
Ethylene-O_2	17
Cyclopropane	2
	31

If we subtract these cases from the totals presented in Table 12 we find that the incidence of fatality and injury to the patient will be as shown in Table 14.

TABLE 14

INCIDENCE OF PATIENT MORTALITY AND MORBIDITY WITH PATIENT IN ANESTHETIC CIRCUIT AT TIME OF EXPLOSION

Agent	No. of Cases	Deaths	Injuries
Ether-air	0	0	0
Ether-O_2 ($\bar{c}$ or $\bar{s}$ N_2O)	11	3 patients (27%)	1 patient recovered from ruptured lung 7 other patients injured (100%)
Ethylene-O_2	8	3 patients (37%)	2 patients (62%)
Cyclopropane-O_2	13	7 patients (54%)	4 patients—2 recovered from ruptured lung (83%)
	32		

From Table 14 we may reasonably conclude that if a patient is in the anesthetic circuit at the time of a static explosion with ether, ethylene or cyclopropane mixed with oxygen, he is almost sure to be injured irrespective of the type of anesthetic agent. The likelihood of the patient's death appears to be greater with ethylene and cyclopropane than with ether, but such a conclusion is not supported by a sufficient number of cases to be accepted as a proved fact. We must await the accumulation of more data on this point to be able to make a clinical comparison of the lethal tendencies of these three anesthetics. Table 14 does prove, however, that static explosions of ether-O_2, with or without N_2O, with the patient in the circuit, are almost always injurious and often fatal to the patient. This fact will disturb the complacency of many hospital administrators and surgeons.

An explosion in the lung is not necessarily fatal. There have been three instances of ruptured lungs with recovery.

A significant fact is that we have found no explosion of cyclopropane-air ignited by static electricity. This may be an important clue

to the future use of cyclopropane. For every type of cyclopropane explosion we have an exact duplicate involving ethylene or ether. The addition of helium to cyclopropane-O_2 failed to prevent explosions of cyclopropane in 2 cases.

Table 15 shows that most types of anesthetic apparatus have been involved in static explosions, including several whose manufacturers have claimed an immunity which we have found to be non-existent.

TABLE 15

(Reported in 34 cases)

Open Wire Ether Mask	1	McKesson Models	6
Heidbrink Models	12	Shipway Model	1
Foregger Models	8	S. S. White	1
Connell Models	4	Ohio Monovalve	1

We do not believe that there is any machine on the market today which can claim a real superiority with respect to the hazard of static production within the apparatus. Of course this does not apply to the most recent machines equipped with conductive rubber throughout and thereby maintaining the anesthetic apparatus as a single electrical unit from the face piece through to the gas channels and tanks and down to the conductive rubber wheels.

There have been three explosions of cyclopropane with the to-and-fro-canister method of closed circuit administration but in no case did it appear that the absorber or the act of manipulating the absorber caused the static spark that ignited the mixture of cyclopropane.

Table 16 shows that static explosions have occurred under the administration of physician-anesthetists as well as nurse-technicians; in complete rebreathing circuits as well as in partially closed and com-

TABLE 16

Nurse Anesthetists	13	Complete Rebreathing	18
Physician Anesthetists	25	Partial Rebreathing	27
		Insufflation	2

pletely open circuits. It may seem surprising to find the high proportion of physician-anesthetists involved, but this is easily understood when we note that many of these physician-anesthetists were internes who, in most hospitals today, we must admit, possess less knowledge of anesthesia usually than do nurse-anesthetists. Also, physician-anesthetists have been more thoroughly canvassed by our inquiry than technician-anesthetists. Furthermore, we have found that a very large percentage of specialists in anesthesiology have long neglected the practical application of the most elementary methods of static prevention.

Complete rebreathing failed to prevent the occurrence of static explosions in 18 cases. This finding was unexpected because most anes-

thetists have felt that this type of administration would go a long way toward preventing static explosions. Nevertheless, complete rebreathing circuits were frequently broken at a time when a combustible mixture was in the circuit. Simultaneously, the method of breaking the circuit favored the production and discharge of spark of static electricity produced on the outer surfaces of the rebreathing circuit.

The 63 case reports clearly show that the greatest single hazard of explosion has been in the anesthesia machine together with the rebreathing tubes, bags and masks. During the past twenty years we have seen many inadequate and incomplete attempts to remove or circumvent this source of static electricity. Our case reports show that all of these recommended measures, when applied singly or combined to only a small degree, have signally failed in many instances. The use of internal intercoupling wires, "personal" intercoupling, external wire intercoupling, wet flow-meters, wet rebreathing apparatus, grounded floors, artificial maintenance of relative humidities greater than 55 per cent. —all of these have been steps in the right direction but only small steps —steps much smaller than their advocates had hoped—steps that most anesthetists did not take.

To show how little protection is usually to be found in the operating rooms, we have tabulated the efforts at grounding and humidification as reflected in the case reports. (See Tables 17 and 18.)

TABLE 17

DATA ON GROUNDING

No complete system present in any case	
Partial grounding, confined to the machine	5 cases
Broken ground wires in rebreathing tubes	2 "
Anesthetic apparatus disconnected from ground at time of explosion	2 "
No grounding	42 "
Grounding data not reported	12 "

TABLE 18

DATA ON RELATIVE HUMIDITY

Humidity 60% or more	2 cases
Humidity 54–55%	3 "
Humidity lower than 50%	32 "
Humidity data not reported	26 "

We have tabulated the seasonal incidence of static combustions and it confirms the general impression that such accidents are more common in the seasons of the year in which the operating room relative humidity is usually below the desired range of 60–65 per cent. (See Table 19.)

Further confirmation of the influence of humidity on the frequency of static explosions is the fact that there has never been a static explosion in Australia; and there has been, as far as we know, only 1 static explosion in England. This occurred in an air-conditioned oper-

TABLE 19

SEASONAL INCIDENCE OF STATIC CASES

Agent	Winter	Fall	Summer	Spring	Season Not Known
Ether	5	6	1	3	8
Ethylene	6	2	1	7	9
Cyclopropane	7	2	0	6	
	18	10	2	16	17

ating room in which the relative humidity was artificially maintained too low and many serious static hazards were present.

The two explosions which occurred in the presence of a relative humidity of 60 per cent. or more, and the three cases in the presence of 55 per cent. humidity were caused by very potent static generators (such as a woolen blanket, rubber soled shoes, a rubber cushion) which have long been known—certainly since 1930—to be impossible of prevention by humidification up to even 80 per cent. Such cases do not warrant the discarding of humidification as a generally valuable prophylactic measure.

Artificial air-conditioning has been criticized as dangerous by Drs. Newcomer and Horton. The only explosions, in our records, which have occurred in air-conditioned operating rooms do not warrant this assertion because in all four instances there were glaring faults in static prevention technics, e.g., low relative humidity, the use of a rubber cushion or woolen blanket.

Ethylene and cyclopropane should not be used for intermittent obstetrical analgesia except under the complete set of safeguards feasible only in the operating room. There have been 3 explosions of ethylene-oxygen; one fatal to the patient, during intermittent obstetrical analgesia.

The only combustible anesthetic mixture which is safe for the patient to receive in an operating room unprotected by static precautions is ether-air.

Today, we who have been educated by the sad experiences revealed in these 63 static explosions and fires, find that our perspective is much clearer and broader. We believe that there is no longer any basis for a controversy between the advocates of grounding and the proponents of humidification. We know now that no single measure is sufficient to prevent all static sparking and that all means of prevention should be simultaneously applied in a comprehensive system.

Within the period of the existence of this investigation by the American Society of Anesthetists, Inc. there have appeared two real advances in our knowledge of the prophylaxis of static sparking in the operating room. First, Prof. Horton has determined the optimum degree of electrical resistance needed in intercoupling grounding devices

to protect against electrical shock and increased capacity for static sparking; the two disadvantages which forced many anesthetists to avoid this means of prophylaxis. Secondly, in England and in the United States, various engineers and rubber manufacturers have simultaneously announced the perfection of conductive rubber—a feature long known to be desirable and recommended by Dr. Horatio Williams in his report of 1930. Many ideas, e.g., conductive rubber, conductive machines, calcium chloride, and humidification, were first advocated by Prof. Horatio B. Williams in 1930, but remained unused because of the lack of an intelligent and sustained interest in anesthetic explosions.

At last there is available today a safe, comprehensive and probably completely effective system for the prevention of static sparking in the operating room. None of the 63 static fires and explosions occurred under a set-up which we now regard as offering the maximum protection against static sparking in the operating room. In fact, in none of these 63 cases was there present even such safeguards as were being recommended at the time these explosions occurred.

The first and most important phase of the scheme of prevention is the education of the medical profession, especially the anesthetist and hospital superintendents, in the basic principles of anesthesiology as it is related to the physics and chemistry of anesthetic combustions. Our records clearly demonstrate the deplorable lack of knowledge and low standard of practice of the current means of prevention in the great majority of operating rooms.

Second, all anesthetic apparatus should be made completely conductive by the use of all of the safe and effective measures known to date.

Third, humidification of the internal and external atmospheres above a minimum of 60 per cent. should be attained and maintained by the use of all methods appropriate to the weather, the operating room and the type of anesthetic circuit.

Fourth, measures should be taken for the elimination of all static production in the operating room outside of the anesthetic apparatus by the use of flooring of proper resistance and conductivity, with which conductive contact is maintained by all persons and apparatus in an operating room.

Fifth, there should be eliminated from anesthesia and operating rooms all especially potent generators of static electricity, such as those objects covered by wool, silk, rayon and rubber.

SUMMARY

We have collected and analyzed 230 fires and explosions involving all anesthetic substances. Seventy per cent. of these explosions and 60 per cent. of the deaths of patients were caused by igniting agents

other than static, and were completely preventable by measures known at the time of their occurrence.

Sixty-three combustions were ignited by static electricity. In no case were there in use *all* of the safeguards which were known and recommended by competent authorities at the time of the explosion.

The findings reported in the 230 cases do not contradict the assertion with which we conclude—that our present day knowledge of the etiology and prophylaxis of all anesthetic fires and explosions is sufficient to prevent all further anesthetic combustions.

-2-

PREVENTION OF IGNITION OF ANESTHETIC GASES BY STATIC SPARK

Philip D. Woodbridge, J. Warren Horton, Karl Connell

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PREVENTION OF IGNITION OF ANESTHETIC GASES BY STATIC SPARK

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As a result of our investigation of a fatal anesthetic explosion in Boston in October 1938, a means of preventing ignition of anesthetic gases by static spark has been devised which we believe to be of sufficient value to warrant general adoption in climates in which static sparks are frequent.

The explosion in question occurred despite the presence of from 60 to 65 per cent relative humidity in the operating room, electrical connection by chain between the operating table, the gas machine and the floor, and connection between the gas machine and the patient by wire wound around the breathing tubes and embedded in the rubber of the mask and thence by dangle chains to the patient's face. The floor was of terrazo with embedded brass grids and was grounded. The anesthetist's stool was of painted metal with rubber feet and was covered with a sponge rubber pad finished with a felt-like cloth and protected by a casing of a textile similar to oilcloth or fabricoid. The mask was held in place by a rubber strap passed behind the patient's head. No electrical apparatus was in use other than the usual floor and ceiling lights. Cyclopropane had been administered by the carbon dioxide absorption method in the closed circuit of a Connell DeLuxe

From the Department of Anesthesia, the Lahey Clinic, Boston.
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machine for about twenty-five minutes. Oxygen had been running at about 250 cc. a minute, no cyclopropane had been added for the last ten minutes and the bag had been staying about half full. It appeared, therefore, that there was no gross leak. As the wound was about to be sutured, the surgeon left the table and had reached a corner of the room when the explosion occurred. There was no other approach to or departure from the vicinity of the operating table and gas machine.

After the explosion the mask was still strapped to the patient's face, with the cushion ruptured. The posterior pharyngeal wall was lacerated, blood oozed from the trachea, subcutaneous emphysema developed rapidly and the patient died about fifteen hours later. The

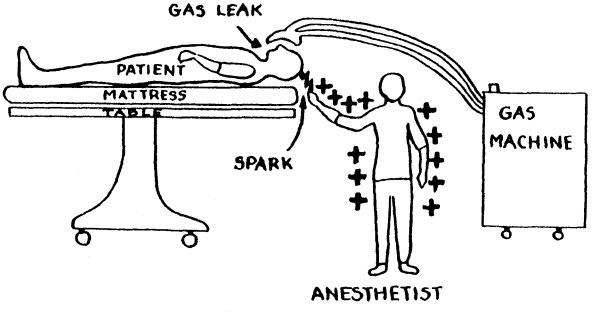

Fig. 1.—Danger from a charged person approaching a gas leak, as in the reported case.

machine was damaged, the rubber parts being ruptured throughout. Accessible parts of the breathing circuit were found drenched with water, apparently ample to couple electrically the patient and the machine up to the time of the explosion. The inspiratory flutter valve was jammed into its seat and the expiratory valve was blown off the machine, indicating that the explosion started not in the machine itself but in the vicinity of the mask and breathing tubes.

At a later date conditions were set up which duplicated as nearly as possible those existing at the time of the explosion, and various observations were made. Even in the presence of approximately 65 per cent relative humidity, sparks of sufficient intensity to ignite explosive mixtures were obtained. The magnitude of charges which could be developed was measured by an

electrostatic voltmeter. The most important finding was that an anesthetist wearing cotton garments acquired a potential of several hundred volts merely by sliding forward on the cushioned stool and then rising. When woolen street clothes were worn, the potential was considerably greater. Other less dangerous sources of potential were observed. A draft of air accompanying the opening of a door raised the potential of the operating table 50 volts. The placing of the drapes gave the patient a potential of 40 volts to ground. The insertion of gauze pads between the sterile sheet and the neck raised the patient's potential 150 volts. The removal of the stand for the instrument tray from the foot of the table gave the patient a potential of 50

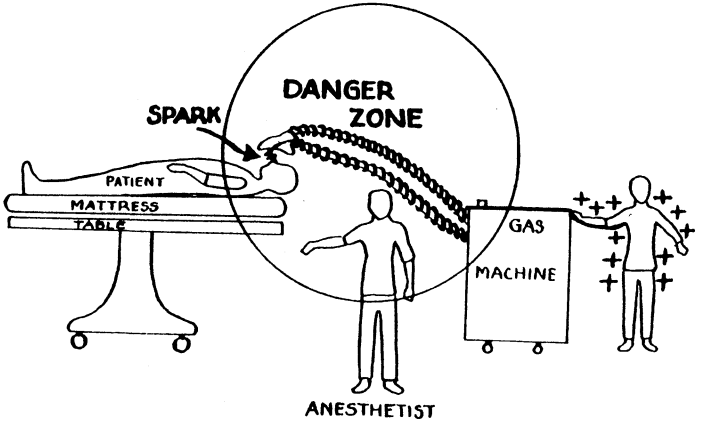

Fig. 2.—Danger from placing intercoupling wires on or in the breathing tubes.

volts. The investigation led to the conclusions which follow:

1. Adequate protection against electrostatic sparks is not necessarily obtained by providing a relative humidity as high as 60 per cent. It has been suggested that air conditioning equipment of the air washing type, as in this case, may remove carbon dioxide or other electrolyte from the air and thus defeat one of the main objects of humidification. The effects of atmospheric conditions on electrostatic phenomena are being investigated further.

2. Cushions on the anesthetist's stool constitute such a serious hazard that they should not be permitted. It is quite possible that the explosion in this case occurred

as a result of a spark between the anesthetist and the patient after the anesthetist had slid forward on the stool (fig. 1). In other cases similar unsuspected factors may precipitate explosions if the protective measures which we advise are not used.

3. Intercoupling near the gases, as by wire wound around the breathing tubes and metal contact to the patient's cheek, is believed to present the following serious hazard: If, when the mask is being removed, the interruption of the connection between the chain and the face should occur simultaneously with some event tending to produce a charge on the patient or on the machine, there might well be a spark discharge between the face and the chain. This spark would of

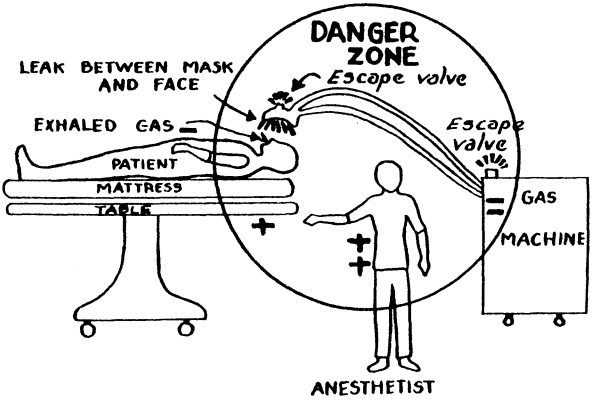

Fig. 3.—Danger from gas leaks in the absence of intercoupling.

necessity occur directly in the spill of explosive gas from the machine (fig. 2). There is a further hazard due to the possibility of a break in the wire where it is embedded in the rubber. This break may occur in such a way as to introduce a spark gap directly into the explosive mixture. If metallic electrical connection is to be maintained between the patient and the gas machine, the conductor should be placed at a distance from the breathing tubes and mask. It must be so arranged that it need never be disconnected while explosive gases are present, because disconnection of an effective conductor will produce a gap across which a spark could jump.

4. Previous reports as to the hazard involved by wool and silk were confirmed. Woolen blankets and silk

and woolen outer garments should never be allowed near explosive gases. Undergarments of either silk or wool do not constitute an electrical hazard. To produce a charge from such fabric it is necessary first to rub it with some other material and then to separate the two. If the two are not separated there can be no electrical potential.

5. It was immediately obvious that the ideal method for completely removing the possibility of an electrostatic potential between any two objects in an operating room, and thereby for preventing any spark discharge which might ignite an explosive mixture, would be to

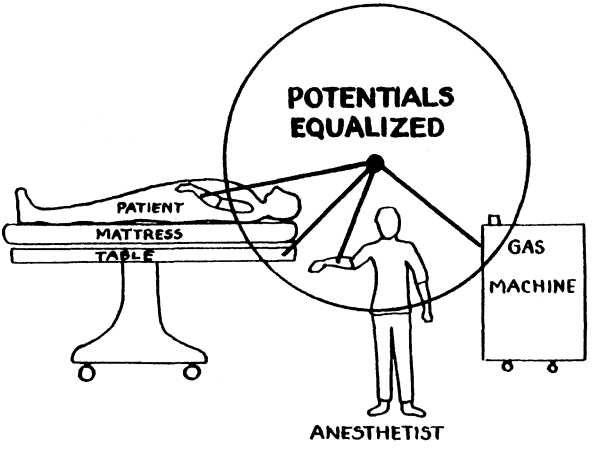

Fig. 4.—Intercoupling of patient, gas machine, anesthetist and table.

interconnect all objects and persons by conductors between these bodies or from these bodies to a conducting floor, which would then serve as a common interconnector. This method is believed to be impracticable with any means that have as yet been made available. However, it is possible by intercoupling to reduce certain specific hazards of frequent occurrence. The method here proposed is based on the assumption that under normal conditions of administering anesthetic gases no mixture of explosive concentration is likely to exist in an operating room outside a region of about a foot in radius surrounding any gas leak. Consequently considerable reduction in risk is obtained if the occurrence of sparks within such restricted danger

zones is prevented. The places where gas leaks most commonly occur are at the escape valve and between the mask and the patient's face. Gas also escapes from the breathing tubes and the patient's respiratory tract after the mask has been removed (fig. 3). Leaks may also occur at other points in the gas channels of the apparatus. If, therefore, the patient, the gas machine and the anesthetist are so intercoupled electrically that sparks cannot occur between them, the major portion of all electrostatic potentials having dangerous possibilities is eliminated. The operating table may be included in this group with advantage (fig. 4).

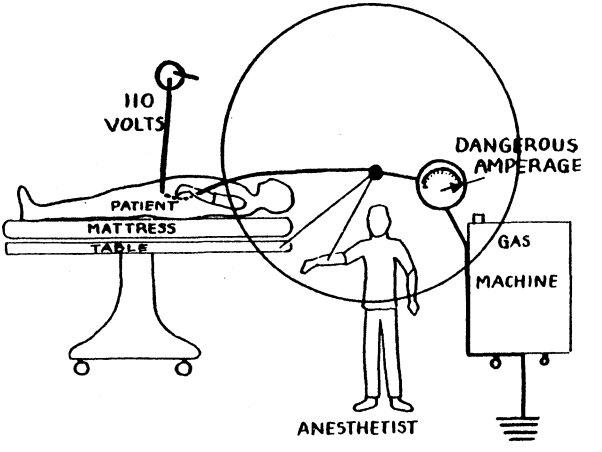

Fig. 5.—Danger to patient through low resistance intercoupling in the presence of defective electrical equipment.

There are two objections to electrical intercoupling when made by conductors of high conductivity, such as wire. One is the increased hazard from electrical shock. A patient forming part of such an intercoupling system suffers a greater chance of being grounded than does a patient not so connected and hence runs a greater risk of serious injury from accidental contact with the lighting circuit, as from defective electrical equipment (fig. 5). A second objection is that such an intercoupled group has greater electrostatic capacity than any one of its component bodies alone. This increase in capacity results in a more intense spark from any charged body that may make contact with the group (fig. 6). These two objections may be overcome by making the intercoupling connectors of high resistance, so arranged that

the resistance between any two bodies in the intercoupled group is of the order of 1 megohm (1,000,000 ohms) (fig. 7). Such intercoupling limits any current from a 60 cycle, 110 volt lighting circuit which might accidentally pass through these connections to 0.1 milliampere (fig. 8). Various published reports place the minimal lethal current at from 50 to 100 milliamperes. Therefore through its possible connection of the patient to ground, 1 megohm intercoupling cannot subject him to a current of more than 1 per cent of the minimal lethal current.

One megohm intercoupling also effectively reduces the tendency of the intercoupled bodies to act as a

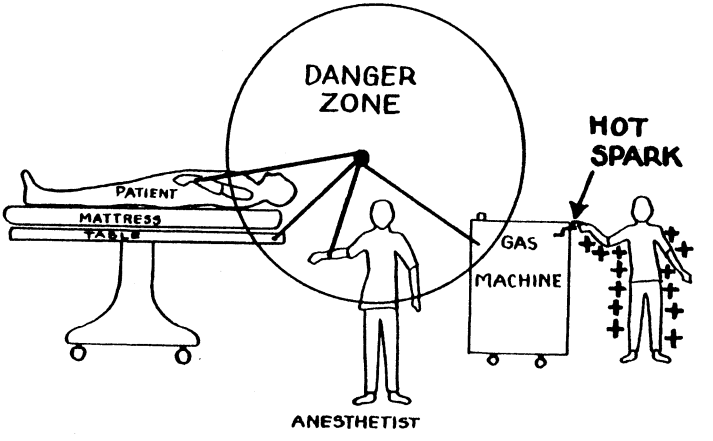

Fig. 6.—Danger of increasing spark energy by low resistance intercoupling.

single body of high electrostatic capacity. Although the group may receive more energy from any charged body than would one member alone, a considerable portion of the excess is dissipated harmlessly in the resistors (fig. 9).

Most important of all, the introduction of high resistance between the intercoupled bodies does not materially increase the time required for equalization of charges. Using the values of electrostatic capacity present in the interconnected group, as determined by actual measurement,[1] it has been found that any poten-

1. Measurements of electrostatic capacities of the patient to the table, of the anesthetist to the ground and of the table to the ground have shown that the order of magnitude of any capacity involved in the interconnection is from 100 to 200 micromicrofarads.

tial which may be established will be reduced to 1 per cent of its value in one one-thousandth second (fig. 10). This indicates that the duration of any charge which may be placed on any member of the group is extremely short. It also indicates that in most cases charges will be removed as rapidly as they can be put on and hence that dangerous potentials cannot be established. It is evident, therefore, that when connectors of 1 megohm resistance are used for intercoupling, electrostatic sparks between connected objects will be adequately prevented.

If the floor of the operating room is electrically conductive, it should be included in the intercoupled group. Then all persons with conductive shoes who enter the

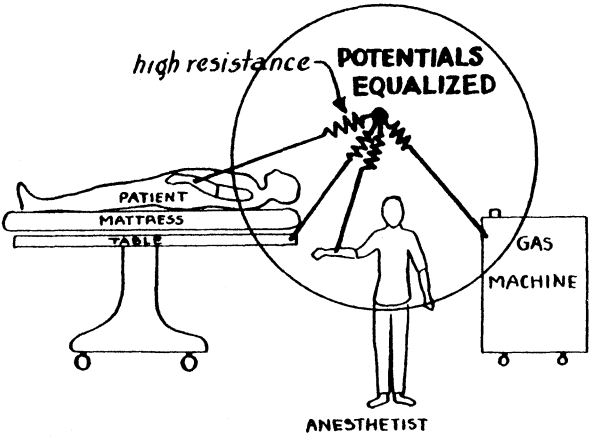

Fig. 7.—Safety through high resistance intercoupling.

room and many other objects in the room will automatically join the intercoupled group through the medium of the floor. Similarly, connection to the building ground will bring all grounded bodies to the same electrostatic potential as the intercoupled group. In order that such grounding shall introduce no hazard of electrical shock, it must be made through high resistance. By bringing these additional bodies to the same potential, connection of the intercoupled group to the conductive floor or to the ground furnishes considerable additional protection against static spark.

A unit to maintain the desired interconnection has been made available.[2] It consists of a small metal case

2. Obtainable from the Technequipment Company, 9 Station Street, Brookline, Mass.

containing a network of resistors so arranged as to present four terminals, between any two of which there is a resistance of 1 megohm. The case itself forms one terminal, and from three other terminals run three wires. The intercoupler may be attached to the operating table and the three wires run to the gas machine,

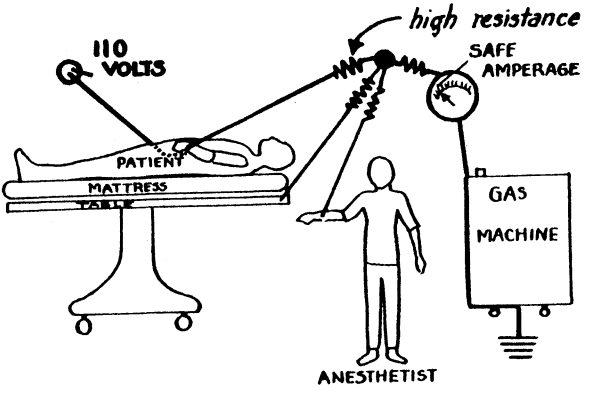

Fig. 8.—No danger from short circuit to ground from defective electrical equipment through high resistance intercoupling.

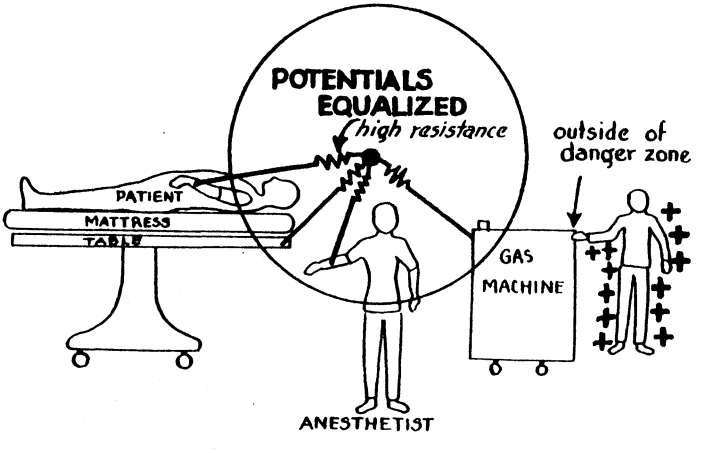

Fig. 9.—Reduction of tendency of intercoupled bodies to act as a single body of high electrostatic capacity by high resistance intercoupling.

the patient and the anesthetist (fig. 11). It may, if more convenient, be attached to the gas machine and the wires run to the table, patient and anesthetist. Bracelets are used to make connection to the patient and anesthetist. Contact with a conductive floor may be made by a drag chain from the gas machine or by a wire from

a fifth terminal with which some of the intercouplers are equipped. The fifth terminal may also be used for connection to the ground.

In the absence of such mechanical means of intercoupling, connection frequently exists through contact of the anesthetist's hands with the gas machine and with the patient (fig. 12). By some this is done without thought of the safeguard which it provides, but by others it is carefully planned and conscientiously carried

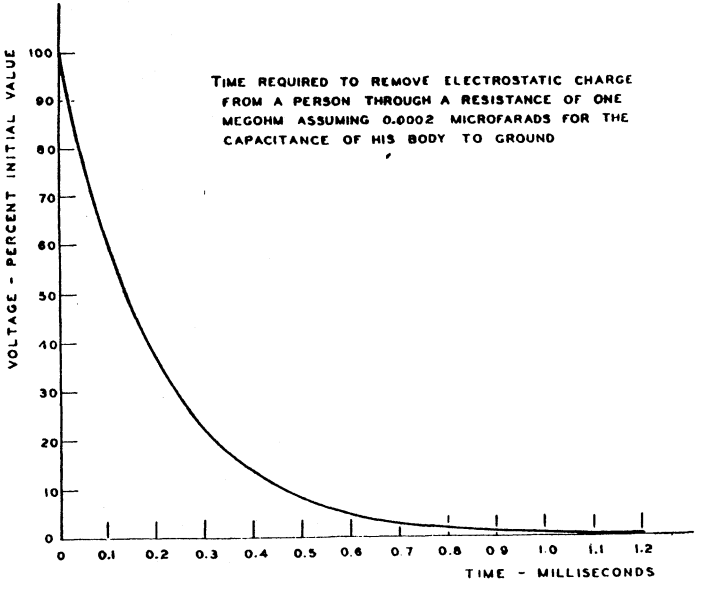

Fig. 10.—Reduction of any potential to 1 per cent of its value in one one-thousandth second.

out as a protection against static spark. However, any interruption, even though extremely brief, in the contact of the anesthetist with the patient and the machine, would introduce the possibility of a spark when contact is reestablished. We believe that such practice is too dependent on unremitting vigilance to be recommended.

Whatever method of intercoupling is used, all connections should be made before anesthesia is started and maintained until after the mask has been removed at the end of anesthesia and explosive gases have been flushed out of the machine and the patient. Any unintercoupled person or object must not be

allowed near regions of possible escape of explosive gas (mask, breathing tubes or escape valve) without first making contact with one of the group at a point remote from such regions. Even if he is highly charged and a spark occurs, it will then be outside the danger zone

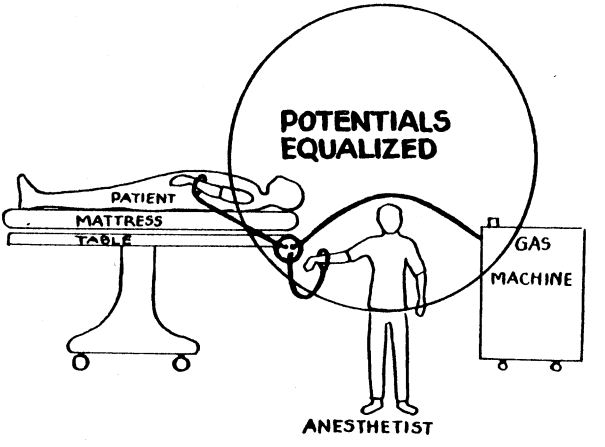

Fig. 11.—Resistance of one megohm between intercoupled bodies by means of the Horton Intercoupler.

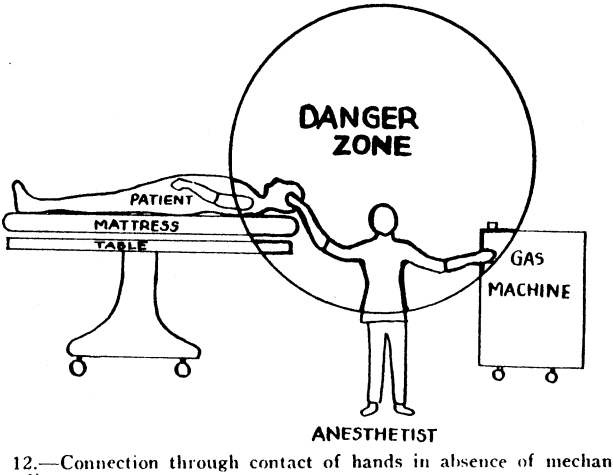

Fig. 12.—Connection through contact of hands in absence of mechanical intercoupling.

of explosive mixtures and therefore harmless (fig. 13). If the anesthetist has to leave the group, he must reapproach the group in the same manner as should any other unintercoupled person.

The use of high resistance intercoupling in no way eliminates the need for other precautions against static

spark. High relative humidity should be maintained where equipment permits, because it is an additional, though unreliable, means of intercoupling. The carbon dioxide absorption method offers two distinct safeguards: Gases are not constantly blown out into the room to come in contact with various sources of ignition, and after the first few breaths the moisture within the apparatus furnishes a very considerable degree of protection against internal static spark. Additional protection would be provided by rapid dilution of any gas that does escape by a stream of air in the vicinity of the mask and the escape valve. Rubber parts should be wet before they are used. Cloth covers should not be

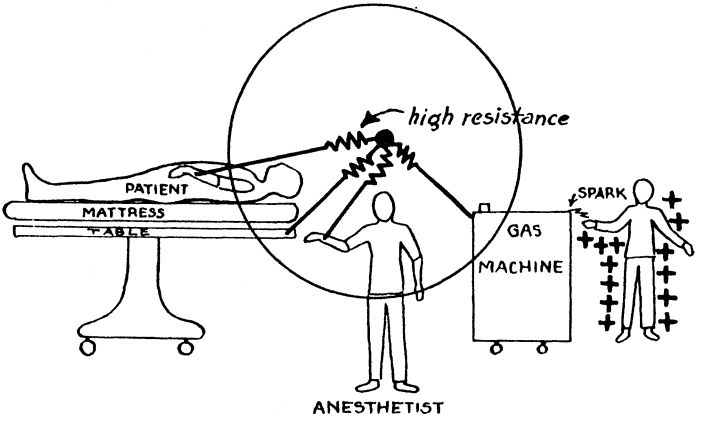

Fig. 13.—Safe manner for a body to approach intercoupled group: spark (if any) outside danger zone.

used on gas machines. To disconnect any portion of the breathing apparatus while it contains explosive gas is to invite danger, which is reduced but probably not always eliminated by intercoupling. The unnecessary and extremely dangerous habit of removing the breathing bag during anesthesia to dump its contents is probably responsible for more than one of the recent fatal explosions. If the bag hangs from the machine by a metal to metal slip joint, the two pieces of metal should be chained or wired together. If this is not done and the bag should fall, its collapse would force gas to flow through the newly created gap and at the same instant might produce a charge which could spark across that gap. One recent explosion may have occurred in this manner.

Protection against sources of ignition other than static spark does not fall within the realm of this discussion. Nevertheless a few warnings must be sounded. Too often it is forgotten that ether, vinyl ether and ethyl chloride form highly explosive mixtures in air, in oxygen and in nitrous oxide. It is frequently forgotten that flushing inflammable gases from the machine with oxygen is extremely hazardous, that nitrous oxide supports combustion as does oxygen, and that a brief flushing of the patient and the machine with a nonexplosive mixture does not render conditions safe for the use of the cautery on the lung or on the neck. Machines are still in common use and are still commonly produced by some manufacturers through which gases may pass under high pressure from one tank into another. Electrical apparatus used in operating rooms is often astoundingly defective in design and in maintenance, cautery apparatus being among the worst offenders.

CONCLUSIONS

High resistance intercoupling is not a panacea against explosion, yet if properly carried out it will eliminate an important source of ignition that lies in the group frequently referred to as the most baffling to control, namely static sparks. Such intercoupling introduces no hazard in itself. The majority of the explosions presumably initiated by static spark that have recently come to our attention would have been prevented by this type of intercoupling.

NOTE.—Since this article was written, progress has been made by one of us (J. W. H.) in developing a method for the more nearly complete elimination of dangerous electrostatic potentials from the entire operating room and from all persons and objects in it. A description of the method will be published as soon as experimental tests have been made and specifications prepared. Pending the development of this method and its installation in operating rooms, we advise intercoupling as described in this article.

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SOME CHEMICAL AND PHYSICAL FACTORS IN THE DEVELOPMENT OF FLUOTHANE

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MY assignment tonight is to talk about the way in which chemistry and physics can help in the choice of compounds to be tested pharmacologically as candidate anaesthetics, and I shall illustrate this by reference to the work which led to the discovery of halothane (Fluothane). I shall suggest that of the properties which are wanted in an anaesthetic there are three which can be fairly closely related to chemical and physical properties. These are (1) absence of chemical toxicity, (2) absence of inflammability and explosive hazards, and (3) anaesthetic potency itself, and I shall show how one may attempt to design a molecule which will have these properties, and conclude with a general discussion of recent theories of relationships between molecular structure and anaesthetic potency, with especial reference to the work of Ferguson and of Mullins.

The first question we had to ask when, in 1951, we began thinking about searching for new anaesthetics was just what a good anaesthetic ought to do. We consulted anaesthetists and were a little taken aback by the answer. A good anaesthetic, we were told, should provide rapid and smooth induction not unpleasant to the patient with no irritation of the respiratory tract, good muscular relaxation, and rapid and easy control of the depth of anaesthesia, a good margin of safety, absence of sweating and of secretion from the mucosae, no increase in capillary bleeding, no cardiac irregularities or adverse effects on any organs, compatibility with adequate oxygen, controllable blood pressure, good recovery with absence of vomiting and nausea, stability over soda lime, and that it should be non-inflammable and nonexplosive—a formidable list. Of course, we understand that some anaesthetists prefer to have each physiological response under the control of a separate drug.

It might be thought that since the biological processes involved in anaesthesia are so little understood, it would be impossible to rationalize the selection of compounds to test as anaesthetics. This is not so. Of course, it is quite impossible to assess from chemical and physical properties whether a compound will be a practical anaesthetic; far less could one hope to predict that a compound would be superior to those already in use. The verdict of the pharmacologist and of the anaesthetist himself cannot be anticipated; but although one cannot predict how a compound will show up in the all important finer points of anaesthesia, one may, by following the leads which are available, increase the chance of success by selecting the most profitable area of search.

Let us take first the question of toxicity. One way of reducing the risk that a compound will prove toxic is to work with compounds which are chemically inert and therefore unlikely to become involved in metabolic chemistry. One group of compounds which possesses a high degree of chemical stability is that of the fluorinated paraffins, in which chlorine and bromine may also be present.

Table I shows the formulae of some of these compounds which are widely used as refrigerants

TABLE I

Some typical Arctons

CF_2HCl	Arcton 4
CF_2Cl_2	Arcton 6
$CFHCl_2$	Arcton 7
$CFCl_3$	Arcton 9
$CF_2Cl.CF_2Cl$	Arcton 33
$CF_3.CHBrCl$	Halothane (Fluothane)

* Lecture delivered to the Section of Anaesthetics, Manchester Medical Society, May 15, 1957.

and in aerosols. When manufactured by I.C.I. they are known under the trade name, Arcton. The first two in the table, Arcton 4 and Arcton 6, are used as refrigerants. Arcton 6, Arcton 9 and Arcton 33 are used as propellants in aerosols. Paint, shaving soap, insecticide or perfume is packed under pressure with these low boiling compounds. When pressure is released through a simple valve the mixture is ejected usually as a fine spray, the Arcton evaporates, leaving the other ingredient behind. Also in the table is the formula of halothane. In passing we might note that the second carbon atom of halothane has bonds with four different atoms and halothane should therefore exist in two optically active isomers. The commercial product should be the racemic mixture, but we do not know how to resolve it into the dextro- and laevorotatory forms.

The Arcton compounds owe their use as refrigerants and in aerosols largely to their volatility, low toxicity and noninflammability, properties which are desirable in an anaesthetic inhalant. The first to suggest that the Arcton type of compound might be used as anaesthetics appear to have been Booth and Bixby (1932) who tested $CFHCl_2$ and CF_2HCl on mice. Both compounds produced convulsions. It is unfortunate that compounds of the Arcton type which are gases at room temperature frequently produce convulsions, as one might hope to find among these low boiling compounds, an anaesthetic of sufficient power to permit its use with adequate oxygen but weak enough to serve some of the purposes to which nitrous oxide is put.

In 1946 Robbins tested forty-two compounds on mice and, with the more promising, on dogs (Robbins, 1946). He recommended four compounds for further tests but no clinical trials ensued. Robbins's results were of especial interest when examined in the light of Ferguson's (1939) work, as will later be described. They did not, however, suggest any particular compound not tested by Robbins as a potential practical anaesthetic.

I might mention here that one difficulty in assessing the reliability of reported tests of compounds as anaesthetics is doubt as to the degree of purity of the samples used, which is rarely indicated. One cannot be certain that when undesirable side effects are reported, they are due to the compound under test and not to some undetected impurity. But in the last few years very searching analytical techniques have come into use, notably the gas chromatograph and the mass spectrometer, and we would not consider a compound as suitable for test as an anaesthetic unless it were about 99.95 per cent pure.

Of course, application of these specialized techniques calls for the co-operation of specialists in analytical fields, and one cannot overstress the fact that the discovery and industrial development of even so simple a compound as halothane calls for the co-operation of very many skilled workers, chemists, engineers, physicists—quite apart from the work that is necessary on the biological side. The development of halothane has been very much a team effort.

We had at Widnes laboratory considerable experience in the specialized techniques for manufacturing the Arcton type of compound and in our desire to make further practical use of the special properties of these substances we decided to search among them and other fluorine containing compounds for an anaesthetic.

Now the chemical inertness of these compounds is a consequence of the strong chemical bond between carbon and fluorine as a result of which the fluorine atom is extremely unreactive. The inertness of fluorine is especially pronounced in compounds containing the groups CF_3- or $CF_2=$, which are not only very stable themselves but also stabilize links between adjacent carbon atoms and halogen. Thus in halothane the CF_3- group reduces the reactivity of the chlorine and bromine on the adjacent carbon atom. It seemed probable, therefore, that compounds containing the groups CF_3-, or $CF_2=$ would, because of their high chemical stability be unlikely to interfere chemically with body metabolism. They should therefore have low toxicity.

So we hoped to minimize chemical toxicity by synthesizing very stable molecules. There is, of course, the other type of toxicity which is produced, like general anaesthesia, not by a chemical, but by a physical mechanism, when an excessive concentration of the compound in the body produces undesirable and sometimes irreversible toxic symptoms. The ratio of this toxic concen-

tration to that concentration which produces satisfactory anaesthesia, which I believe you call margin of safety or anaesthetic index cannot be predicted. There is, however, evidence accumulating that, among compounds of the Arcton type, the margin of safety may be greater in polar compounds or in compounds containing hydrogen. By "polar compound" I mean a compound in which the distribution of electrons is asymmetrical, so that all parts of the molecule have not the same electrical charge. The possibility of electrostatic interaction with other molecules is then present.

We decided, in 1951, to concentrate in the first place on compounds containing the groups CF_3- or $CF_2=$ to obtain stability and, we hoped, absence of chemical toxicity. As for making compounds which were noninflamable and nonexplosive, we knew that if we kept the percentage of hydrogen in the molecule low, this requirement would be met.

I should perhaps interpolate here a remark about the photochemical stability of halothane. As you may know, unstabilized halothane evolves bromine when exposed for some days to bright light. This evolution of bromine is completely prevented by addition to Fluothane, before sale, of 0.01 per cent w/w of thymol. The thymol acts by mopping up the free radicals produced by light, which would otherwise lead to bromine evolution by a chain reaction. As an added precaution Fluothane is stored in brown bottles, but the thymol itself gives adequate protection.

The remaining problem was the choosing of compounds with adequate anaesthetic potency. It might be thought that this would be a difficult matter, but, in fact, it is not, thanks principally to the work of Ferguson (1939, 1951), who was responsible for initiating the search which led to the discovery of halothane. In this, his earlier work on the theory of narcosis proved of great value. I am using the term "narcosis" to denote the reversible inhibition of any biological function.

Ferguson's contribution to the theory of narcosis, and therefore of anaesthesia, was to point out that the significance of data on narcosis is much greater when the concentrations of the drugs administered are expressed on a thermodynamic scale rather than in more usual ways, for example as percentages by volume.

Let us see how this works out. Table II shows results obtained by Meyer and Hemmi (1935) in experiments in which mice were anaesthetized by the compounds listed. The first column of figures gives the volume percentage of these compounds which were sufficient to produce anaesthesia. You will observe that the figures vary from 0.5 to 100 per cent, that is by a factor of 200.

TABLE II
Anaesthesia of Mice

Substance	Anaesthetic concentration per cent by volume	Relative saturation for anaesthesia p_a/p_s
Nitrous oxide	100	0.01
Acetylene	65	0.01
Methyl ether	12	0.02
Methyl chloride	14	0.01
Ethylene oxide	5.8	0.02
Ethyl chloride	5.0	0.02
Ethyl ether	3.4	0.03
Methylal	2.8	0.03
Ethyl bromide	1.9	0.02
Dimethylacetal	1.9	0.05
Diethylformal	1.0	0.07
Dichloroethylene	0.95	0.02
Carbon disulphide	1.1	0.02
Chloroform	0.5	0.01

Data for Meyer and Hemmi (1935): table from Ferguson (1939).

In the second column of figures the concentrations producing anaesthesia are expressed, as sugested by Ferguson, as relative saturations, that is to say, as the ratio of the partial pressure producing anaesthesia (p_a) to the saturated vapour pressure of the compound at the temperature of the experiment (p_s). (This ratio, the relative saturation, when applied to water in the atmosphere gives the familiar relative humidity). You will notice that, when anaesthetic concentrations are expressed in this way, the range of the values is greatly reduced. In this case it is 0.01 to 0.07, a factor of 7, compared with a factor of 200 when volume percentages are used.

The calculation of the ratio p_a/p_s should be clear from tables III and IV which give results with the Arcton type of compound in anaesthesia of mice. These tables include the saturated vapour pressure of the anaesthetic at 20°C p_s (either deter-

termined experimentally or estimated from known vapour pressure curves of similar compounds) and the partial pressure for anaesthesia p_a calculated from observed percentage by volume anaesthetic concentrations. The pressure at which the experiment is conducted is assumed to be 760 mm Hg, so that the partial pressure for anaesthesia equals anaesthetic concentration per cent by volume × 760 ÷ 100. Variations from 20°C and 760 mm Hg likely to occur during normal atmospheric conditions would not affect significantly the values for p_a/p_s which are given to one significant figure only.

The ratio p_a/p_s, the relative saturation for anaesthesia, has a fundamental thermodynamic significance which I shall mention shortly, but first I shall give two more series of results in which anaesthetic concentrations are again expressed as gaseous volume percentages and also as relative saturations.

Table III gives some results obtained by Robbins. The range of concentrations in volume percentage is 0.4 to 25 but in relative saturations 0.03 to 0.08. Unpublished results of Raventós and Suckling, also with mice, are given in table IV. The figures for the last three compounds are of interest in that the relative saturations required to produce anaesthesia are greater than with the other compounds in table IV and the compounds in table III. This may probably be attributed to the absence of hydrogen in the three compounds with the consequent effect on polarity or hydrogen bonding. It seems in fact that absence of hydrogen tends to reduce anaesthetic potency—expressed on this relative saturation scale—but it has less effect on lethal concentration expressed on the

TABLE III
Anaesthesia of Mice

Substance	Boiling point	Vapour pressure at 20°C p_s mm Hg	Anaesthetic concentration per cent by volume	Partial pressure producing anaesthesia p_a mm Hg	Relative saturation for anaesthesia p_a/p_s
$CF_3.CHBr_2$	73	104	0.4	3	0.03
$CF_3.CH_2Cl$	6	1400	8.0	60	0.04
$CF_3.CH_2Br$	26	600	2.8	21	0.04
$CF_3.CHCl_2$	29	550	2.7	21	0.04
$CFCl_2.CH_3$	32	470	2.5	19	0.04
$CHF_2.CH_2Cl$	36	420	2.2	17	0.04
$CF_2Cl.CH_2Cl$	47	280	1.3	10	0.04
$CF_3.CH_2I$	55	200	1.3	10	0.05
$CHF_2.CH_2Br$	57	190	1.3	10	0.05
$CF_2Cl.CH_2Br$	68	130	0.8	6	0.05
$CF_2Cl.CH_3$	−10	2300	25	190	0.08

Anaesthetic concentrations by volume from Robbins (1946).

TABLE IV
Anaesthesia of Mice

Substance	Boiling point	Vapour pressure at 20°C p_s mm Hg	Anaesthetic concentration per cent by volume	Partial pressure producing anaesthesia p_a mm Hg	Relative saturation for anaesthesia p_a/p_s
$CF_3.CHBrCl$	50	243	0.9	7	0.03
$CF_3.CHBr_2$	73	104	0.6	5	0.05
$CF_2Cl.CHCl_2$	72	110	0.8	6	0.05
$CF_3.CHBr.CH_3$	49	260	2.2	17	0.07
$CF_2Br.CF_2Br$	46	290	4.1	31	0.11
$CF_3.CCl_3$	47	280	4.6	35	0.13
$CF_2Cl.CFCl_2$	48	270	5.6	43	0.16

same scale. (The figures for lethal concentrations are not shown in the table). This suggests that, in the class of compounds which we have studied, those containing no hydrogen will have a smaller margin of safety and a lower potency compared with similar compounds containing hydrogen.

The results in tables II and III suggest the tentative hypothesis that any compound which is not chemically toxic will probably produce anaesthesia, if administered at a relative saturation of 0.03 to 0.08. Such generalizations are, however, not strictly true (Ferguson, 1951) and I shall comment on some striking exceptions later. Nevertheless, this generalization holds as a rough rule for a surprisingly large number of compounds of relatively low molecular weight. The higher the boiling point of a compound the lower will be its saturated vapour pressure at any temperature. So we can get a good idea of how potent a compound will be as an anaesthetic from its boiling point.

While on the subject of boiling point I might mention that we do bear in mind the fact that compounds boiling below about 30°C will have the practical disadvantage of necessitating storage in cylinders under pressure. On the other hand compounds with too high a boiling point may be excreted too slowly and delay recovery.

To return to the main theme. For one looking for an anaesthetic, the principal advantage to be gained from Ferguson's work is not that one can calculate in advance the approximate anaesthetic potency of a compound, useful though this is. It is, I think, that Ferguson's treatment shows that a very large part of the difference between the anaesthetic potencies of compounds when measured on the usual volume percentage scale is due to differences in saturated vapour pressure at the operative temperature. When these are allowed for, by expressing results as relative saturations, a much more uniform picture emerges, which shows, however, a previously unsuspected fine structure. Study of the residual differences which make up this fine structure can lead, in fact has led, to a much better understanding of the problem. Some otherwise obscure correlations are illuminated by Ferguson's concepts. For example, it had been argued that the chlorine atom possessed some peculiar power of confering anaesthetic potency on a compound, and it had been suggested that this might be due to some special effect in the brain. But Ferguson's work shows clearly that chloroform is a much more powerful anaesthetic than methane because its vapour pressure (p_s) is always much lower than that of methane. Therefore, if anaesthesia is produced by both at the same relative saturation (p_a/p_s) a much lower partial pressure (p_a) of chloroform will suffice to produce anaesthesia than will be necessary with methane. Thus what was believed to be a peculiar property of the chlorine atom is brought into line with the behaviour of any group or atom which, when substituted for hydrogen in a molecule tends to raise the boiling point. Ferguson (1951) has made a preliminary exploration of the relation of chemical constitution to narcotic potency measured on the thermodynamic scale.

I have now told you of some of the chemical and physical background which we had to help us when we started the work which led to the discovery of halothane. Some of the compounds which we chose to test were chosen because they were readily available but halothane, which was at the time an unknown compound, was selected on the basis of the considerations which I have outlined and specially made for testing as an anaesthetic.

I should like in the short time left me to bring up to date the discussion of the relationships between physical properties and anaesthetic potency. First by saying a little more about Ferguson's work and then by alluding briefly to recent theories advanced by Mullins. I have time for no more than a very quick and therefore imprecise exposition. Those who wish to know more of the subject will find the papers by Ferguson and by Mullins (1954) well worth perusal.

Let us return first to the factor p_a/p_s, which has a more fundamental significance than I have so far explained. The factor p_a/p_s is approximately equal to the thermodynamic function known as "activity". Thermodynamic activities are always referred to an arbitrary standard state to which unit activity is assigned. In this paper the pure liquid is taken as the standard state with unit thermodynamic activity.

It is a fundamental property of thermodynamic

activity of a substance, one expression of which is, as I have explained, p_a/p_s the relative saturation, that it is equal in all phases in equilibrium. By equilibrium is meant a steady state in which the rate of loss of anaesthetic from the tissues is exactly balanced by the rate of uptake. It follows that, when an anaesthetic has become distributed in equilibrium between the inspired air and the body tissues, its thermodynamic activity will be p_a/p_s in all the body tissues. This helps to circumvent the difficulty, which often arises in biological work, that one can discuss the concentration of a drug only as it is in the ambient medium, in the inspired air for example, when one is most interested in concentrations in the tissues.

There is a major group of compounds which diverge from Ferguson's generalization in that they exhibit no anaesthetic power and no toxicity at any thermodynamic activity. These are the perfluoro compounds such as perfluoropentane. Mullins found that the saturated vapour of pentane C_5H_{12} anaesthetized mice in 15 minutes, whereas the saturated vapour of C_5F_{12} perfluoropentane, had no effect whatever after one hour. Similar observations have been published by Banks, Campbell and Rudge (1954).

An explanation for these facts is offered by Mullins (1954). Mullins correlates narcotic potency with the work required to replace a molecule in some biological tissue by a molecule of the narcotic. This work depends on the difference between the cohesive energy densities of the tissue and the narcotic. The cohesive energy density, as its name implies, is a measure of the forces holding a liquid together. Cohesive energy densities are dependent partly on molecular size which assumes great importance in Mullins's theories.

If two substances have very different cohesive energy densities, then much work will be required to replace a molecule of one by a molecule of the other. There will be a large heat of mixing. When an anaesthetic and brain tissue form a solution which is far from ideal, the concentration of anaesthetic in both air and brain which is necessary to produce anaesthesia will be much higher than would be expected on the Ferguson basis. Perfluorocarbons have very low cohesive energy densities compared with those of brain tissues, and, even when the inspired air is saturated, enough perfluorocarbon to cause physiological activity is not transferred to the brain.

Mullins suggests that the cohesive energy densities of the brain tissue affected by anaesthesia is lower than that of body tissue in general. Therefore a good anaesthetic should have a cohesive energy density such that it is more readily taken up by the brain than by other organs. In an anaesthetic, like chloroform, which is liable to affect adversely some of the organs of the body, the cohesive energy density is too high and this permits it to be absorbed too readily in tissues other than the brain with consequent undesirable side effects. Mullins suggested that since the low cohesive energy densities of fluorocarbons lead to physiological inactivity perhaps some fluorochloroparaffin (that is Arcton type of compound) might have a suitable cohesive energy density for anaesthesia and still be stable and noninflammable. This suggestion was not made until after the discovery of halothane, although Mullins did not know of it.

I indicated earlier how the anaesthetic potency of a molecule seems to be markedly affected by its polarity. It is unfortunately not possible at present to calculate the effect of polar interactions on cohesive energy densities. We cannot tell whether polarity will be shown, eventually, to be another factor operating by modifying thermodynamic properties and so fit into the general picture, or whether the wheel will make a full turn in that polar interactions, and perhaps hydrogen bonding, will be found to have a specific effect in the production of anaesthesia.

You will have noticed that nothing has been said as to what is the mechanism by which anaesthetics produce anaesthesia. The theories which we have been discussing do not tell much about this, only that the mechanism must be thermodynamically reversible and physical. One may ask, what of the future? The discovery of halothane has led to a revived interest in the Arcton type of compound: many more of them will, no doubt, be tested. Whether as a result, new compounds will find their way into clinical practice remains to be seen. We may, at least, confidently hope that the work will contribute to a better understanding of the mechanism of anaesthesia.

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HALOTHANE ANESTHESIA AS A POSSIBLE CAUSE OF MASSIVE HEPATIC NECROSIS

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Halothane Anesthesia as a Possible Cause of Massive Hepatic Necrosis

Gerald L. Brody, M.D., and Robert B. Sweet, M.D.

HALOTHANE is becoming widely used for a great variety of surgical procedures; it has even been described by Johnstone [1] as "the universal anesthetic agent." Its low toxicity is recognized, and reports of adverse effects from its use are few. Nonetheless, as with all anesthetic agents, care must be employed in its use. Even with the greatest of precautions, complications are possible, even if rare. The following four cases, three of them fatal, implicate halothane as the causative agent in massive hepatic necrosis (acute yellow atrophy).

Case Reports

Case 1. This 70 year old woman presented with flatulence, fatty food intolerance, occasional bouts of nausea and vomiting, and right upper quadrant abdominal pain. Oral cholecystograms disclosed the presence of cholelithiasis. A 12 per cent Bromsulphalein retention was noted. In addition to chronic cholecystitis, a slight degree of arteriosclerotic heart disease and hypertension of 170/80 mm. of mercury were present. The patient was mildly diabetic and was admitted to the hospital for cholecystectomy. Immediately before the operation alkaline phosphatase level was 6.0 King-Armstrong units; total bilirubin, 0.3 mg./100 ml., one-minute direct of 0.1 mg./100 ml. The thymol turbidity level was 2.0 units. The levels of total proteins and albumin/globulin ratio were normal. Prothrombin time was 61 per cent. Cholecystectomy and an incidental biopsy of the liver were performed during halothane anesthesia.

The preanesthetic medication consisted of meperidine 75 mg. and atropine 0.4 mg. given intramuscularly 35 minutes prior to induction of anesthesia with 200 mg. of 2 per cent thiamylal. Anesthesia was maintained with a combination of nitrous oxide, oxygen, and halothane. The system was an endotracheal semiclosed circle, carbon dioxide absorbing one, with a flow rate of 3 liters each of nitrous oxide and oxygen, and a concentration of halothane varying from 0.4 per cent to 0.8 per cent was administered through a "copper kettle" vaporizer. Six milligrams of *d*-tubocurarine were administered intravenously just prior to opening the peritoneal cavity. Assisted and controlled respirations were used throughout the operative procedure. During the induction of anesthesia the patient's blood pressure dropped from 150/80 to 110/60 mm. of mercury but returned to 140/80 mm. of mercury at the onset of the operative procedure and remained at approximately this level. The pulse rate remained between 72 and 80 beats per minute. At the conclusion of the operative procedure the patient was reacting and was returned to the recovery room in a satisfactory condition. The time of anesthesia was two hours and 50 minutes, and the anesthetic course was uneventful.

The gallbladder was the site of chronic inflammation; the liver histologically showed only minimal lipidic infiltrate (fig. 1). The patient received no blood during the operation. Her postoperative course was afebrile, uneventful, and she was discharged on the seventh postoperative day.

On the seventeenth postoperative day, the patient was readmitted in coma. She had been vomiting for five days, had been jaundiced for two days, and became comatose on the way to the hospital; on admission she responded only to pain. The abdomen was distended and there was guarding on the right side. Bowel sounds were not heard. The blood pressure was 140/70 mm. of mer-

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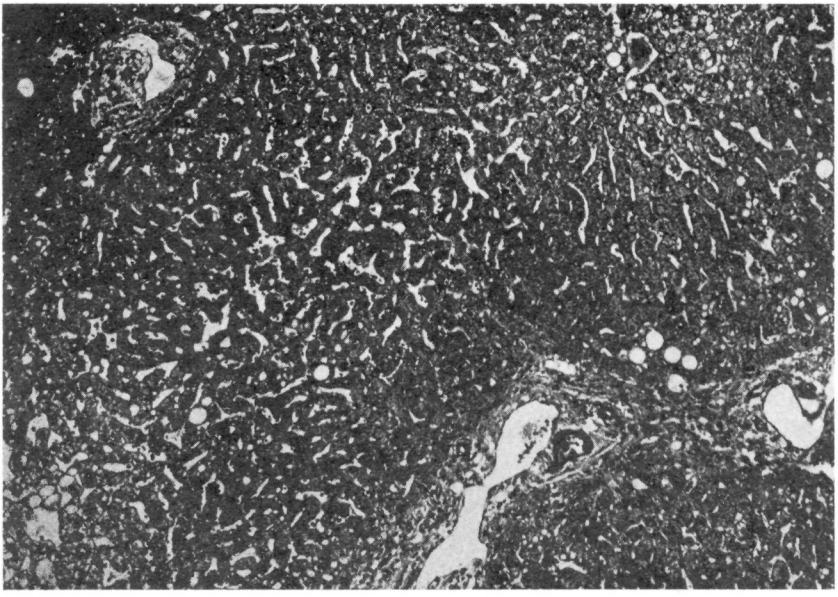

FIG. 1. *Case 1:* Liver biopsy at the time of cholecystectomy. Three hepatic triads and two central veins are shown; the latter are in the lower left and upper right hand corners. Slight degree of lipidic change is present; the amount of lipidic change is common and not significant. (Hematoxylin and eosin, from 90 ×.)

cury. The white blood cell count was 16,000/mm.^{3} and rose to 24,000 the next day. The alkaline phosphatase was 5.9 King-Armstrong units; the total bilirubin level, 11.8 mg./100 ml.—one-minute direct, 5.4 mg./100 ml.; and prothrombin time, less than 10 per cent. By the next day the bilirubin level had risen to 19 mg./100 ml.—one-minute direct, 9.4 mg./100 ml. The serum transaminase level was 1,100 units. Her condition deteriorated; she became hypotensive, required blood transfusions, and during the last two days of life she was oliguric. The patient expired on the twentieth postoperative day.

At necropsy the primary finding was massive hepatic necrosis. The liver weighed 600 g. and presented the typical gross appearance of acute yellow atrophy. Severe centrolobular and midzonal necrosis which had extended in many areas to involve entire hepatic lobules was present in the histologic sections. The surviving hepatic cells at the periphery of the lobules were the site of vacuolar degeneration of the cytoplasm. Fresh hemorrhage was present in the centers of the lobules and there was abundant lipochrome pigment in reticuloendothelial cells. The portal spaces contained leukocytes but there was no suggestion of ascending cholangitis. Hepatic endophlebitis was not seen (fig. 2). The hepatic artery was carefully dissected and was uninjured and patent throughout. In addition to the hepatic findings, there was evidence of multiple hemorrhages, including massive melena from an acute gastric ulcer.

Case 2. For 30 years this 74 year old woman had had attacks of right upper quadrant pain which had increased in frequency before hospital admission. With the attacks she had noted occasional light-colored stools and dark urine, but she denied jaundice. Between attacks she enjoyed a good appetite

and had not lost weight. Cholecystograms after bunamiodyl* disclosed gallstones. Liver function tests were normal. Cholecystectomy, common bile duct exploration, and an incidental biopsy of the liver were performed.

The preanesthetic medication consisted of pentobarbital 75 mg. and atropine 0.4 mg. administered intramuscularly one hour and 20 minutes prior to induction of anesthesia with 130 mg. of 2 per cent thiamylal intravenously. Anesthesia was maintained with a semiclosed circle, carbon dioxide absorbing, endotracheal system with nitrous oxide, oxygen, and halothane; the latter was in concentrations of 0.4 per cent to 1 per cent from a "copper kettle" vaporizer. The oxygen concentration, as determined by flow rates, varied from 33 per cent to 50 per cent with a total flow rate varying from 2 liters per minute to 8 liters per minute. During the operative procedure the patient received 200 mg. of gallamine intravenously. Respirations were assisted or controlled. The patient's blood pressure remained relatively stable throughout the operative procedure, varying from a low of 110/60 to 150/90 mm. of mercury. The anesthetic time was three hours, and the patient's anesthetic course was believed to be satisfactory. She received no blood.

Cholelithiasis and chronic cholecystitis were found; the liver biopsy was normal (fig. 3). Postoperatively, she did very well for eight days. At this time a cholangiogram was obtained through the T-tube; no obstruction was seen. The day following the cholangiogram she began to have fever of 103° F. Coagulase positive *Staphylococcus* was isolated from the T-tube drainage, and it was believed that she had an ascending cholangitis. She was given appropriate antibiotics, but the fever continued unabated for seven days, after which time the temperature was relatively normal. However,

* In the form of Orabilex, F. Fougera and Company, Incorporated, Hicksville, New York.

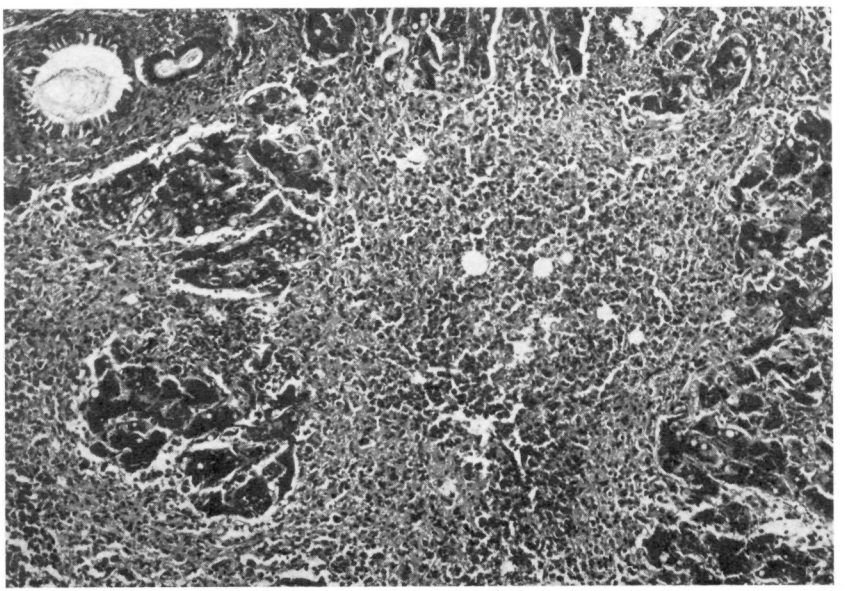

FIG. 2. *Case 1:* The liver at necropsy. Complete centrolobular and midzonal necrosis is present. Clumps of peripheral cells survive. The inflammatory infiltrate is minimal and there is lipidic change in the surviving cells. Otherwise the liver is indistinguishable from that of viral hepatitis. (Hematoxylin and eosin, from 90 ×.)

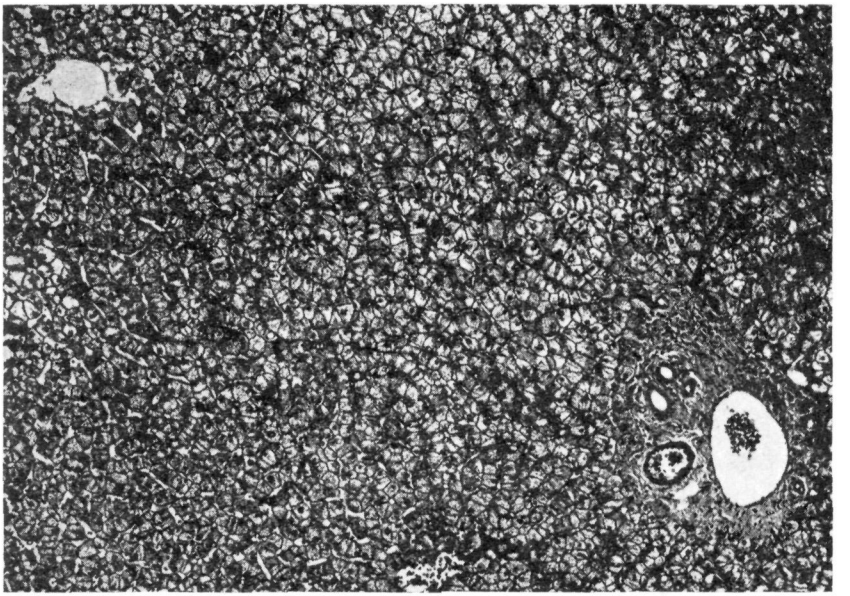

FIG. 3. *Case 2:* Liver biopsy at the time of cholecystectomy. The liver is normal. The vacuolated appearance of the hepatic cells is the result of glycogen content. (Hematoxylin and eosin, from 90 ×.)

in the week before death she had a fever of 101.8° F. Sixteen days before death the alkaline phosphatase level was 13.7 King-Armstrong units; total bilirubin, 32.4 mg./100 ml., one-minute direct, 14.8 mg./100 ml.; serum transaminase, 330 units; prothrombin time, 14 per cent; and cephalin flocculation, 4 plus at 48 hours. Bromsulphalein retention was 77 per cent. Two days before death alkaline phosphatase was 26 King-Armstrong units and the total bilirubin, 52 mg./100 ml. During this time her condition remained at first unchanged, but later she developed an asynchronous tremor and became comatose. The patient expired 43 days postoperatively.

At necropsy the liver weighed 780 g. and presented the usual gross appearance of massive necrosis; 2,700 ml. of cloudy, yellow ascitic fluid were present. No abscesses were found in the liver. The hepatic arteries, the portal vein, and the common bile duct were carefully examined and were found to be normal. A T-tube was in place in the common bile duct. In many of the histologic sections no viable liver tissue could be identified; large areas of coagulation necrosis, containing many "ghost" cells, were present. In the areas where some hepatic parenchyma survived, necrosis was centrolobular and midzonal. The surviving cells were the site of lipidic change. Hepatic endophlebitis was not seen. There was slight regeneration of hepatic cells but no proliferation of bile ducts. Many bile plugs were present in distended intralobular canaliculi. The portal spaces contained only a few lymphocytes. There was no evidence of ascending cholangitis (fig. 4).

Case 3. This 63 year old man was admitted with a recurrent left retinal detachment; he had had a cataract removal four months previously and a retinal detachment imbricated one month previously; both of these procedures were carried out in another hospital. The first operation was performed with local anesthesia and was uneventful. The second operation was during thiopental, nitrous oxide,

oxygen and halothane anesthesia with a 0.2 per cent succinylcholine intravenous drip. The concentrations of halothane used at this time were not available, but the patient's vital signs showed no deviation from normal and he reacted at the conclusion of a two hour and 40 minute period of anesthesia. At the time of the admission to The University of Michigan Hospital he felt well except for the ophthalmic difficulties. Laboratory findings were normal except for evidence of mild diabetes. A second scleral imbrication with a silicone implant was carried out with endotracheal halothane, 3 liters each of nitrous oxide and oxygen per minute flow rate in a semiclosed circle filter carbon dioxide absorbing system following induction with 340 mg. of 2 per cent thiamylal intravenously. The halothane concentration varied from a high of 1.2 per cent to a low of 0.8 per cent. Respirations were assisted throughout an uneventful operative procedure. The duration of anesthesia was two and one half hours. No blood was given. His postoperative course was uneventful and he was discharged on the seventh postoperative day.

He was readmitted seven weeks later with recurrent retinal detachment. His general health was excellent and laboratory findings were normal. A scleral imbrication with silicone sponge implantation was again performed. The anesthetic agents were endotracheal halothane, nitrous oxide, and oxygen in a semiclosed, carbon dioxide absorbing, circle filter system. Anesthesia was induced with 300 mg. of 2 per cent thiamylal, intravenously. The concentration of halothane, throughout the uneventful operative procedure, varied from 0.8 per cent to 1 per cent.

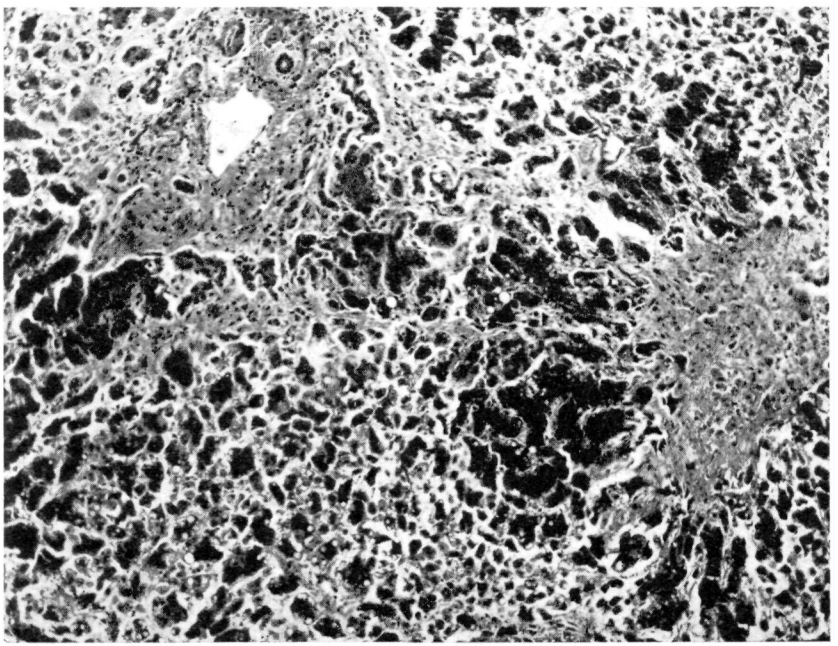

FIG. 4. *Case 2:* The liver at necropsy. In the lower left and extreme upper right hand corners there are necrotic hepatic parenchymal cells. The surviving cells are in the periphery of the lobules and are the site of lipidic change. No inflammatory cells are present. The fibrous area in the middle right hand portion of the photograph is collapsed stroma. This lesion is felt to be most consistent with toxic hepatitis. (Hematoxylin and eosin, from 90 ×.)

The anesthesia lasted for two hours and 45 minutes. The patient reacted at the conclusion of anesthesia and was returned to the recovery room in a satisfactory condition. No blood was given.

By the third postoperative day he was "depressed"—a state most unusual for this patient who was invariably cheerful. He was anorexic, lethargic, completely tired out, and frequently slept. He was discharged on the sixth postoperative day. Shortly thereafter nausea and jaundice became apparent. He expired ten days later of hepatic failure, 16 days after the last operative procedure.

A necropsy was performed at an outside hospital. The liver was reported to be "very small with some necrosis grossly." Specimens of liver and other tissues were sent to us. Histologically, early cirrhosis of postnecrotic type was present. Regenerative activity was prominent; condensation of the supporting connective tissue and proliferation of bile ducts were present. In addition, there were wide areas of recent necrosis. The portal spaces contained many lymphocytes and neutrophils. Bile stasis was evident in distended intralobular canaliculi.

Case 4. This 51 year old woman came to the hospital with a painful mass in the left breast which had been present for two months. She complained of intolerance to fatty foods and flatulence for many years. Physical examination was negative except for a mass in the left breast. An excision of the mass in the breast was performed during 2 per cent thiamylal, nitrous oxide, oxygen, and halothane anesthesia. The 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 concentration of halothane varied from 0.6 per cent to 1 per cent. The anesthetic course was uneventful, and the patient's vital signs remained stable throughout. She reacted at the conclusion of anesthesia and was returned to the recovery unit in satisfactory condition. The duration of anesthesia was one and one half hours.

The breast lesion proved to be a ruptured epidermal cyst. On the second postoperative day she developed right upper quadrant pain, nausea, vomiting, temperature 100.8° F., and leukocytosis, 15,500/mm.^{3} A diagnosis of acute cholecystitis was made. An oral cholecystogram using bunamiodyl disclosed nonvisualization of the gallbladder. Because the symptoms did not abate after 24 hours, a cholecystectomy and common bile duct exploration were carried out.

The anesthesia for this procedure consisted of semiclosed, endotracheal halothane, nitrous oxide, and oxygen in a system with a total gas flow of 6 liters per minute following induction using 400 mg. of 2 per cent thiamylal, intravenously. Oxygen was maintained at a concentration of at least 33 per cent, and the halothane concentration did not exceed 1 per cent at any time. Gallamine, 160 mg., was used for muscular relaxation during the operative procedure. During the course of anesthesia the blood pressure dropped from a normal of 134/90 mm. of mercury to 100/80 mm. of mercury on two occasions, but for the most part, it was maintained at approximately 120/90 mm. of mercury. At the conclusion of anesthesia the blood pressure was 118/84 mm. of mercury, pulse 100 per minute; the patient was returned to the recovery unit reacting and in a satisfactory condition. Anesthetic time was three and one half hours. No blood was given.

A large, distended, edematous gallbladder filled with small stones was found. The appearance of the liver was unremarkable; it was not biopsied. Liver function tests on the morning of the operative procedure were normal.

Immediately postoperatively the patient did well; temperature returned to normal as did white blood cell count. On the fifth postoperative day she developed urticaria and fever. She had received penicillin and this was promptly discontinued. The urticaria abated but the fever persisted, ranging from 102° F. to 104° F. Operative and postoperative cholangiograms were normal. By the eleventh postoperative day scleral icterus had appeared. The white cell count was 17,000/mm.^{3} Total bilirubin level was 3.8 mg./100 ml., one-minute direct, 2.0 mg./100 ml.; alkaline phosphatase, 16.0 King-Armstrong units, and serum transaminase, 1,160 units. By the twentieth postoperative day the bilirubin level had risen to 13.3 mg./100 ml., 7.0 mg./

100 ml. direct; alkaline phosphatase was 18 King-Armstrong units but transaminase had dropped to 618 units. The T-tube continued to drain clear yellow bile. The patient was lethargic, anorexic, and seriously ill. An exact diagnosis was not established, but coincidental acute viral hepatitis was considered. Neither obstructive jaundice nor hemolysis were considered to be a factor. Ascending cholangitis was considered but the liver was not tender. She gradually recovered and was discharged 35 days after operative procedure. Since that time she has been followed in the Out Patient Department and has improved; liver function tests have returned to normal.

Discussion

In 1958 Virtue and Payne [2] reported a postoperative death after halothane anesthesia that was virtually identical to the first two cases of this report. Their patient was a 39 year old woman who underwent cholecystectomy and exploration of the common bile duct with insertion of a T-tube. She died on the eleventh postoperative day with acute yellow atrophy of the liver and acute pancreatitis. The liver was the site of severe central, midzonal, and peripheral necrosis without abscesses; the hepatic vessels were intact. The authors commented that the clinical course was similar to that of delayed chloroform poisoning, except that the patient did not begin to have difficulty until the sixth postoperative day. Our patients' symptoms began on the twelfth, ninth, third, and fifth postoperative days respectively. Virtue and Payne stated that there was no proof that delayed halothane poisoning had occurred in their patient but that the circumstances warranted presentation of the information.

Burnap, Galla, and Vandam [3] reported two patients in whom histologic examination of the liver was possible after halothane anesthesia. The first was a 48 year old man who died on the sixth postoperative day following aortic valvuloplasty; he had had severe aortic stenosis, heart failure, and hepatic dysfunction preoperatively, secondary to the heart failure. At the time of necropsy, marked centrolobular necrosis of the liver was present. This was consistent either with prolonged chronic passive congestion or with chloroform poisoning, and in this case it was impossible to state the etiology of the necrosis. The second case was a 46 year old man who presented with postnecrotic cirrhosis ten weeks after a frontal sinusectomy performed under halothane anesthesia. There was no history of alcoholism, jaundice, exposure to hepatic toxins, or an illness resembling hepatitis. This case resembles the present case 3, also with postnecrotic cirrhosis.

Barton [4] reported two cases of jaundice following halothane anesthesia. The first, a man with a retropubic prostatectomy, developed jaundice of such severity that three weeks after the first operative procedure an exploratory laparotomy was performed to exclude obstructive jaundice; no obstruction of the biliary tree was found; and three weeks following laparotomy jaundice subsided. The second case was that of an 11 year old child who had had halothane anesthesia for a fractured patella. Jaundice persisted after one week; further details were not given.

Dobkin [5] pointed out that Barton did not give details of anesthetic technique, premedication, or postoperative drugs. He suggested that the possibilities of transfusion reaction, homologous serum jaundice, or coincidental infectious hepatitis should be checked.

At the time that the present cases were in the hospital, the attending physicians had difficulty in establishing diagnoses. Two of the patients, cases 1 and 2, had incidental liver biopsies at the time of cholecystectomy, and in both these were normal. Two of them had T-tubes (cases 2 and 4), through which normal operative and postoperative cholangiograms were obtained. Extrahepatic obstructive jaundice appeared to have been excluded although intrahepatic obstruction remained a possibility; ascending cholangitis was also considered in both cases; necropsy findings in case 2 unequivocally disproved these diagnoses. Severe hepatocellular damage was present; the clinical diagnosis of coincidental acute viral hepatitis was made in all four cases. None of the four patients had received blood transfusion during operative procedures.

These four cases offer no proof that halothane was the direct cause of the massive hepatic necrosis; however, the implications that such is the case are strong. The two pa-

tients with normal liver biopsies first had clinical symptoms of hepatic disease on the twelfth and ninth postoperative days and expired on the twentieth and forty-third postoperative days respectively. The duration of clinical liver disease, then, was eight and 34 days. The third patient became ill on the third postoperative day and expired after 13 days of illness. Durations of these illnesses are compatible with viral hepatitis. Lucké and Mallory [6] described the acute fulminant form of hepatitis in 94 cases, under ten days' duration. Many of the patients were wounded soldiers who had received transfusions of blood and plasma, but many were "spontaneous" cases who had received no such treatment. Nevertheless, it is unusual that our three cases had short courses. The fact that the liver biopsies were normal at the time of the operative procedures does not preclude the possibility of hepatitis; the patients could have been in the incubation phase at that time. It does, however, prove that the patients did not have clinical hepatitis or other hepatocellular disease at that time.

The histologic differentiation between acute toxic hepatitis and acute viral hepatitis, especially in cases in which there is massive or submassive hepatic necrosis, can be very difficult and often impossible. Lucké [7] and Popper and Franklin [8] describe differences but these are subtle. The hepatic endophlebitis that occurs in viral hepatitis was not seen in the present cases nor was the extensive inflammatory infiltrate of that disease present. Indeed, in case 2 there were few inflammatory cells present. In case 3 significant numbers of neutrophils were present; their presence may suggest toxic hepatitis rather than viral hepatitis but this is not a specific finding. In cases 1 and 2 there was lipidic change in surviving cells, a point in favor of toxic hepatitis. Lucké and Popper emphasized that in acute viral hepatitis necrotic liver cells were not seen; that they quickly were lysed and disappeared. In toxic hepatitis, coagulation necrosis, fatty change, and evidence of slow cell death may be more apparent; these changes were seen in case 2 as there were broad areas of "ghost" cells and cells that had undergone coagulative necrosis. Changes in cases 1 and 3, however, are indistinguishable from those seen in examples of viral hepatitis.

The most intriguing aspect of these cases is that three of the four patients were women on whom cholecystectomy and (in two) common bile duct exploration were performed. Virtue and Payne's case (*vide supra*) was similar. Liver function tests in all three were normal preoperatively although case 1 did have 12 per cent Bromsulphalein retention and prothrombin time of 61 per cent. What specific effect this type of operative procedure has, we are unable to say at this time. Two patients received bunamiodyl which has been reported by Bolt, Dillon and Pollard [9] to produce transient elevation of serum bilirubin; the effect is said to be temporary and to be gone by two days after the ingestion of the dye. As these patients first became ill on the ninth and fifth postoperative days it seems unlikely that the drug was a significant cause of the hepatocellular damage although it is possible. Case 3 had only an ophthalmic surgical procedure and received no hepatotoxic drugs. Two of the patients (cases 3 and 4) had more than one period of anesthesia with halothane. Case 3 had three halothane anesthetics in a period of four months; case 4 had two anesthetics in four days. What effect the repeated anesthetics had upon the liver, we cannot say.

The anesthetic course in each instance in the four patients presented would appear to be quite unremarkable and there is no suggestion that the patients suffered hypoxia or hypercapnea at any time. The vital signs throughout the course of the operative procedures remained remarkably stable in all instances and the patients' anesthetic records would appear to be typical of thousands of others in which anesthesia was conducted with this agent.

Summary

Four case histories are presented, three of them fatal in which the patients developed massive hepatic necrosis (acute yellow atrophy) following surgical procedures under halothane anesthesia. Liver biopsies from two of these patients were normal at the time of the operative procedure. The possible causative

factors involved are discussed and evaluated. We believe it to be significant that three of the four patients presented had surgical procedures on the biliary tract.

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SUMMARY OF THE NATIONAL HALOTHANE STUDY; POSSIBLE ASSOCIATION BETWEEN HALOTHANE ANESTHESIA AND POSTOPERATIVE HEPATIC NECROSIS

National Academy of Science
National Research Council
Committee on Anesthesia
Subcommittee on the National Halothane Study

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Summary of the National Halothane Study

Possible Association Between Halothane Anesthesia and Postoperative Hepatic Necrosis

Subcommittee on the National Halothane Study of the
Committee on Anesthesia, National Academy of Sciences-National Research Council

Following extensive laboratory investigation, halothane (Fluothane), 1,1,1-trifluoro-2,2-bromochloroethane, was introduced to clinical anesthesia in England in 1956 and in the United States in 1958, and in its early years of use appeared to have an impressive record of safety. Careful consideration had been given to the possibility that halothane, in common with many other halogenated compounds, might damage the liver. Studies of hepatic function in the experimental animal and in man gave no indication of halothane-induced hepatic damage, but isolated reports of massive hepatic necrosis following halothane anesthesia soon appeared[1-3] and suggested the need for further investigation. In December 1961, the Committee on Anesthesia of the National Academy of Sciences-National Research Council (NAS-NRC) designated a study group to report periodically on all clinical aspects of halothane anesthesia and to give special attention to any evidence of association with fatal postoperative hepatic necrosis. In October 1962, a subcommittee of three was appointed to make recommendations on the need for and the feasibility of a clinical study of the relationship of halothane anesthesia to hepatic necrosis.

The subcommittee found the evidence insufficient to establish or refute a causal relationship between halothane and postoperative hepatic damage. Postoperative mortality from all causes was estimated at approximately 2%, but the number of deaths attributable to massive hepatic necrosis was thought to be very small, perhaps one death in 10,000 operations. No data were available on the incidence of hepatic necrosis in patients receiving other anesthetics or on the role of preexisting hepatic disease, viral hepatitis, or prolonged operative shock as etiological factors in postoperative hepatic failure. For these reasons, preliminary plans were drawn up for a randomized clinical trial, and a pilot study was begun in one medical center.

In May 1963, a drug warning was issued by the manufacturer on the basis of 12 new cases of fatal hepatic necrosis that followed surgical procedures in which halothane was used; several of the deaths followed cholecystectomy. The warning stated that "the administration of halothane to patients with known liver or biliary tract disease is not recommended." In the same month the NAS-NRC Subcommittee on the National Halothane Study was appointed, its members representing anesthesiology, statistics, internal medicine, pathology, and surgery. The National Halothane Study was initiated in June with funds provided by the National Institute of General Medical Sciences. It was recognized at the outset that the study would be large and difficult, but it was agreed that halothane was a drug of such potential value as to justify the most careful examination of the imputed risk as well as overall safety.

Before the subcommittee completed its plans for a cooperative study several additional cases of hepatic necrosis were reported. Some institutions had come to the point of sharply restricting the use of halothane to a few specific indications, but most potential collaborators probably would have cooperated in a randomized trial, and they did continue to use halothane during the course of the National Halothane Study. Thus, the ethical issue might not have been an overriding factor if the clinical trial had seemed the only way of obtaining data on which to base an inference. Considerations of feasibility and effort, however, strongly favored the retrospective survey as a first step and one that could possibly make a large clinical trial unnecessary. The plans for a clinical trial were discontinued in favor of a survey of experience in the years before the issue of hepatotoxicity had been seriously raised.

Fifty-four medical centers volunteered to participate in the collaborative retrospective study. When provided the exacting requirements of the proposed

For complete list of participants, see page 788.
Reprint requests to 2101 Constitution Ave NW, Washington, DC 20418 (Dr. Sam F. Seeley).

protocol, 16 of them, in view of limitations of personnel and problems in record retrieval, decided against participation. The protocol was tested and refined in a pilot study of the December 1962 records of the remaining 38 institutions. Three withdrew, and 35 contributed data on the four-year period from 1959 through 1962; 34 met the requirements of the protocol, and their data constitute the basis of the subcommittee's report.

The following is a summary of the major findings. A complete report will be published by the NAS-NRC.

Objectives

The primary objective of the study was to compare halothane with other general anesthetics as to incidence of fatal massive hepatic necrosis within six weeks of anesthesia. An equally important objective was to compare halothane with other general anesthetics as to total hospital mortality within six weeks of anesthesia, because it was recognized that, even if halothane were responsible for death from hepatic necrosis more often than were other anesthetics, the incidence would probably be small compared to an estimated overall operative mortality of approximately 2%. Indeed, a slight superiority in overall mortality for halothane could well outweigh any excess of deaths resulting from massive hepatic necrosis.

Design of the Study

It was anticipated that the incidence of fatal massive hepatic necrosis could be very small and that differences in the effects of anesthetics on total mortality might also be small. If the death rate is about 2% and it is desired to detect differences measured in tenths of 1%, then it is necessary to take a sample large enough to include many thousands of deaths. The experience of 1 million operations appeared to constitute a study of appropriate size. To bring so large a body of experience under scrutiny, it was necessary to obtain data from a large number of hospitals for a period of several years. A four-year period was chosen, and the participation of many hospitals served to broaden the medical experience upon which any conclusions ultimately would be based. Since it was in 1963 that several new reports of massive hepatic necrosis following halothane anesthesia precipitated widespread concern, and since this concern may well have subsequently influenced the selection of anesthetics, the survey was limited to the four-year period 1959 through 1962.

Deaths.—To determine the number of deaths, the protocol required each hospital to report postoperative deaths that occurred in the hospital within six weeks of general anesthesia and to abstract the case records, categorizing them by the type of anesthetic used at the patient's last operation.

Population Sample.—To provide information on the population of patients from which the deaths were gathered, each hospital was required to report the number of administrations of general anesthetics in the survey period, categorized by anesthetic agents, and to abstract the records for a randomly selected sample of these cases.

Death Rates.—The information from deaths and population sample was used to calculate crude rates and to adjust these crude death rates within each anesthetic practice for differences in type of operation and such variables as age, sex, and physical status. For technical reasons, death rates are defined as deaths over deaths plus estimated administrations. This differs slightly from the usual method of calculating death rates but does not interfere with comparisons and interpretations.

Massive Hepatic Necrosis.—All deaths which were thought to represent massive hepatic necrosis were reported, and a photocopy of the chart as well as sections of hepatic tissue were submitted for review by an invited panel of six pathologists with a special interest in hepatic disorders. The protocol provided that members of the panel of pathologists should independently (1) describe the morphologic features in each tissue submitted and estimate the degree of necrosis without knowledge of the anesthetic or the clinical history; and (2) review, following step (1), an abstract of the clinical history, again with the anesthetic unknown, and express an opinion as to possible etiologic factors which might have caused the microscopic lesion.

Monthly Reports.—The protocol required that the participating institutions provide for each month: (1) a count of the total number of cases in which general anesthesia of all types was used; (2) for the random sample of general anesthetics, a list of individual cases along with chart number and date of operation; (3) a list of all hospital deaths occurring within six weeks of the administration of a general anesthetic, along with the patient's chart number and date of death; (4) coded abstracts of the clinical records of all patients who died within six weeks of general anesthesia and of those identified in the random sample, containing chart number, age, sex, date of discharge or death, whether necropsy was performed, whether massive hepatic necrosis was described at necropsy or given as a clinical diagnosis, cause of death, other clinical diagnoses, anesthetics used, physical status (evaluated preoperatively), duration of anesthesia, operations in the previous four years, and previous exposure to halothane; 100 two-digit operation codes were provided for coding operative procedures; (5) a list of final diagnoses for each abstracted case in which necropsy was performed; (6) photostatic copies of the relevant portions of the clinical record and blocks or slides of hepatic tissue from all cases with indications of massive hepatic necrosis, possible massive hepatic necrosis, or hepatitis.

Institutions were identified only by code numbers. After tabulation and coding, when the data were transferred from punch cards to computer

tapes, institutional code numbers were changed to afford maximum anonymity.

Results

During the four-year period of study, general anesthetics were administered approximately 856,500 times in the 34 hospitals providing data for this report. There were 16,840 deaths, and in 11,289 of these necropsy was performed; 10,171 of the necropsies included examination of the abdomen. Thus, complete necropsies were done in 60.4% of the cases.

Variations in Anesthetic Practice.—For comparisons anesthetic agents were separated into the following anesthetic practices: (1) halothane, (2) nitrous oxide-barbiturate, (3) cyclopropane, (4) ether, and (5) "other." When combinations of halothane, cyclopropane, and ether were used, they were placed in the fifth category, called "other." General anesthetics not included in the first four classes were also classified as "other."

The use of halothane increased from 11% in 1959 to 48.5% in 1962 (Table 1); simultaneously the use of nitrous oxide-barbiturate, cyclopropane, and ether fell proportionately. There were marked differences in anesthetic practice from one institution to another; these are shown in Table 2. Thus the use of ether varied from none to 38.5%, cyclopropane from 0.2% to 48%, and nitrous oxide-barbiturate from 1.9% to 73.3%. The use of halothane varied from a low of 6.2% to a high of 62.7%.

The choice of anesthetic used for several representative operative procedures is listed in Table 3. Certain anesthetics used frequently for one operation were used rarely for another. For example, cyclopropane was used commonly for hysterectomy but almost never for craniotomy. There was also considerable variation in the choice of anesthetic for patients of differing physical status. A striking example of this, as will be seen later, was the increased use of cyclopropane in patients of poor physical status and in patients undergoing emergency surgery, while ether was rarely used under these circumstances.

The physical status of patients was recorded preoperatively in accordance with the classification of the American Society of Anesthesiologists as follows: (1) no complicating systemic disturbance, (2) moderate complicating systemic disturbance, (3) severe complicating systemic disturbance, (4)

Table 1.—Percentage Distribution of Anesthetic Practice, by Year*

Year	Halothane	N-B†	Cyclopropane	Ether	Other	Estimated No. of Administrations
1959	11.0	35.5	20.5	17.3	15.7	207,261
1960	22.7	28.4	18.8	14.3	15.8	211,421
1961	35.1	23.4	16.4	9.6	15.5	210,728
1962	48.5	15.5	13.4	6.9	15.7	227,105
Total %	29.8	25.5	17.2	11.9	15.6	
Number	254,896	218,221	147,358	102,014	134,026	856,515

*Numbers vary slightly or may not add to the exact total due to rounding.
†N-B=nitrous oxide-barbiturate.

Table 2.—Percentage Distribution of Anesthetic Practice, by Institution

Institution	Halothane	N-B	Cyclopropane	Ether	Other	Estimated No. of Administrations
1	41.7	38.6	0.2	14.4	5.1	39,891
2	43.9	19.3	19.7	6.0	11.1	9,537
3	10.6	57.0	11.1	2.0	19.2	24,828
4	38.9	26.9	12.1	9.2	12.8	29,232
5	22.8	16.2	48.0	2.7	10.2	32,887
6	27.9	39.4	3.0	6.0	23.8	30,261
7	23.6	12.4	37.6	6.2	20.2	11,419
8	39.8	17.6	1.6	28.0	13.1	91,225
9	13.1	35.0	6.0	38.5	7.3	55,455
10	46.3	19.5	17.8	10.8	5.7	29,230
11	35.4	16.4	10.3	22.6	15.4	26,255
12	32.6	12.0	47.3	0.9	7.2	25,137
13	32.3	8.5	23.0	2.6	33.7	6,893
14	19.2	23.8	26.4	0.5	30.1	27,086
15	13.2	27.8	31.6	10.8	16.6	30,272
16	11.3	51.1	8.7	1.4	27.5	16,076
17	17.4	12.9	3.6	38.3	27.7	19,760
18	24.0	23.0	26.9	18.9	7.2	8,900
19	39.1	34.8	15.5	2.8	7.9	18,329
20	6.2	10.7	45.8	14.7	22.5	47,509
21	34.4	23.1	19.5	2.5	20.5	65,154
22	45.4	12.1	25.1	4.2	13.2	31,162
23	21.7	38.4	34.8	0	5.1	9,776
24	16.2	73.3	5.6	1.2	3.7	15,291
25	37.5	8.4	25.7	3.6	24.8	8,447
26	46.2	34.4	5.0	4.9	9.5	37,661
27	33.2	16.1	17.3	6.3	27.1	27,259
28	43.1	41.8	0.7	12.4	2.1	7,062
29	62.7	5.7	11.1	1.2	19.3	3,917
30	52.3	22.7	7.6	0	17.4	4,407
31	32.8	26.5	19.0	10.8	10.8	12,490
32	53.3	11.8	13.9	1.1	19.9	15,532
33	21.2	39.9	9.0	9.7	20.2	26,826
34	11.3	1.9	42.7	2.8	41.4	11,354
Total	29.8	25.5	17.2	11.9	15.6	

Table 3.—Percentage Distribution of Anesthetic Practice, by Selected Operations

Operation	Halothane	N-B*	Cyclopropane	Ether	Other	Estimated No. of Administrations
Hysterectomy	20.0	16.1	31.6	15.6	16.7	41,018
Cholecystectomy	28.9	17.3	30.8	12.3	10.7	13,783
Cholecystectomy and/or common-duct exploration	32.0	20.6	23.9	10.6	12.9	6,263
Cholecystectomy and other procedures	23.4	17.3	27.9	16.4	15.0	7,631
Gastrectomy	19.1	11.7	30.0	22.3	16.9	16,065
Craniotomy	56.3	22.3	1.0	11.9	8.5	16,773

*N-B = nitrous oxide-barbiturate.

extreme complicating systemic disturbance, (5) emergency classes 1 and 2, (6) emergency classes 3 and 4, and (7) moribund.

Hepatic Necrosis.—The panel on pathology examined sections of the liver microscopically in 946 cases in which massive hepatic necrosis was suspected. In 222 cases, the panel confirmed the presence of hepatic necrosis not obscured by autolysis and not explainable by tumor, infarct, or abscess. Eighty-two of the 222 were scored as massive necrosis, 115 were intermediate, and 25 minimal.

The extent of necrosis was rated by each pathologist independently on a scale from zero (none) to 4+ (total parenchymal destruction). These ratings were averaged and the cases were separated into three categories: massive, average score 2.6+ or above; intermediate, 1.6+ to 2.5+; and minimal necrosis, 1.5+ or below. Minimal necrosis was considered to be a commonplace and negligible occurrence in any necropsy population and these cases were thereafter disregarded.

The 82 cases of massive hepatic necrosis were collected from the 10,171 necropsies, or approximately one in 125 necropsies, and approximately one in 10,000 administrations of general anesthesia. Careful checking and rechecking of data-collection procedures ensured that practically all instances of massive hepatic necrosis among the necropsied cases were detected. There was no reliable way, however, of estimating the incidence of hepatic necrosis in the 5,551 cases in which necropsy was not performed or in the 1,118 in which partial necropsy, which did not include abdominal examination, was performed.

If the 115 cases of intermediate hepatic necrosis are added to the 82 with massive destruction, the combined incidence is 1 in 4,400 (or 2.3 in 10,000) administrations of general anesthesia. On the other hand, any inferences drawn from the data on intermediate necrosis should be weighed with caution. The study was designed to detect massive hepatic necrosis, and cases with less than massive necrosis were culled only to avoid missing an occasional instance of the more extensive lesion. Accordingly, principal attention was directed, as planned, to the group with massive hepatic necrosis.

Operations were grouped for purposes of analysis on the basis of low, middle, and high death rate. The low-death-rate category consisted of operations on the mouth and eye, herniorrhaphy, dilatation and curettage, hysterectomy, cystoscopy,

Table 4.—Observed and Expected* No. of Cases of Massive Hepatic Necrosis Following High-, Middle-, and Low-Death-Rate Operations

Operation Group and Status†	Halothane	N-B‡	Cyclopropane	Ether	Other	Total
Low death rate						
Necrosis observed	2	0	1	0	0	3
Necrosis expected	0.7	0.9	0.6	0.4	0.5	3
EA	86.7	105.3	67.5	50.1	57.4	367.0
Rate, per 10,000 EA	0.23	0	0.15	0	0	0.08
Middle death rate						
Necrosis observed	13	6	17	4	7	47
Necrosis expected	16.1	11.1	7.5	4.9	7.9	47
EA	146.2	101.3	68.1	44.3	67.5	427.4
Rate, per 10,000 EA	0.89	0.59	2.50	0.90	1.04	1.10
High death rate						
Necrosis observed	11	9	7	1	4	32
Necrosis expected	11.3	6.0	6.1	3.9	4.7	32
EA	21.8	11.6	11.7	7.6	9.1	61.7
Rate, per 10,000 EA	5.05	7.78	5.99	1.31	4.40	5.18
Operation unknown						
EA	0.2	0.1	0	0	0.1	0.4
Total						
Necrosis observed	26	15	25	5	11	82
Necrosis expected	24.4	20.9	14.1	9.8	12.8	82
EA	254.9	218.2	147.4	102.0	134.0	856.5
Rate, per 10,000 EA	1.02	0.69	1.70	0.49	0.82	0.96

*The rates of necrosis expected were computed by distributing the observed necrosis cases proportional to the number of estimated administrations. For example,

$$\text{Necrosis expected (halothane)} = \frac{\text{Total necrosis} \times \text{EA (halothane)}}{\text{Total EA}} = \frac{3 \times 86.7}{367} = 0.7.$$

†EA = estimated administrations. Figures for EA are in thousands.
‡N-B = nitrous oxide-barbiturate.

Table 5.—Distribution of Massive Hepatic Necrosis, by Operation and Anesthetic Practice

Operation	Halothane	N-B*	Cyclopropane	Ether	Other	Total	Estimated No. of Administrations
Oral	...	...	1	...	...	1	80,218
Craniotomy	3	...	...	...	...	3	16,773
Endoscopy	1	...	...	...	...	1	15,696
Lung	1	2	1	...	...	4	10,023
Heart with pump	6	9	1	1	2	19	8 683
Heart without pump	1	...	...	...	...	1	7.948
Mediastinum	...	...	1	...	1	2	4,195
Cholecystectomy only	1	...	1	...	...	2	13,783
and/or common-duct exploration	...	...	2	...	...	2	6,263
with other major surgery	...	2	...	...	...	2	7.631
Subphrenic abscess	1	...	...	...	...	1	197
Exploratory laparotomy†	2	...	5	...	2	9	18.370
Gastrectomy	2	...	3	1	2	8	16 065
Small bowel	...	...	2	1	1	4	5.394
Large bowel	...	...	1	...	...	1	17,893
Closure evisceration	1	...	...	...	...	1	1.239
Large vessel	...	2	4	...	3	9	7,212
Sympathectomy, adrenal	1	...	...	...	...	1	3.156
Spleen, liver	2	...	1	1	...	4	3,112
Caesarean section	...	...	1	...	...	1	2,476
Hydrocele	1	...	...	...	...	1	11,648
Fracture, closed	...	...	1	...	...	1	9,535
Muscle	1	...	...	...	...	1	16.884
Fracture, open	...	...	...	1	...	1	10 371
Plastic	2	...	...	...	...	2	40.389
All others	...	...	...	...	...	...	521.361
Total	**26**	**15**	**25**	**5**	**11**	**82**	
No. of estimated administrations	254,898	218,223	147,356	102,015	134,023		856.515

* N-B = nitrous oxide-barbiturate.
† Exploratory laparotomy included inoperable cancer (2), lysis of adhesions (3), and evacuation of hematoma and control of hemorrhage (4).

and plastic procedures. The high-death-rate group included craniotomy, open-heart operations, exploratory laparotomy, and large-bowel procedures. All other operations were arbitrarily categorized as middle death rate. (Mammoplasty, in which no deaths occurred, was omitted from the above classification. Consequently, the total estimated administrations are 528 cases short of the total for the study.)

Hepatic necrosis occurred more frequently after operations associated with high death rates (Table 4). Thus, there were three cases of massive necrosis following 366,992 low-death-rate operations (or approximately 0.1 per 10,000), 47 following 427,355 middle-death-rate operations (1.1 per 10,000), and 32 following 61,719 high-death-rate operations (5 per 10,000). The distribution of massive hepatic necrosis by operation and anesthetic practice is presented in Table 5. Nineteen, or nearly one fourth, of the cases followed open-heart operation with cardiopulmonary bypass, although these procedures accounted for only 1% of all operations in the study. Operations on the large blood vessels (primarily the aorta), gastrectomy, and exploratory laparotomy (such as lysis of adhesions for relief of intestinal obstruction, confirmation of inoperable neoplasm, control of hemorrhage, and drainage of abscess) were also associated with a relatively high incidence of massive hepatic necrosis.

Contrary to expectations, an increased incidence of massive hepatic necrosis following biliary tract operations did not occur. An estimated 27,677 patients underwent cholecystectomy and/or common-duct exploration or with other major surgery, and massive hepatic necrosis occurred in only six of these, a rate somewhat less than for most other abdominal operations. One of the six patients had received halothane, whereas halothane was administered for approximately 30% of the cholecystectomies and/or common-duct exploration (Table 3). Massive hepatic necrosis occurred in an additional three patients who had undergone a biliary tract procedure at a previous operation within six weeks of death, and one of these had received halothane.

The highest rate of massive hepatic necrosis followed administration of cyclopropane, particularly in the middle-death-rate group, as shown in Table 4. Cyclopropane was also the anesthetic with the second highest rate of hepatic necrosis in the high-death-rate group, despite the fact that it was used in only 10% of open-heart operations. The

Table 6.—Observed and Expected No. of Cases of Massive Necrosis Following Multiple Operations,* by Halothane Administration

Massive Hepatic Necrosis	Halothane Administration				
	Last & Previous Operations	Previous Operation Only	Last Operation Only	None	Total
Observed	10	0	0.3	11	24
Expected	4.2	2.7	3.6	13.5	24
Estimated administrations	14,100	9,000	12,000	45,500	80,600

*"Multiple operations" is defined as two or more operations under general anesthesia in the same or successive months.

Table 7.—"Unexplained" Cases of Massive Hepatic Necrosis*

Case No.	Age, yr	Sex	Anesthetic Used	Operative Procedure	No. of Operations Within 6 wk	Day of Post-operative Jaundice†	Day of Death Following Operation†	No. of Previous Exposures to Halothane
55	72	M	Other‡	Cholecystectomy; control postoperative hemorrhage	2	No jaundice	2-2	None
64[6]	70	F	Halothane	Cholecystectomy and biopsy, liver (normal)	1	14	20	None
91	66	F	Halothane	Excision skin cancer, popliteal area; debridement and graft	2	26-3	31-8	1
97[5]	67	M	Halothane§	Closure, perforated ulcer; subtotal gastrectomy	2	19-9	19-9	1
98[5]	16	F	Halothane	Repair lacerated tendons of wrist	1	No jaundice	14	None
99	21	M	Halothane	Craniotomy with biopsy; ventriculojugular shunt	2	No jaundice	14-5	1
122[7]	58	F	Halothane	Endoscopy; cholecystectomy and repair of hiatus hernia; debride and pack of wound; resuture wound dehiscence	4	30-24-5-1	34-28-9-5	3
255	45	F	Halothane	Laparotomy and biopsy	1	28	35	None
352	75	M	Cyclo-propane	Laparotomy and release of adhesions	1	1	1	None

* A case was unexplained if three or more (of four) examiners were unable to explain the extent of hepatic necrosis on the basis of patient's underlying disease, surgical procedure, or recognizable postoperative complication. Evaluation was carried out without explicit knowledge of anesthetic agents used, although four cases had been publicized in the literature.
† Day is given as time following each operation listed.
‡ Nitrous oxide-ether was used for cholecystectomy, ethylene for control postoperative hemorrhage.
§ Alcoholism was a contributing factor.

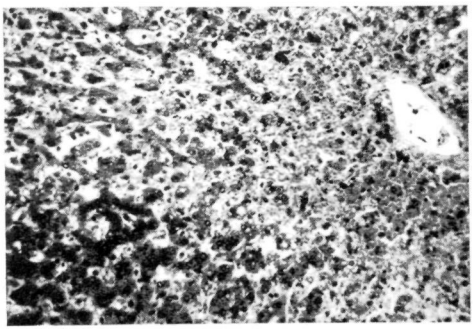
incidence of massive hepatic necrosis following administration of halothane was virtually the same as that following administration of nitrous oxide-barbiturate or "other" anesthetics, slightly more than with ether, and considerably less than with cyclopropane.

There were 80,600 patients who had two or more operations while under general anesthesia in the same or in successive months. In Table 6 it is seen that the incidence of massive hepatic necrosis was considerably higher (24 per 80,600, or 3 per 10,000) in patients who had undergone multiple procedures than in patients who had not (58 per 775,900 or 0.7 per 10,000), and this seemed particularly true of halothane (10 per 14,100 or 7.1 per 10,000).

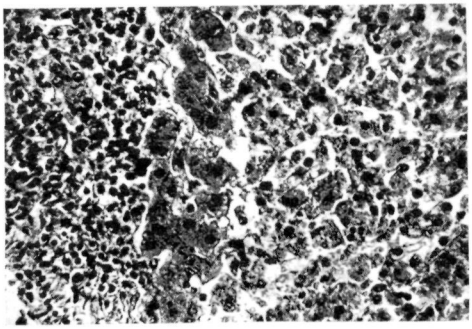
Usually there appeared to be an adequate clinical explanation for the massive hepatic necrosis observed at necropsy: shock, especially with prolonged use of vasopressors; overwhelming infection; severe and prolonged congestive heart failure; and preexisting liver disease. In a few cases, however, the underlying reason for hepatic necrosis was not easily established; accordingly, four members of the subcommittee independently reviewed the 82 cases of confirmed massive hepatic necrosis. They classified each case of necrosis as "explained" or "unexplained" on the basis of whether or not the necrosis could be assigned to a recognizable clinical factor. These ratings were made from a summary of the clinical record in which the identity of the anesthetic agents had been deliberately omitted.

Among the 82 cases of confirmed massive hepatic necrosis nine were considered to be unexplained by at least three of the four members of the subcommittee (Table 7); seven patients had received halothane for the final operation, one had received cyclopropane, and one had received "other" (ethylene). Of the nine patients, five had undergone one or more previous operations within six weeks of the final procedure. Of the five, four had received halothane on at least two occasions and the fifth had received ethylene for the final operation, ether for the previous one.

Unexplained liver failure was usually characterized by fever within two or three days after operation, soon followed by jaundice, which deepened progressively, and a tender, palpable liver. Con-



1. "Shock lesion." Central congestion affects approximately three fourths of hepatic lobule. Liver cells have disintegrated although scattered pyknotic, nuclear fragments are apparent. Kupffer cells contain abundant hemosiderin. There is only negligible inflammatory reaction (×150).



2. Massive hepatic necrosis with thin, irregular rim of disturbed parenchymal cells in periportal region. Rest has undergone necrosis and consists of coagulated, eosinophilic masses of cytoplasm with and without pyknotic, nuclear remnants. Intermingling of histiocytes and neutrophils is modest (×200).

Table 8.—Crude Death Rate, by Institution and Anesthetic Practice, Percentage Dying Within Six Weeks

Institution	Halothane	N-B*	Cyclopropane	Ether	Other	Total
1	1.12	0.36	6.73	0.09	1.85	0.73
2	5.13	4.85	8.62	3.72	8.22	6.05
3	0.94	0.74	0.72	0.21	1.02	0.80
4	0.91	1.23	5.91	3.37	5.00	2.39
5	4.24	4.78	2.14	5.78	5.53	3.51
6	1.06	0.86	2.51	3.00	0.83	1.09
7	5.33	3.09	2.23	7.54	7.58	4.53
8	1.81	0.71	3.47	1.16	1.75	1.46
9	3.47	1.30	3.50	1.09	2.47	1.73
10	1.66	2.60	5.36	1.32	4.72	2.66
11	1.36	1.63	3.00	2.02	3.59	2.07
12	2.13	0.99	1.43	2.95	5.92	1.97
13	3.10	2.02	5.83	1.11	2.64	3.45
14	0.54	0.17	0.78	4.00	0.49	0.52
15	1.58	1.51	1.95	1.83	2.74	1.90
16	3.56	2.99	5.47	1.30	2.54	3.13
17	1.49	0.31	2.62	0.24	1.60	0.93
18	3.30	3.53	4.93	0.59	6.57	3.54
19	3.09	1.24	3.31	0.39	5.20	2.58
20	1.44	0.80	1.11	1.84	2.43	1.51
21	1.10	1.21	1.44	1.19	1.31	1.24
22	1.69	2.38	1.73	0.61	3.14	1.93
23	0.84	1.06	0.56	0/0	1.19	0.84
24	5.59	4.39	21.01	13.04	17.28	6.34
25	3.83	6.55	7.11	7.03	9.23	6.41
26	0.71	1.00	4.01	0.54	1.33	1.03
27	1.07	0.68	2.34	0.35	0.66	1.07
28	0.33	0.17	0.00	0.23	1.34	0.27
29	3.50	6.25	7.46	4.00	3.82	4.18
30	5.34	4.50	7.18	0/0	2.54	4.82
31	1.42	0.69	3.22	0.07	1.31	1.42
32	1.63	0.76	3.05	0.00	1.81	1.75
33	3.57	1.29	4.21	2.36	2.90	2.48
34	0.85	2.28	1.53	1.56	1.76	1.56
Total	**1.87**	**1.49**	**2.54**	**1.35**	**2.51**	**1.93**

*N-B = nitrous oxide-barbiturate.

fusion, somnolence, and a flapping tremor developed within a week after the onset of fever. The confusion usually progressed rapidly to coma and death. Hypotension was a late manifestation, usually appearing only on the day of death. The total duration of the illness was brief, the longest interval between the onset of symptoms of liver failure and death being nine days. The course was similar to that associated with fulminant viral hepatitis[4] and to that associated with delayed chloroform poisoning. In contrast, the patients in whom necrosis was considered explained were seriously ill, usually with shock for many hours or days or, less frequently, with severe congestive heart failure. Half the patients with hypotension became anuric. Jaundice was a less frequent manifestation, usually only terminally. In most cases, hepatic injury was not suspected during life.

The appearance of the liver on histologic examination in the explained cases of massive hepatic necrosis was, in most instances, consistent with that observed in shock or hypoxia, reflecting the severe circulatory disorders which occurred in almost all of these patients prior to death. These sections were characterized by centrilobular congestion and, ultimately, pooling of sinusoidal blood. Paralleling this was attenuation and disappearance of parenchymal cells with relatively little inflammatory reaction. Fatty vacuolization was mild and limited to the cells bordering upon the necrotic zone (Fig 1).

The appearance on histologic examination of specimens from the nine unexplained cases of massive hepatic necrosis varied considerably. Of the seven unexplained cases that followed halothane administration, six presented a lesion which was thought by the majority of the members of the panel on pathology to simulate the lesions of viral or of certain drug-induced forms of hepatitis. In these lesions the hepatic cellular necrosis was coagulative in character and sinusoidal congestion was a minor feature. Intralobular inflammation

Table 9.—Crude Death Rate for Selected Operations, by Anesthetic Practice, Percentage Dying Within Six Weeks

Operation	Halothane	N-B*	Cyclopropane	Ether	Other	Total
Hysterectomy	0.17	0.23	0.26	0.33	0.41	0.27
Cholecystectomy	0.72	0.88	1.21	1.11	2.63	1.16
Cholecystectomy and/or common-duct exploration	2.29	3.16	4.60	3.63	4.16	3.41
Cholecystectomy and other procedures	4.03	3.30	5.05	3.62	5.14	4.29
Gastrectomy	4.19	5.59	6.25	2.67	5.29	4.84
Craniotomy	9.17	9.74	12.37	6.54	18.46	9.91

* N-B = nitrous oxide-barbiturate.

Table 10.—Postoperative Mortality, by Mortality Level of Surgical Procedure and Anesthetic Practice

Mortality Level of Surgical Procedure	Halothane	N-B*	Cyclopropane	Ether	Other	Total	Percent
			Estimated Administrations, Thousands				
Low	86.7	105.3	67.5	50.1	57.4	367.0	42.8
Middle	146.2	101.3	68.1	44.3	67.5	427.4	49.9
High	21.8	11.6	11.7	7.6	9.1	61.7	7.2
Operation unknown	0.2	0.1	0.0	0.0	0.1	0.4	0
Total	**254.9**	**218.2**	**147.4**	**102.0**	**134.1**	**856.5**	**100**
			Number of Deaths				
Low	234	209	175	63	163	844	5.0
Middle	2,562	1,757	2,397	837	2,073	9,626	57.1
High	2,066	1,323	1,270	492	1,205	6,356	37.7
Operation unknown	1	3	3	4	3	14	0.1
Total	**4,863**	**3,292**	**3,845**	**1,396**	**3,444**	**16,840**	**100**
			Death Rate, %				
Low	0.27	0.20	0.26	0.13	0.28	0.23	
Middle	1.72	1.71	3.40	1.86	2.98	2.20	
High	9.48	11.43	10.86	6.47	13.27	10.30	
Total	**1.87**	**1.49**	**2.54**	**1.35**	**2.51**	**1.93**	

* N-B = nitrous oxide-barbiturate.

was variable and usually appeared as an intermixture of histiocytes and neutrophils among the necrotic epithelial cells. The portal areas frequently exhibited a lymphocytic exudate. Fatty degeneration was variable but usually negligible (Fig 2). On occasion, the lymphocytic exudate in the portal area, moderate in the specimen shown in Fig 2, was quite pronounced.

In one of the six unexplained cases following halothane administration in which there was a lesion simulating hepatitis, there were also histological features suggesting superimposed shock. The lesions in the remaining three unexplained cases were consistent with shock; one followed administration of halothane; one, cyclopropane; and one, ethylene ("other").

Death Rates.—The overall crude death rate following general anesthesia and operations was 1.93% (Table 8) with considerable variation among the five anesthetic practices. The lowest overall rate, 1.35%, followed ether administration, and the highest, 2.54%, followed cyclopropane administration. Table 8 also shows that there were large variations in overall death rate among the 34 institutions. The lowest institutional death rate was 0.27%, and the highest was 6.41%, a considerable variation. Some, but not all, of the differences among anesthetic agents and among institutions could be accounted for by differences in operation, age, and physical status. However, the differences among institutions, even after adjustments for such "interfering variables" remain very much larger than the differences among anesthetics.

The mortality for several representative procedures and for the five anesthetic groups is presented in Table 9. In Table 10 is presented the distribution of cases for the five anesthetic practices, divided for analysis into low-, middle-, and high-death-rate operation categories. A large share of the procedures, 43%, and a very small share of the deaths, 5%, were associated with the seven low-death-rate operations. Half the procedures and 57% of the deaths occurred in the middle-death-rate group. The overall death rate in the middle-death-rate operations is about ten times as great as that in the low-death-rate category. The high-death-rate group involves about 7% of the procedures and includes 38% of the deaths; the overall death rate is 45 times as great in the high- as in the low-death-rate group.

Mortality varied considerably among the five anesthetic practices. Mortality following operations with the patient under halothane anesthesia, both overall (Table 8) and following specific procedures (Table 9), was lower than average. Cyclopropane and "other" were generally associated with the highest death rates. The anesthetics compared

Table 11.—Rate of Death (%) Within Six Weeks for Middle-Death-Rate Operations, by Anesthetic Practice and Physical Status of Patient

Physical Status*	Halothane	N-B†	Cyclopropane	Ether	Other	Total
Unknown	1.77	1.52	2.93	1.89	2.31	1.99
1	0.19	0.17	0.33	0.26	0.35	0.24
2	1.52	1.60	2.56	1.49	2.12	1.78
3	6.92	6.92	10.56	5.52	6.89	7.24
4	15.53	15.40	18.64	22.43	18.45	17.27
5	1.12	1.23	1.36	2.08	2.33	1.44
6	10.89	12.19	12.49	14.40	14.41	12.53
7	25.19	23.72	33.75	28.51	38.60	31.48
Total	**1.72**	**1.71**	**3.40**	**1.86**	**2.98**	**2.20**
Standardized death rate	1.94	1.94	2.85	2.12	2.52	2.20
Standard ratio‡	0.88	0.88	1.29	0.96	1.15	

*Physical-status classification is explained in the text.
†N-B=nitrous oxide-barbiturate.
‡Standard ratio is obtained by dividing the standardized rate by figure 2.21, which is the standardized rate calculated by applying average death rates within anesthetic risk categories to the overall population. This ratio shows whether an agent has a higher or lower death rate than "average," ratios larger than 1 being higher, and less than 1 being lower than average.

Table 12.—Percentage Distribution of Patients With Middle-Death-Rate Operations, by Physical Status and Anesthetic Practice

Physical Status*	Halothane	N-B†	Cyclopropane	Ether	Other	Total
Unknown‡	16.2	16.2	14.9	16.3	17.8	16.2
1	45.1	46.3	40.3	45.8	38.0	43.5
2	25.2	24.6	20.7	24.4	25.9	24.4
3	6.1	6.7	5.6	8.2	9.1	6.9
4	0.8	0.6	1.0	0.5	1.2	0.8
5	4.5	3.3	10.9	2.9	4.4	5.1
6	1.8	1.9	5.6	1.6	3.0	2.6
7	0.3	0.3	1.1	0.4	0.6	0.5
Total estimated administrations, thousands	146.2	101.3	68.1	44.3	67.5	427.4

*Physical status classification is explained in text.
†N-B = nitrous oxide-barbiturate.
‡The numbers in "Unknown" row are large because some hospitals do not use the index for classification.

somewhat differently with one another on death rates in the three groups of operations. As examples: ether appears to be best in the high- and low-death-rate groups, but not in the middle group; "other" appears to be worst in both the high and low groups, but not in the middle group. But before attaching any weight to these comparisons of anesthetics, it is important to recognize that the anesthetic populations need to be balanced or adjusted for such features as the age and sex of the patient, his physical condition, and the particular operation performed.

To illustrate an adjustment for one important variable, Table 11 displays the death rates for each of the anesthetic practices for the middle-death-rate operations, categorized by preoperative physical status. The right-hand column shows that the death rate depended strongly on this variable, ranging from about 0.25% to more than 30%; and Table 12 shows that cyclopropane had a disproportionately large share of patients in physical-status classes 5 (emergency), 6 (emergency), and 7 (moribund), which are the high-death-rate categories. The overall death rate for cyclopropane can thus be expected to be higher simply because of its being administered more frequently to patients in these high-risk groups. Standardizing the death rate for physical status is one way of adjusting for this kind of imbalance; it is calculated for cyclopropane, for example, by taking the cyclopropane death rates for each physical-status category and calculating what the overall death rate for cyclopropane would have been had these rates been applied to the population of the study as a whole. Standardization reduces the death rate for cyclopropane from 3.4% to 2.85% (Table 11). Although an adjustment of 0.5% may seem small, when applied to the 68,109 middle-death-rate cyclopropane operations, the difference comes to about 368 deaths, or 286 more than the total number of massive hepatic necroses for the entire study. The standardized rates for the other agents are similarly computed. The standardization for physical status has made halothane, nitrous oxide-barbiturate, and ether look somewhat less favorable than they did before, and both cyclopropane and "other" somewhat less unfavorable. Much of the variation in the crude death rates, that is, merely reflects differences in the selection of patients, classified as to physical status.

The death rates can be standardized for each of the interfering variables one at a time, and in the complete report this has been done. But it is obviously desirable to take account of joint effects by adjusting simultaneously for such variables as age, physical status, and operation before comparing death rates for the various anesthetic practices. Methods for making such simultaneous adjustments in a body of data this large and complex are somewhat experimental in character, and one of the important outcomes of this study has been to strengthen and deepen the statistical methodology for such problems. A variety of approaches has been employed and is presented in detail in the complete report; they all lead to very similar interpretations of the data. Table 13 presents a summary of the data based on one of these approaches, called the "smoothed contingency table analysis." This analysis "smooths" the data of a multidimensional contingency table by replacing the original counts by fitted counts based on the one-, two-, and sometimes three-dimensional margins of the original table.

Table 13 gives the main summary statistics for the entire death-rate study insofar as they are discussed in this summary report. This table shows that, for the low-death-rate operations, "other" had much the highest smoothed death rate, although it is only about one third of 1%, and that nitrous oxide-barbiturate and ether had the lowest. For the middle-death-rate operations, the death rates

Table 13.—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.

Table 14.—Smoothed Death Rates for Cholecystectomies in Patients of Physical Status 1, 2, and 5,* Percentage Dying Within Six Weeks

Sex	Age, Yr	Halothane	N-B†	Cyclopropane	Ether	Other
			Cholecystectomy Alone			
F	0-49	0.05	0.07	0.04	0.04	0.18
M	0-49	0.10	0.14	0.07	0.10	0.43
F	50-69	0.28	0.34	0.35	0.40	0.80
M	50-69	0.54	0.67	0.71	1.12	1.96
			Cholecystectomy and/or Common-Duct Procedures			
F	0-49	0.21	0.31	0.18	0.14	0.34
M	0-49	0.41	0.61	0.36	0.39	0.85
F	50-69	1.01	1.39	1.59	1.42	1.44
M	50-69	1.93	2.67	3.17	3.84	3.50

*Physical-status classification is explained in the text.
†N-B = nitrous oxide-barbiturate.

were generally about ten times higher, and ether, halothane, and nitrous oxide-barbiturate definitely had the lowest rates in this category, with "other" and cyclopropane greater by a large margin. The high-death-rate operations exhibited exactly the same pattern as the middle-death-rate operations, except that cyclopropane stood out even more clearly as having the highest death rate among the five.

In this study, the reliability of death rates for ether is much poorer than for the remaining commonly used anesthetics. Not only is ether used less often than the other agents but also it is used much less widely. Half of the institutions used ether in fewer than 5% of surgical operations, and about one half of all the exposures occurred in a particular two of the institutions. These limitations in the basic data require great diffidence in interpreting the death rates for ether.

Cholecystectomies.—The complete report includes death rates associated with specific operations, among which cholecystectomies are of special interest. Table 14 shows smoothed death rates associated with cholecystectomy alone and for cholecystectomy with common-duct exploration, for both sexes, two age groups, and the better physical status groups (1, 2, 5). For these selected groups (chosen because they had cases enough to make them worth presenting), the anesthetics had similar death rates, and halothane had as low a rate as any.

Table 15 shows standardized death rates for cholecystectomies in patients of physical-status classes 1-6; halothane had the lowest rate by 0.4%; nitrous oxide-barbiturate, cyclopropane, and ether had nearly identical rates; and "other" had the highest rate. Standardization was based on operation code, sex, age, and physical status. To check whether halothane's good overall record came primarily from its better performance with patients in good preoperative physical condition, death rates were also computed for patients in poorer physical-status classes (3, 4, 6) for cholecystectomy and for cholecystectomy and/or common-duct exploration (physical status 7 omitted because of too few cases). For these patients, halothane had lowest or second lowest death rates.

Table 15.—Percentage Distribution of Death Rates Standardized for All Cholecystectomies in Physical Status 1-6*

	Halothane	N-B†	Cyclopropane	Ether	Other	Total
All Patients	2.05	2.57	2.53	2.44	3.18	2.47
Estimated administrations, thousands	7.8	5.0	7.8	3.6	3.4	27.6

*Physical-status classification is explained in the text. Patients from physical status 7 were omitted because there were too few cases.
†N-B = nitrous oxide-barbiturate.

Craniotomy.—The use of halothane for craniotomy was also singled out for careful examination, since the drug warning of May 1963 had also cautioned that halothane may increase intracranial pressure and, by implication, that it might be unsafe for craniotomy. Halothane and nitrous oxide-barbiturate were the most frequently used anesthetics for craniotomy (Table 3), with halothane used 2½ times as often as nitrous oxide-barbiturate and cyclopropane used rarely. Among patients under age 50, halothane had a lower death rate than nitrous oxide-barbiturate; among patients age 50 and over, nitrous oxide-barbiturate had the lower death rate. Ether was used only half as often as nitrous oxide-barbiturate, and ether's death rate was the lowest.

Comment

Hepatic Necrosis.—Massive hepatic necrosis occurred infrequently following general anesthesia and operation in the experience of the 34 hospitals during the years 1959-1962. When necrosis did occur, it could usually be attributed to shock, overwhelming infection, or preexisting liver disease. Nevertheless, there were nine cases among the 82 cases of massive hepatic necrosis for which no clear explanation could be found; in these cases it is reasonable to consider the possibility that hepatic necrosis could have been caused by the anesthetic.

Seven of the nine patients with unexplained massive hepatic necrosis had received halothane during the final operative procedure. Five of the seven died following clinically evident liver failure; this was in contrast to the patients whose massive necrosis was considered explained by prolonged shock or overwhelming sepsis, and in most of whom liver failure was not suspected clinically. The pattern of hepatic injury displayed upon microscopical examination in six of the seven unexplained cases which followed halothane administration resembled that observed in viral or in certain drug-induced forms of hepatitis, again in contrast to the pattern

of the explained group, which was in almost every case consistent with the effects of shock.

It is not possible to say whether these very few cases of unexplained hepatic necrosis, or the apparent small excess of cases of liver necrosis following two or more exposures to halothane, were caused by halothane or whether they occurred by coincidence; for example, they might have been the result of preexisting or unrecognized viral hepatitis, which they resembled both clinically and pathologically. The principal considerations which bring us to question the validity of a cause and effect relationship in these cases are as follows.

There was no certain way to determine whether a patient who died with clinical evidence of liver failure might have been more likely to undergo necropsy if halothane had been administered. A small number of such cases could result in the apparent excess of unexplained massive hepatic necrosis among patients who received halothane, and yet not have a detectable effect on overall necropsy rates, which were almost identical for the five groups. The period of study, 1959-1962, was explicitly chosen to antedate the widespread concern that began early in 1963 and to minimize the likelihood of necropsy bias. Massive hepatic necrosis following halothane administration had been reported as early as 1958,[1,2] however, and some suspicion must have been entertained during the period of the study.

The possibility of necropsy bias is of even greater concern in view of the approximately 40% of deaths without necropsy (or with partial necropsy in which the abdomen was not examined). This 40% "nonresponse" in necropsy represents such a large rate of nonresponse that confidence limits on rates computed from the completed necropsies would be either so broad as to be useless or based on strong assumptions that we are in no position to verify.

Reports of four of the seven cases of unexplained massive hepatic necrosis following halothane administration had been published,[5-7] and an additional two were known to the participating institutions before the study began. The five institutions from which these six known cases came were invited or volunteered to join the study at least in part because of these cases. Thus, the inclusion of these cases in any comparison of hepatic necrosis rates for different anesthetics could lead to a "volunteer" bias in the overall estimate of massive hepatic necrosis following halothane administration. To illustrate the possible effect: if an event has a low rate of occurrence, perhaps 0.2 per institution per observation period, and we were to pick only institutions in which at least one event had occurred, then the method of selection would yield an average of about 1.2, or an upward bias of 1. The effect in the present study is smaller than that in the example because only a few institutions were subject to the effect, but qualitatively it is the same and quantitatively more than enough to explain the apparent small excess of halothane cases.

Whatever the role of such a "volunteer" bias may have been, one might reasonably ask why care was not taken to ensure a selection of institutions which could have prevented such a possibility. The answer is that the National Halothane Study was designed to detect differences of a very different order of magnitude. It was originally feared that for every reported case of hepatic necrosis following halothane administration there were many unreported and that large differences among various anesthetics might be found. A most important observation of this study is that the many cases of massive hepatic necrosis which were expected to follow general anesthesia and operation did *not* materialize. We must conclude, therefore, that if there is a halothane-related hepatic necrosis, it occurs rarely.

Although the study failed to establish a causal relationship between halothane and hepatic necrosis, no study of this type could completely exclude the possibility of rare causation. Accordingly, until the matter is finally settled, unexplained fever and jaundice in a specific patient following halothane administration might reasonably be considered a contraindication to its subsequent use in that patient. The grounds for this position are to be found, not in this study, but in the usual medical doctrine that any treatment followed by ill effects should ordinarily not be repeated.

Although attention has been directed to patients who received halothane, the possible effect of other anesthetics should not be overlooked. Cyclopropane was followed by a greater incidence of massive hepatic necrosis than any of the other anesthetics. Since all but one of the 25 cases that followed cyclopropane administration were classified as explained, there is reason to believe that the disproportionately large total number might well have been related to the selective use of this agent for patients in shock. The possibility that cyclopropane damages the liver cannot be excluded, however. For example, it is possible that the splanchnic vasoconstriction which occurs as a result of cyclopropane and which is in part responsible for the support of blood pressure may, by decreasing hepatic blood flow, increase the likelihood of hepatic damage in shock.

Finally, it should be noted that since the initiation of the National Halothane Study there have been nine reports published of retrospective surveys of massive hepatic necrosis associated with anesthesia and operation.[8-16] The total number of anesthetic administrations represented by these reports is 370,000 or more than a third as many as in the present study. The overall incidence of massive hepatic necrosis in these nine institutions was essentially the same as that of the present study, and the incidence of necrosis was almost the same for patients who received halothane as

for those who did not (0.88 and 0.73 per 10,000, respectively). These published reports lend further strength to our conclusion that the harmful effect, if any, of halothane on the liver is very small.

Death Rates.—The death rates reported in Tables 10 through 15 must be interpreted with caution. They can be trusted merely as a summary of experience involving some 856,500 surgical procedures with the contrasts among anesthetic agents largely disentangled from certain other variables which tend to affect surgical death rate: age, physical status, operation, and sex. It cannot be assumed, however, that the differences among death rates are definitely "caused" by the anesthetics. The reason is that we may not have adjusted for the effects of other variables, perhaps very important ones, which also affect the death rate and which may be related, for example, to how the anesthetic agent was chosen. To make the point clear, suppose that in some operations experienced surgeons worked with anesthetists who prefer one of the anesthetics and less-experienced surgeons worked with anesthetists who prefer others. Since these data take no cognizance of the experience of surgeons or of anesthetists, we cannot disentangle the effects of the variable "experience" from the apparent effect of the anesthetic. Bias due to such conceivable interfering variables can be prevented (even if their existence is not recognized) by the use of a randomized clinical trial. Inasmuch as we did not do such a randomized study, we cannot claim the strength of inference that can be obtained only by the use of that methodology. One of our concluding recommendations is that such a study be considered. However, the observed differences in death rate corresponding to the anesthetic make it clear that the overall death rate problem is of an order of magnitude larger in its implications for patient care than that of massive hepatic necrosis.

Toxicology of Dichlorohexafluorobutene.—A possible explanation for hepatic necrosis following anesthesia with halothane was suggested early in the course of this study by the demonstration of a toxic impurity in stock preparations of halothane. It was shown in 1963 that trace concentrations of dichlorohexafluorobutene (DCHFB) were present in halothane as a result of the manufacturing process.[17] It was later established that, while the average concentration of DCHFB in stock halothane was 0.018%, the concentration could increase to 0.03% during administration and storage in anesthetic vaporizers. A large number of animal experiments (mouse, rat, rabbit, dog, and monkey) established the extreme toxicity of this material upon inhalation.[18] Considerable species variation was found in the organ systems affected and in the concentration lethal to 50% of the animals. The latter varied over a tenfold range, but in the more sensitive species was uncomfortably close (a factor of five to ten) to the concentrations administered to patients. The lungs and kidneys were the organs primarily affected and hepatic lesions were demonstrated only in the rat and monkey; in the monkey it was shown that DCHFB was both concentrated in and metabolized by the liver.

On the basis of the animal findings it was recommended that this contaminant be removed from halothane. This suggestion was adopted by the manufacturer (John B. Jewell, MD, Ayerst Laboratories, written communication, Nov 23, 1965), and the halothane now used in the United States is essentially free of DCHFB. Thus, although it was not possible to establish a causal relationship between DCHFB and hepatic necrosis, neither can we completely rule out this possibility. From a practical point of view, the hazard no longer exists.

Summary and Conclusions

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. Special attention was paid to a comparison of halothane and other commonly used anesthetics with respect to hepatic necrosis and postoperative 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 gallbladder 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.

5. Of special interest and concern were the large differences in postoperative mortality occurring among the participating institutions. These differ-

ences could not be accounted for by the variations among hospital populations by any of the criteria measured in this study. This matter is discussed further in the full report.

Recommendations of the Committee on Anesthesia and the Subcommittee on the National Halothane Study, National Research Council

1. *We recommend that consideration be given to the initiation of limited randomized studies of death rates associated with anesthetic agents.*

The present study provides baseline data on death rates, frequency of various procedures, and similar data which should be particularly valuable in planning such studies. This study has left unexplained the relatively high death rate of cyclopropane and the observed but possibly misleading low death rate of ether. Although we can trust the indications that ether, nitrous oxide-barbiturate, and halothane had lower death rates, we are not able to say whether they *lead* to lower death rates, rather than merely being in association with them, possibly through bias due to selection. Such trials should not be undertaken unless, when compared to other uses of medical resources, it is thought worthwhile and feasible to realize a reduction in mortality of the order of one in 200 or unless firm baselines for death rates are in themselves regarded as highly valuable. If such objectives are to be sought, it would be advisable to choose operations for the study which have the following characteristics: (1) two or more anesthetics are regarded as equally suitable for the operation; (2) the death rate for the operation is appreciable, say at least 2%; (3) the operation is one which is frequently performed; and (4) necropsy rates can be anticipated to be sufficiently high if necropsies are needed to assure success of the study.

2. *We recommend the establishment of a cooperating group of institutions to serve as a panel-laboratory for the acquisition of trustworthy information on new drugs (not merely anesthetics) as they come into use.*

In the history of medicine, it is doubtful whether any drug was ever more extensively studied both before and after its introduction than halothane. Yet after halothane had been given to patients perhaps 10 million times it was impossible to give firm, reliable answers to many basic questions about its effects. Two such questions were: How does the death rate following operations performed with the patient under halothane anesthesia compare with death rates when other anesthetics are used? Does halothane induce significantly more hepatic dysfunction than other widely used anesthetics? The National Halothane Study attempted to answer these questions by using existing records. Although 856,500 operations were brought under scrutiny, the answers given are predictably and regrettably short of those desired. For example, the important question of nonfatal liver injury was not taken up by the study. The limitations of knowledge on halothane are certainly not peculiar to it. Limitations at least equally compelling apply to nearly any drug introduced in the past. Had a few scores of thousands of administrations of halothane been given in the context of an experimental information-gathering system, similar in kind to a cooperative randomized clinical trial, reliable information might have been acquired for overall death rates, and possibly for nonfatal liver injury as well.

3. *We recommend consideration of the establishment of a registry for the collection of clinical, laboratory, and pathological findings in cases of hepatic necrosis.*

Massive hepatic necrosis is a rare, but usually fatal disease. In some patients it follows what appears to be typical viral hepatitis. Massive hepatic necrosis may also follow certain major surgical procedures, shock, congestive heart failure, and the use of large amounts of pressor drugs. But in some patients the cause of hepatic necrosis is not so apparent. A number of the recently introduced drugs, such as iproniazid phosphate and zoxazolamine, are thought perhaps to be occasionally responsible; similar suspicions concerning halothane formed the basis for the present study.

The National Halothane Study has not entirely ruled out a rare relationship between halothane and massive hepatic necrosis. It will be important to know, as further data accumulate, whether this association will continue, increase, or disappear. New, possibly hepatotoxic, drugs will continue to be introduced and, because of its infrequency, any associated massive necrosis may go unnoticed unless looked for with care. The proposed registry would provide the mechanism for collecting such information.

In designing such a registry, it must be recognized that for many, if not most, purposes effective interpretation of the data requires knowledge of the size and composition of the population from which the registered cases arise. Some registries have no provision for obtaining such "denominator" data and are hampered in carrying out their mission. Possibly such a registry should be developed in relation to a panel such as that mentioned in the second recommendation above, so that the needed background information would be readily available, or in association with an existing registry that has access to information about its population.

In establishing this registry the most careful consideration must be given to the many inherent limitations and pitfalls. These include (1) the historical, nonexperimental nature of the study; (2) the very low incidence of the variable of interest; (3) the loss of data by nonresponse, such as missing laboratory data and failure to obtain necropsy. In addition, there will doubtless be other, possibly serious, difficulties which will become apparent only as experience with such registries develops. It is apparent that, unless the greatest efforts are

made to identify and overcome these problems, neither this nor any other registry can achieve its goal. To the contrary, it will likely generate misleading or erroneous information.

Finally, a decision to establish a project of the magnitude of such a registry should be made in the light of the total needs of the public health and the availability of medical resources.

Generic and Trade Names of Drug

Halothane—*Fluothane.*

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METABOLISM OF VOLATILE ANESTHETICS

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Review

Metabolism of Volatile Anesthetics

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CLINICAL anesthesia has been a reality for over a century and some of the agents used to produce anesthesia are among the oldest known drugs. Nevertheless, the information available to us concerning the biological disposition of anesthetic agents is extremely meager, while such information on other kinds of newer drugs is plentiful. One reason for this seems to be a universal acceptance of the notion that the volatile anesthetic agents are biochemically inert. For this and other reasons few workers have previously made any serious attempt to to look for possible breakdown products of these agents.

Another possible explanation for this lack of interest in the biotransformation of the volatile anesthetics is the fact that most, if not all, theories of narcosis involve physical, rather than chemical, interaction. For this reason, investigators in this field may have felt little could be gained by investigating the chemical activity of the volatile anesthetic agents. However, Pittinger has recently commented [1] on the possibility that chemical reactivity plays a role in narcosis, and we shall attempt to add to this.

The information available in the literature is still extremely meager. However, we hope that the small fraction of work which has been completed will stimulate others to pursue this idea to its ultimate end.

Earlier studies on the disposition of the volatile anesthetics suffered in large part from lack of sensitivity of the methods employed. With the introduction of the use of radioactive isotopes, sufficient sensitivity has been achieved to perform studies on the biotransformation of these compounds. Indeed, it is only with radioactive isotopic techniques that such studies have been made successfully. An inherent difficulty in these studies is the fact that following a single dose, which is about the only practical method, the volatile anesthetics are removed so rapidly from the body by exhalation that comparatively little metabolism is expected or found. With continuous administration of the anesthetic, the major portion of the anesthetic is present in areas of the body that do not participate in the metabolic process and therefore the extent of metabolism appears to be extremely small. In reality, certain organs metabolize a high percentage of the anesthetic presented to them. Therefore, in studies of this type the percentage of administered anesthetic which is metabolized is small but on an absolute basis the amount of metabolism is fairly large. In general those anesthetics which have been found to be metabolized are converted to CO_2 and urinary metabolites, to the extent of 1.5 to 12 per cent of a given dose.

It is important to note that the metabolism of volatile anesthetics occurs in microsomes for it is in the microsomes where most of the drug metabolizing enzymes now known are found. In addition, most of the drug metabolizing reactions require reduced nicotinamide adenine dinucleotide phosphate (NADPH), the cofactor responsible for hydrogen ion transfer. Thus, while it is not certain which of the many enzymes found in microsomes are involved in metabolism of volatile anesthetics, it is reasonable to assume they are subject to the same variation in amount and activity as has been found to be the case for other drug metabolizing enzymes.

A key, but often overlooked, consideration is the purity of the material used for study. It is extremely important that the purity of the labelled anesthetics be as high as possible and also that the impurities, if present, be known, for many such microcontaminants are unstable under any conditions and yield falsely positive results.

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Hydrocarbons

Ethylene is the simplest of the anesthetic hydrocarbons, and while previously it had been considered not to be metabolized [2] recent preliminary experiments [3] suggest otherwise. In these experiments it has been found that ^{14}C-ethylene in rats is converted to ^{14}C-carbon dioxide and labelled urinary products but the exact amounts have not as yet been determined. The problem with the determination of the metabolism of ethylene is two-fold, for the gas is difficult to administer quantitatively and is rapidly eliminated from the lungs by exhalation.[4] Because of these difficulties, any indication of metabolism may be significant but at the same time not easily quantitated.

Ethylene is not, strictly speaking, a material foreign to animal tissue: it has been found by several investigators to be produced by liver mitochondria under certain conditions, *in vitro*.[5, 6] Thus, the metabolism that seems to occur is not surprising because the organism may have the ability to metabolize the ethylene endogenously produced. An analogue of ethylene, tetrafluoroethylene has recently been found to combine with cyanocobalamine, an active cofactor form of vitamin B_{12}.[7] The combination occurs between the tetrafluoroethylene and the cobalt which indicates that this analog of ethylene is biochemically reactive.

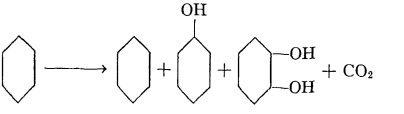
Propylene has not undergone a study of transformation.[8] It would be of interest to determine this if only to ascertain whether it is more readily metabolized than ethylene. Acetylene likewise has undergone no study of its metabolism,[8] thus evidence for or against metabolism is lacking. A recent finding that acetylene combines with derivatives of vitamin B_{12} [9] indicates a possible site of reactivity and a means of metabolism.

Alicyclic Hydrocarbons

The simplest of the cyclic compounds which produce anesthesia is cyclopropane. This compound has been found to be eliminated almost entirely by the lungs.[8] Recent preliminary evidence has suggested that ^{14}C-cyclopropane is converted to ^{14}C-carbon dioxide in rats [10]; but again, as in the case of ethylene, quantitation is difficult as is maintenance of a particular concentration within the experimental animal. Therefore, until better methods are available, the data must remain preliminary. The cyclopropane ring is known to occur in nature (hypoglycin A, certain fats) and, if biosynthesized, it is reasonable to suppose it is degradable.

Cyclopentane and cyclohexane can also be considered at this point inasmuch as both can produce anesthesia.[11] Cyclopentane itself has not been studied *in vivo*. However, cyclopentylacetic acid and cyclopentenylacetic acid have been examined and appear to be metabolized completely.[12] Thus, it follows that the cyclopentane ring can be completely metabolized.

The metabolism of cyclohexane has been extensively studied.[13] This compound has been found to be metabolized to the hydroxylated hexanol. According to Elliot, the break-down of cyclohexane is as follows:



Unchanged 30 per cent — 45 per cent — 6 per cent — 10 per cent

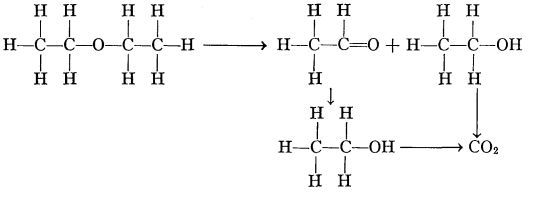
Ethers

It has been known for some time that certain ethers are metabolized by microsomes (Axelrod [14]). Until recently, the ether molecular structures ruptured did not include the anesthetic ethers. These short chain aliphatic ethers have been considered to be eliminated unchanged.[15, 16] Recent work has indicated that, while a large amount of a given dose of ^{14}C-diethyl ether is rapidly eliminated in the expired air, there is a measurable amount converted to ^{14}C-carbon dioxide and labelled urinary metabolites.[17] This provides the evidence that in some manner the short chain ether is cleaved. Additional evidence will be presented below, when the halogenated ethers are discussed.

There exists a certain, as yet unexplained, interaction between ethanol and anesthetics. Lee *et al.*[18] have found that during the development of ethanol tolerance in rats, there is a stormy and prolonged induction period with diethyl ether and methoxyflurane. It has

also been stated that delirium is likely to occur in alcoholic patients [19] when anesthesia is induced. This may be more than a fortuitous relationship since diethyl ether and ethanol are strong hydrogen bonding molecules. This may indicate a similar mode of action, or that they pass through the same intermediates during degradation.

It is highly likely that the mechanism of cleavage of the ether linkage in diethyl ether is by the enzymatic addition of a hydroxyl group at this point to form acetaldehyde and ethanol. The proposed mechanism is as follows:



The formation of an aldehyde intermediate is based on the fact that the product of O-demethylation, which is an ether cleavage, results in the formation of formaldehyde.[20]

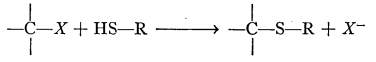
Other anesthetic ethers, such as methylpropyl ether, methylethyl ether, isopropylmethyl ether, ethylpropyl ether and divinyl ether have not been studied in terms of the metabolic transformation which they might undergo. However, since diethyl ether has been found to undergo metabolism it would not be surprising to find the others to be metabolized. Ethylvinyl ether is discussed later under the heading of halogenated ethers.

Paraldehyde, a cyclic polyether, has been shown to have mild hypnotic effects. Its metabolic fate has been studied to the extent that it is known to be excreted unchanged in rats, but in dogs the glucuronide is formed.[11] There are no data for man. Paraldehyde has been found to decompose readily to acetic acid when exposed to air and light.[21] This may provide a clue as to the route of breakdown in biological systems.

Halogenated Hydrocarbons

The chloromethanes have been well studied as to distribution and metabolism. Several recent publications indicate that both chloroform and carbon tetrachloride are converted to carbon dioxide both *in vivo* and in the presence of liver slices.[18, 22-25] The biochemical aspects pertaining to carbon tetrachloride poisoning have been particularly well covered in a recent review.[26]

As early as 1947, it was shown by Heppel and Porterfield that a number of halogenated compounds are dehalogenated by enzymes found in a mixture of cell supernate and microsomes prepared from rat livers.[27] Furthermore, they found that the enzyme responsible could be concentrated by means of ammonium sulfate fractionation. Unfortunately, it was not possible to state exactly where the enzymatic activity is located since no attempt was made to separate microsomes and cell supernate. Among the compounds found to be actively dehalogenated in this system were bromochloromethane, dibromomethane, dichloromethane, 1,2-dibromoethane, chloroform, bromoethane and 1-bromo-2-chloroethane. Bray *et al.*[28] have found that liver extracts are capable of a non-enzymatic liberation of chloride atoms from a number of aliphatic chlorine compounds. This appears to be the result of the formation of a carbon-sulfur bond with the loss of organic halogen. Bray also has shown a decrease in free sulfhydryl groups as a result of this alkylation. This type of reaction is interesting in that it evidently takes place for certain chloromethanes in the absence of enzymes: it also takes place for certain chlorinated aryl compounds, but only in the presence of an active cell supernatant enzyme which Boyland *et al.*[29] have labeled glutathiokinase. In the latter case, glutathione is required for the reaction but, in the former, any sulfhydryl containing compound will react as follows:

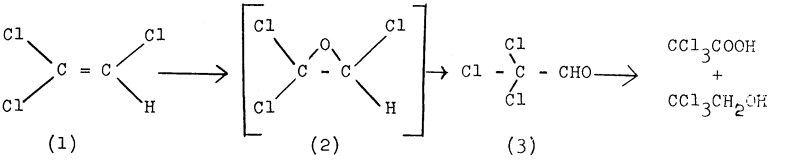


It is apparent that two variants of chloride removal may occur and the prevalent reaction is dependent upon the carbon skeleton to which the chlorines are attached, as well as other substituents of the carbon which is reacting with the sulfhydryl. A third means of chloride removal will be described when halothane and methoxyflurane are discussed.

Butler [30] and Paul and Rubinstein [24] have reported the transformation of carbon tetrachloride to chloroform both *in vivo* and in the presence of liver slices. Butler also has shown the further reduction of chloroform to methylene chloride. It is evident from these reports that there is a non-enzymatic chloride removal as outlined above, also enzymatic chloride removal.

Methyl chloroform, while not suitable as a clinical anesthetic, is, nevertheless, a very potent anesthetic according to Krantz.[31] In addition, this material has been shown to be of extremely low toxicity.[32] Hake *et al.*[33] using ^{14}C labelled material have shown that the metabolism of methyl chloroform is extremely low, with 0.5 per cent conversion to carbon dioxide, and approximately 1 per cent conversion to trichloroethanol.

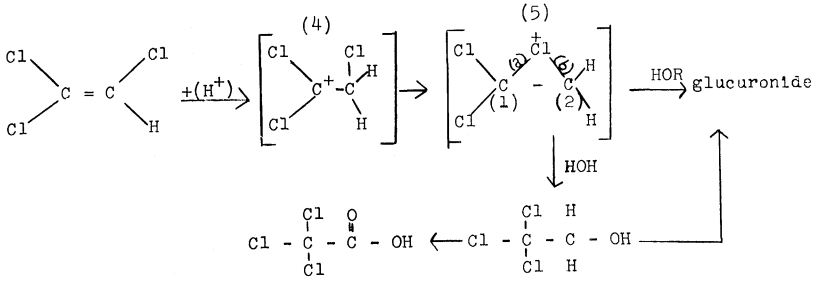
Several reports and reviews have appeared [34, 35, 36] on trichloroethylene and tetrachloroethylene. The urinary metabolites of these two compounds appear to be trichloroacetic acid, trichloroethanol and inorganic chloride, while *trans* 1,2-dichloroethylene is found in expired air. Powell [37] originally proposed the following mechanism for the breakdown of trichloroethylene:



The brackets shown in this and the following schemata indicate unstable intermediates which have not been isolated, either because this has not been possible or because isolation has not been attempted.

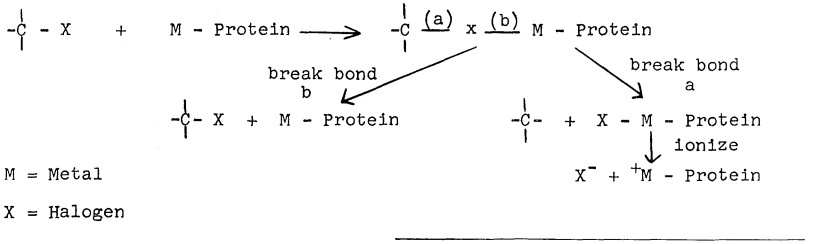
In this reaction one would expect interchange of the free chlorine on (2) with the body chloride pool, in the passage to (3). This, however, does not occur. According to Daniels,[37] the specific activity of the ^{36}Cl-labelled products is the same as the specific activity of the administered ^{36}Cl-labelled trichloroethylene.

Therefore, the reaction shown below with the key intermediates at (4) and (5) is perhaps more accurate.



Because of the strong electrophilic nature of the halogens, halogen bridges of this type are known to occur [38] and the halogens may effect two bonds. If carbon 2 on intermediate no. 5 is attacked by a hydroxyl ion, bond (b) will be broken, resulting in trichloroethanol. This may even be enzymatically controlled. In addition, intermediate no. 5 may react directly with glucuronic acid to form the glucuronide of 1,1,1-trichloroethanol which is one of the urinary products; or it may react with the hydroxyl of water to yield the alcohol which is oxidized to the acid. In some cases, bond (a) may be broken with the addition of an hydroxyl at this point. Since this results in an unstable situation, chlorine would be detached from carbon and replaced with hydride ion, resulting in monochloroethanol, which is also an excretion product of trichloroethylene. As will be seen later, certain dechlorinations require NADPH which is able to transfer hydride ion; this mechanism is therefore, within the realm of possibility.

It is perhaps appropriate to indicate a general enzymatic mechanism for the removal of the halogens in these several halogenated materials. It is conceivable that the reaction occurs as follows:



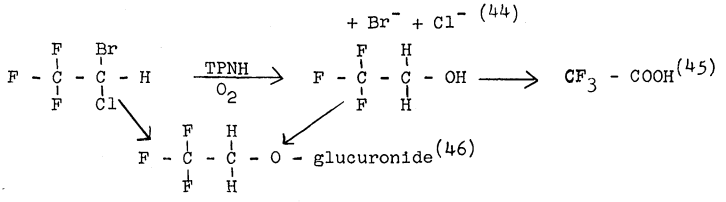
In the above scheme the possibility of rupture exists of either of the bonds labelled (a) or (b). Which bond is broken is dependent upon two factors. One is the metal bound to protein. Of all the metals present in biological systems the metal most likely to foster this reaction is copper. Iron is also a possibility but is not as effective as copper. This reaction is similar to others which have been reported.[39, 40] Secondly, the character of the replacement for *X* at C is equally important. If there are provisions for adding a hydroxyl to C, this will enhance rupture of bond (a). If the electron donating ability of the metal is great enough, this will cause break of bond (a) leaving $-\overset{|}{\underset{|}{C}}^{(-)}$, which in turn may react with a proton: the net result would be a reductive dehalogenation. If the two conditions as outlined above are not met, the bond (b) will not exist for very long and the complex will dissociate. However, if the concentration of the halogenated material is high, another molecule will instantly replace the first; in other words, a dynamic equilibrium is established.

Halothane (1,1,1-trifluoro-2-bromochloroethane) has recently been shown to be metabolized both in rats *in vivo* [41] and *in vitro* [42] using 1-^{14}C halothane and ^{36}Cl-halothane. Presumptive evidence for the removal of the bromide *in vivo* in man has also been reported,[43] while more definitive data have appeared recently.[44, 45]

It is interesting to note that the carbon-fluorine bond in halothane is not easily broken [41] as evidenced by the fact that 1-^{14}C halothane gives rise to very little $^{14}CO_2$. Using ^{36}Cl-halothane, it has been found that the carbon-chlorine bond is broken enzymatically by enzymes found in microsomes, this reaction requiring NADPH and oxygen.[42] There is no chloride removal by the cell supernate alone. It is not known if the carbon-bromine bond is broken under the same conditions, although preliminary evidence indicates that this is so. Therefore, the major products of the metabo-

lism of halothane are chloride, bromide and trifluoroacetic acid.

Biotransformation of halothane is proposed as follows:



It has been assumed that dechlorination and/or debromination of halothane is the source of the urinary products found in the metabolism studies. Since the enzymes responsible for the dechlorination are microsomal enzymes requiring NADPH, it follows that these should be increased by pre-treatment with a known microsomal enzyme inducer such as phenobarbital, as found to be the case with other drugs.[47] This has been shown to occur using labelled halothane.[48] There is a two to four-fold increase in the urinary products following pre-treatment with phenobarbital. An increase of CO_2 production from halothane does not occur, probably because of the fact that the carbon-fluorine bond is still not easily broken, whether or not enzymes are induced.

Teflurane (1,1,1,2-tetrafluoro-2-bromoethane), a newer and still experimental volatile anesthetic, has not been studied in regard to metabolism. However, it is conceivable, in view of the findings with halothane, that the bromine would be removed biologically but the fluorines not.

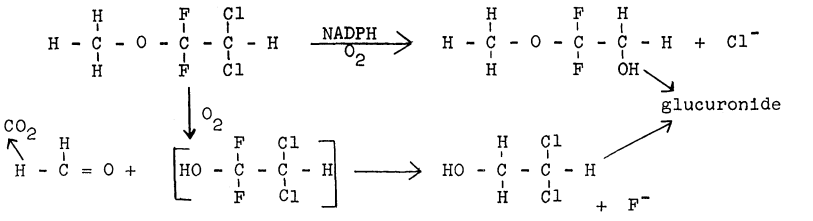
Halogenated Ethers

The fluorinated ethylvinyl ether, fluoroxene, (1,1,1-trifluoroethylvinyl ether) has been studied with regard to metabolism using the 1-^{14}C trifluoroethylvinyl ether.[49] This material has been found to be metabolized in a manner similar to halothane: that is, there is very little carbon-fluorine bond cleavage since little $^{14}CO_2$ is found, but the rest of the molecule is extensively metabolized as evidenced by large amount of urinary metabolites. It appears that the vinyl portion of the ether is easily attacked by a biological system. It has not been ascertained whether this is the result of an enzymatic reaction or if this represents a natural instability of the vinyl ether under biological circumstances.

The evidence for the metabolism of the trifluoroethylvinyl ether suggests that the non-fluorinated analog, ethylvinyl ether, is likewise metabolized. It may be assumed that the fluorines would have no influence on the biochemistry of the ether linkage; thus the products would be similar.

Methoxyflurane (2,2,-dichloro-1,1-difluoroethylmethyl ether) has been extensively studied with regard to metabolism and distribution under several conditions.[17, 42] ^{36}Cl and methyl-^{14}C-methoxyflurane were used in these studies. These reports present evidence that both the ether linkage and the carbon-chloride bond are enzymatically cleaved. Furthermore, these reactions are mediated by microsomal enzymes and at least one, the carbon-chlorine bond cleavage, requires reduced NADP. This has been found by studying the reaction in a liver microsome preparation and by assaying the influence of known enzyme inducers on the extent of metabolism *in vivo*. Both the ether cleavage and break of the carbon-chlorine bond can be enhanced by pretreatment with phenobarbital, 20-methyl-cholanthrene or chronic exposure to methoxyflurane vapors.[48] Evidence for some instability of the C-F bond in this compound was obtained by analysis of the long bones of rabbits chronically exposed to low concentrations. Inorganic fluoride levels were increased in these animals.

The following is a summary of the proposed route of biotransformation of methoxyflurane:



interaction of the nitrous oxide with a material normally found in bone marrow.

Inorganic Anesthetics

Under this category are found the "rare gases" xenon and krypton as well as nitrogen, nitrous oxide and carbon dioxide. All of these gases have in common the fact that they are comparatively weak anesthetics, that is, they require high partial pressures to produce anesthesia and in some cases elevated pressures are required.

It is difficult to imagine the rare gases, xenon and krypton, as being changed in any way *in vivo*. However, xenon can enter into chemical reactions.[50, 51] While these reactions do not occur under conditions found in biological systems, nevertheless they point up the fact that xenon is not completely inert and may possibly have some slight biochemical reactivity. Furthermore, it is an accepted fact that xenon and krypton are capable of a weak association with certain metals.

Nitrogen narcosis has been extensively studied by Bennett.[52] In his studies, he found that azacyclonol in a dosage of 150 mg./kg. prevents development of nitrogen narcosis in rats. Chenoweth [53] repeated this experiment but rather than using nitrogen as the anesthetic, used methoxyflurane. In these experiments he was not able to show an antagonism between the anesthetic and azacyclonol.

Little is known about the metabolism of nitrous oxide although it is actually quite a reactive chemical. Its distribution and excretion have been studied.[54] A pertinent series of papers has appeared [55, 56, 57] describing a leukopenic effect of nitrous oxide, and it may be that this effect is the result of a chemical

Implication of Metabolism in Anesthesia

The fact that inhalation anesthetics undergo biotransformation perhaps, places them in the same position as many other drugs. The important questions to be asked are: what are the metabolites, how is the transformation carried out, *i.e.*, is it enzymatic or non-enzymatic, and does transformation influence the course of anesthesia? The answers to these questions for the most part must await further investigation, but an attempt can be made to answer them at this time. It must be emphasized that metabolic transformation is not necessary for the anesthetic properties of the volatile anesthetic, but their metabolism does indicate a biochemical reactivity.

Such metabolism of the volatile anesthetics as takes place in the liver probably does not influence the degree or extent of anesthesia as produced by these anesthetics. Since the volatile anesthetics are continuously administered insuring a constant blood concentration of unchanged anesthetic. If this were not the case, the effects of metabolism of volatile anesthetics would be as noticeable on the duration of anesthesia by these agents as it is on the duration of anesthesia by the barbiturates.

The metabolism of some of these volatile anesthetics has been found to occur in brain tissue although to a lesser extent than that found to occur in the liver. This metabolism in the brain tissue may be of extreme importance. This fact may require a re-evaluation in our thinking about theories of anesthesia. Could this mean that certain of the volatile anesthetics require a particular chemical reactivity to act as anesthetics?

Through the years several theories of action of anesthetics have been proposed and they have been summarized in a review.[1] These hypotheses have been based on the assumption that volatile anesthetics are biochemically inert and act because of certain physical properties they express. Recently Pauling [58] and Miller [59] have both proposed new and similar theories of the mode of action of anesthetics based on the ability of the anesthetic molecule to enter a clathrate structure. It is this clathrate structure which is assumed to block physically the passage of the impulse along a nerve fiber.

While the Pauling and Miller hypotheses, as well as certain of the other theories on mode of action of anesthetics may contain important considerations as to why a particular material may be anesthetic, they do not go far enough. For example, the clathrate concept may explain the process of transport from the lungs to the central nervous system, but at this point there must be inserted an additional factor to account for those materials with good hydrate forming ability which are non-anesthetic.[60]

Since it is now known that many of the volatile anesthetics are not biologically inert, it may be necessary to consider that chemical reactivity on the part of the anesthetic molecule is essential for anesthesia to occur. There are certain considerations which make this an interesting theory. In the first place we have presented above, data indicating that the most potent anesthetics (as well as the most popular) are metabolized. If one looks carefully enough, probably most anesthetics can be shown to undergo some biotransformation. Secondly, there is the interesting, but as yet only partially explored observation, that ability to undergo metabolism parallels potency of the anesthetic. Thirdly, there is the fact that all anesthetics have in common the ability to associate or form weak bonds with metals, particularly copper and, to a lesser extent, iron. These facts when considered and studied further perhaps will bring new meaning to the state of anesthesia.

Implication of Metabolism to Toxicity

A great deal of discussion has taken place recently on the possible hepatotoxicity of certain volatile anesthetics.[61] In this regard most of the anesthetic show some hepatotoxicity although the degree of toxicity varies. One of the factors to be considered in this review is whether metabolism of anesthetic results in detoxification or the formation of toxic products.

In regard to the question of the formation of toxic products, it is evident from the preceding discussion that the various volatile anesthetics are metabolized by different routes which makes it difficult to consider a uniform mechanism of toxicity. As an example of metabolism by different routes one can always refer to the fact that the carbon-chlorine bonds are ruptured by different means depending on the type of molecule to which they belong. The fact that halothane and methoxyflurane are dechlorinated enzymatically while chloroform is partially dechlorinated by non-enzymatic means demonstrates clearly the possibility of obtaining different types of products. The problem is further complicated by the fact that a potentially toxic material may be either a stable intermediate or an intermediate of the free radical type. This type of reaction has been discussed by Butler.[30]

In addition to these possibilities, there is also the question as to whether an observed toxic reaction is due to the unchanged anesthetic molecule. Such a mechanism could be similar to the one already discussed, in which an anesthetic molecule forms bonds or associates with certain metals. This could lead to interference with the results of reactions in which a metal such as copper or iron is important, as a change in oxidative phosphorylation.

The fact that toxic manifestations are relatively rare suggests that pharmacogenetics as proposed by Kalow [62] is an important consideration. There may be an inborn difference among individuals, either in their ability to metabolize anesthetics, or a difference in the intermediary metabolism which renders some more liable than others to adverse anesthetic reactions.

Perhaps pertinent to this discussion is a series of articles concerning the toxicity of halothane in rats.[63-66] These studies have shown that rats under certain conditions show an LD_{50} to inhaled concentration of 2.8 per

cent for 10 minutes, while in other cases rats fail to show any adverse effect to an intraesophageal administration of 100 per cent. Furthermore, this variation shows daily periodicity according to Matthews, *et al.*[67] According to these workers, a simple manipulation of the daily exposure to light is sufficient to alter the periods of susceptibility. Presumably, this is a result of the daily fluctuation in the normal intermediary metabolism. If this same periodicity occurs in man, this would have a great influence on the possible toxicity of all volatile anesthetics. It was noted that the metabolism of diethyl ether, chloroform, halothane and methoxyflurane *in vivo* showed a large individual variation.[17] It was not determined at the time if circadian rhythms played an important role in this variation in metabolism, but this may be worthy of consideration.

Summary

Evidence has accumulated to the effect that the volatile anesthetics are biodegradable. Direct evidence has been shown for the most popular and potent anesthetics, diethyl ether, chloroform, halothane and methoxyflurane. Indirect evidence for the biotransformation of other less potent anesthetics can be shown.

This information offers a fresh approach to certain questions concerning the action of anesthetics and the toxicity of the anesthetics. This will place the anesthetics in a position to be studied as chemical reactants rather than as physical inhibitors and offer a more positive approach to the study of their mechanism of action.

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A CLINICAL EVALUATION OF METHOXYFLURANE IN MAN

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A CLINICAL EVALUATION OF METHOXYFLURANE IN MAN

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ROBBINS in 1940 [1] studied a large series of fluorinated hydrocarbons; however, none of these agents was tested in man. In 1953 Krantz, Carr, and Bell[2] introduced trifluoroethyl vinyl ether (Fluoromar), and in 1956, Raventós [3] and Suckling [4] introduced 2-bromo-2-chloro-1,1,1-trifluoroethane (Fluothane) as a clinically useful anesthetic. Beginning in 1956, Van Poznak and Artusio investigated a series of fluorinated hydrocarbons and fluorinated ethers in the dogs.[5, 6, 7] Based upon its performance in the dog, the compound 2,2-dichloro-1,1-difluoroethyl methyl ether (Methoxyflurane) was subjected to trial in man.[8] This paper reports on the anesthetic properties of Methoxyflurane in man and reviews the results of its administration in 100 patients.

PHARMACOLOGY

Physical Properties. Methoxyflurane is a clear, colorless liquid which boils at 104.8 C. ± 0.2 degree at 760 mm. of mercury; the freezing point is — 35 C. with a latent heat of vaporization of 49 cal./gm. It has a specific gravity of 1.4279 (d_4^{20}). The compound has a fruit-like odor and is pleasant to inhale. The explosive limits are 4.0 per cent (60 C.), 28 per cent (105 C.); however, at 20 C. in air and oxygen they are 0. The flash point, by the Cleveland open-cup method, is 133 F. However, this compound does not sustain burning at 190 F. Its solubility in water is 0.22 grams/100 grams (98.6 F.), and it is miscible in olive oil in all proportions. Air/blood partition coefficients have not yet been determined. The vapor pressure at 20 C. is approximately 25 mm. of mercury. This compound is stable and is not decomposed by air, light, or alkali. For absolute safety, 0.01 per cent dibenzylamine has been added to prevent acid formation.

Blood concentrations for surgical anesthesia in dogs have been approximately 120 to 160 parts per million, with a persistence of the compound in the blood at a level of about 20 parts per million, even after apparently complete recovery 24 hours after anesthesia.[9] Methods for analysis of concentration in blood and air are under study in the laboratories of The Dow Chemical Company.

The circulation and respiration were well maintained throughout anesthesia in the dog; salivation was minimal to absent and the animal did not exhibit twitching or convulsive movements. Intravenous epinephrine up to 8 gamma/kg. produced only occasional extraventricular complexes and did not cause ventricular fibrillation.[7]

METHOD OF ADMINISTRATION TO MAN

INDUCTION TECHNIQUES: The nature and time of induction was similar in each technique; however, several techniques are described because of the difference in the mechanical systems of the anesthesia apparatus used.

The Closed Circle CO_2 Absorbing System. A satisfactory method of administering Methoxyflurane was by the closed CO_2 absorption circle system. All cases in which this system was employed were with the Heidbrink Kinetometer machine equipped with the ether vaporizer no. 8 on either the inspiratory or expiratory side of the system. Since the agent is weakly irritating to the tracheobronchial tree, it may be given with oxygen or may be preceded by nitrous oxide and oxygen or a thiopental-nitrous oxide and oxygen sequence. Methoxyflurane was introduced into the system at setting no. 5 using the standard no. 8 vaporizer on the expiratory side of the circle; however, if the vaporizer was on the inspiratory side of the circle, it was introduced using the no. 2 setting. The lower

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setting of the vaporizer on the inspiratory side was used to prevent coughing from too high an initial concentration of the vapor.

The anesthetic induction usually proceeded without excitement, and surgical anesthesia generally was achieved smoothly as determined by the regularity of the respiration and the relaxation of the muscles of the jaw and extremities. If the patient had not received premedication, approximately 14 minutes were required before tracheal intubation could be accomplished with ease. However, the use of succinylcholine or *d*-tubocurarine permitted tracheal intubation within one to three minutes following the introduction of Methoxyflurane.

Semiclosed with O_2 or with N_2O and O_2 Added. A second technique for the administration of this drug was to add it to semiclosed N_2O and O_2 anesthesia. N_2O and O_2 were given at a flow of 6 liters of N_2O and 2 liters of O_2 per minute. Methoxyflurane was added as necessary from a Heidbrink no. 8 vaporizer to reinforce N_2O-O_2 anesthesia, to control phonation or movement, or to produce the necessary peripheral muscular relaxation.

Copper Kettle Semiclosed. This agent has been used via the high flow semiclosed "copper kettle" technique. Induction was begun with 1,000 ml. of oxygen flowing through the kettle, which produced a relatively easily respirable mixture. The flow through the "copper kettle" was then gradually increased to 3,000 ml. per minute. This could not be done too rapidly, however, because the patient would cough owing to too high a vapor concentration. With a slower increase in concentration coughing usually failed to occur. (The "copper kettle" used in these studies was redesigned to allow 3,000 ml. of oxygen to pass through it.) Using this technique, the patient would lose his response to the spoken voice within 9 minutes, and be ready for tracheal intubation within 12–14 minutes. There was minimal "bucking" on the endotracheal tube as it was passed, and if it did occur, it subsided rather rapidly. Excitement or delirium during induction of anesthesia with this agent rarely occurred. Nausea and vomiting did not occur during induction with either technique.

Open Drop. Methoxyflurane was allowed to drop on a Yankauer open-ether mask at a rate dependent upon the ability of the patient to respire the mixture. The rate of flow proceeded until surgical anesthesia was obtained, and was then continued at a rate that provided adequate operating conditions without significant depression of blood pressure.

MAINTENANCE: *General Maintenance.* Upon the establishment of surgical anesthesia (with or without tracheal intubation), the administration of the drug was adjusted, depending upon the reaction of the patient to painful afferent stimuli or upon the desired degree of muscle relaxation. A lowered blood pressure, which usually meant overdose, could be reversed within 1–2 minutes by decreasing the concentration of the agent in the inspired mixture, usually without affecting the operating conditions. However, the blood concentration of anesthetic agent appeared critical, since the patient might have profound peripheral muscle relaxation and then move following a small decrease from the critical concentration.

The maintenance of the anesthesia during the first half hour of the procedure appeared to require partially open vaporizers. However, thereafter the anesthetic agent can be turned off or placed in the 1–2 position on the no. 8 Heidbrink vaporizer or at 300 ml. of O_2 flowing through the copper kettle vaporizer.

This is a potent anesthetic; however, the safety lies in the fact that its saturated vapor pressure is only 25 mm. of mercury at 20 C. The pupils remained small throughout the induction period and the period of early maintenance, and dilated only in great depth of anesthesia. As soon as the individual could no longer respond to the spoken voice, his eyes became central and fixed, and did not oscillate during light surgical anesthesia.

Respiration. There was no change in respiratory rate or tidal volume during the induction phase of anesthesia using this agent. However, all premedication had been accomplished with a barbiturate and belladonna drug. During surgical anesthesia, there was a decrease of respiratory minute volume (R.M.V.), more in tidal volume than in rate. Because of the decrease in the R.M.V., we believe that the patient's pulmonary ventilation should be assisted or controlled during the surgical level of anesthesia. If at any

particular time, painful stimuli are perceived, an increase in respiratory rate occurs.

No increase in mucous or salivary secretions has been observed throughout the induction or maintenance phases. We believe that the compliance of the lung and chest wall increased following administration of this drug, as resistance to inflation of the lungs appeared minimal.

Circulation. The effect of this agent on the cardiovascular system was the one significant sign of deep anesthesia or anesthetic overdose. Blood pressure could be maintained at normal levels throughout surgical procedures even with profound abdominal relaxation. However, if the patient did become hypotensive, it was important that the concentration of the anesthetic agent in the inspired mixture be decreased. When hypotension occurred it was usually to a level of 80–90 mm. of mercury systolic.

Cardiac rate slowed slightly in association with a depression in blood pressure. The cardiac rhythm was stable, and we have seen no changes in rhythm other than a wandering pacemaker. We have not observed ventricular complexes in association with the administration of this anesthetic. Abnormal rhythms in a few patients have returned to normal sinus rhythm during the administration of the agent.

Most patients had satisfactory skin color throughout the administration of the anesthesia. A few geriatric patients had an unexplained pallor of the face during surgical levels of anesthesia.

The Effect of the Anesthetic on the Muscular System. Any degree of muscle relaxation could be produced by this agent. However, with light levels of anesthesia, muscle relaxation was produced with *d*-tubocurarine or succinylcholine. No changes in blood pressure were associated with the administration of these drugs. The dose-response relationship of *d*-tubocurarine or succinylcholine appears to be similar to that used with diethyl ether.

The Electroencephalogram as a Guide to Depth. In light anesthesia with Methoxyflurane, a low voltage pattern of fast activity was seen. During surgical anesthesia a higher voltage pattern of slow activity appeared. This electroencephalographic pattern was unlike that characteristic of diethyl ether, since an immediate transition from fast activity of low voltage to slow activity of high voltage

TABLE 1

TYPE OF SURGERY UNDER METHOXYFLURANE ANESTHESIA

100 PATIENTS

Nervous system, extradural	15
Nervous system, intradural	19*
Head and neck	9
Upper abdomen	12
Lower abdomen	10
Urological	8
Gynecological	12
Extremity	5
Intrathoracic	6†
Extrathoracic	3
Other	1
Total	100

* Includes nine hypophysectomies.
† Includes one mitral, one ductus, and four lung.

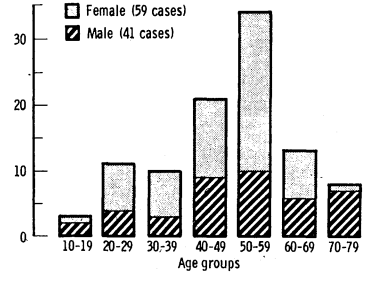

Fig. 1. Age and sex distribution of patients receiving Methoxyflurane.

TABLE 2

COMPARISON OF BROMSULPHALEIN RETENTION FOLLOWING METHOXYFLURANE AND DIETHYL ETHER ANESTHESIA

Postoperative Day	Ether (18 Patients)*		Methoxyflurane (13 Patients)	
	Normal	Abnormal	Normal	Abnormal
Control	4.3	6.4	0.9	15.6
Third	25.0	29.0	11.6	37.8
Fifth	23.0	23.8	12.7	38.4
Tenth	14.5	17.8	5.7	18.7

* Fairlie and associates.[10]

TABLE 3

FOUR DEATHS FOLLOWING USE OF METHOXYFLURANE
100 PATIENTS

Age	Sex	Anesthesia	Operation	Course	Autopsy	Remarks
58	M	Thiopental Succinylcholine Methoxyflurane	Pulmonary lobectomy for carcinoma	Progressive cyanosis and dyspnea; death on third postoperative day	Bronchopheumonia, emphysema and fibrosis	Unrelated to anesthesia, Insufficient functional pulmonary tissue remaining
55	M	Thiopental Methoxyflurane *d*-Tubocurarine	1. Hemicolectomy for cancer of colon 2. Reoperation for intestinal obstruction	Progressive renal failure; death 5 days after second operation electrolytic imbalance	Proximal convoluted tubules showed cloudy swelling and disruption and loss of nuclei	Not related to anesthesia
41	F	Thiopental Methoxyflurane	Exploratory laparotomy for diffuse carcinomatosis	Gradual declining course; death in uremia	Widespread sarcoma	Not related to anesthesia
52	F	Thiopental Methoxyflurane	Clipping of aneurysm of left middle cerebral artery	Satisfactory immediate postop course, later development of cerebral edema and respiratory and cardiovascular failure; death on third postoperative day	Massive cerebral edema	Not related to anesthesia

did not occur. However, extreme depth of anesthesia was accompanied by very low voltage or very slow waves of high voltage, both of which gradually became depressed to a straight line. This depth was never necessary during clinical anesthesia. Profound abdominal relaxation occurred when a pattern of rapid activity and low voltage was interspersed with short bursts of high voltage slow waves.

The Electrocardiogram. The electrocardiogram indicated normal sinus rhythm in the majority of cases where the anesthetic agent was given and only in one instance was a wandering pacemaker observed. S-T segment depression such as was seen in the dog was not observed in man. Electrocardiographic monitoring indicated to us that the cardiac conducting system is stable during Methoxyflurane anesthesia.

EMERGENCE: The administration of Methoxyflurane should be stopped 10–15 minutes prior to the end of the surgical procedure. This maneuver decreased the emergence time. We have allowed the patient to breathe oxygen during emergence or have attempted Methoxyflurane desaturation with a nitrous oxide-oxygen rapid flow technique.

The emergence was quiet without delirium. Postanesthetic hypotension related to the anesthetic agent has not been seen. Nausea and vomiting were minimal, and appeared less than seen with commonly used anesthetic agents.

TABLE 4

COMPLICATIONS FOLLOWING THE USE OF METHOXYFLURANE
100 PATIENTS

Age	Sex	Operation	Course	Remarks
67	M	Bilateral chordotomy for intractable pain from metastatic carcinoma	Hypotension for 2 days following operation; treated with vasopressors; discharged improved	Hypotension probably related to sympathectomy at time of chordotomy
51	M	Decompression of trigeminal nerve	Benign postoperative course; readmitted with Guillain-Barré syndrome 10 days after operation; satisfactory course	Not related to anesthesia
44	M	Right pneumonectomy for carcinoma	Tension pneumothorax on third postoperative day; supraventricular tachycardia on sixth postoperative day; responded to digitalization	Not related to anesthesia
75	M	Transurethral resection for benign prostatic hypertrophy	Uneventful course until septicemia on third postoperative day; responded to antibiotics	Not related to anesthesia

Results

There were 41 males and 59 females in this series whose ages ranged from 10 years to 79 years (fig. 1). These patients underwent operative procedures as indicate in table 1. Bromsulphalein retention studies were performed on 13 patients and the results compared to a similar study by Fairlie and associates [10] who used diethyl ether (table 2). Ninety-two patients had a completely uneventful postoperative course. There were four deaths (table 3) and four complications (table 4). None of the deaths or complications was believed to be related to the administration of Methoxyflurane.

Discussion

This is the first unsymmetrical methyl ethyl ether used for clinical anesthesia in man. It is nonexplosive and nonflammable at 20 C. in all concentrations in air as well as in oxygen. In our experience, induction has been smooth and without incident, anesthesia maintenance easily controllable, and depth of anesthesia readily reversible. This agent appears to be a complete anesthetic in that profound muscle relaxation can be produced and the depth of surgical anesthesia regulated at will. Cardiac rhythm has been stable. Intravenous epinephrine in doses up to 8 gamma/kg. did not produce ventricular fibrillation during administration of this agent in the dog.[7] The absence of postoperative delirium and hypotension is, we believe, a good feature of this drug. The fact that it can be used as a total anesthetic by itself or as part of a balanced technique makes this a versatile agent. There is no increase in capillary bleeding during surgery. This drug depresses the blood pressure by a mechanism not yet understood. The depression of blood pressure appears to be the most reliable sign of anesthesia depth or overdose, and should be a warning to decrease the concentration of the anesthetic agent in the inspired mixture.

The need for postoperative narcotics appears diminished, but this should be studied statistically. The premedication need not be changed from that used prior to other anesthetic agents, although narcotics may cause respiratory depression during anesthesia with this agent. Anesthesia can be conducted for several hours with small quantities of the compound; after the first hour of anesthesia, the amount necessary to maintain a desired level is almost negligible using the closed system.

Although this is a potent anesthetic agent, we believe there is safety in the low saturated vapor pressure and difficulty of vaporization. The slow induction is most likely due to the high boiling point and low saturated vapor pressure, and the small amount of agent required for anesthesia is due to its high potency following vaporization. The prolonged emergence is probably due to the high fat solubility with subsequent slow release of the agent into the blood, thus maintaining an anesthetic concentration in the brain.

The pharyngeal and tracheal reflexes are obtunded and the patient may move before reacting upon an airway or endotracheal tube. Extubation at the end of operation has not been accompanied by laryngeal spasm in our experience.

We have seen no untoward reaction using this drug with *d*-tubocurarine or succinylcholine. The effect shown by liver function tests is about the same as diethyl ether. We have not studied the effect of Methoxyflurane on renal or hemopoietic mechanisms.

Summary

A nonexplosive and nonflammable fluorinated unsymmetrical ether, Methoxyflurane, has been studied in 100 patients. This agent was administered by open drop, semiclosed, closed, or nonbreathing systems. Premedication was with a barbiturate and a belladonna derivative. The induction was smooth and emergence without dilirium or hypotension. We have not seen ventricular arrhythmias during administration of this drug, but have observed definite electroencephalographic changes associated with increasing depth of anesthesia. Nausea and vomiting and the need for analgesic medication appeared decreased in the immediate postanesthetic period.

Original samples of the material were synthesized by The Dow Chemical Company. The current clinical supply was received from Department

of Medicine, Abbott Laboratories, North Chicago, Illinois.

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NEPHROTOXICITY ASSOCIATED WITH METHOXYFLURANE

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Nephrotoxicity Associated with Methoxyflurane Anesthesia

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Among 94 cases in which methoxyflurane was used, 16 developed a toxic nephropathy characterized by diuresis. A seventeenth case which occurred 2 years previously in an affiliated hospital is also reported. Variations in the severity and duration of water loss modified the clinical features which, in well-defined cases, consisted of: urine volume of 2.5 to 4 liters per day with a negative fluid balance and pronounced weight loss for 6 to 10 days; elevation of serum sodium, chloride, osmolality and blood urea nitrogen; a relatively fixed urine specific gravity; urine osmolality in a range close to that of the serum and poorly responsive to a challenge test of fluid deprivation, rapid infusion and Pitressin. In most cases renal functional impairment was transient (10–20 days), but in 3 cases an elevated blood urea nitrogen remained 12, 16 and 29 months after onset.

EVIDENCE has accrued that during the period of a year in which methoxyflurane was used as the anesthetic agent in 94 patients at this hospital, 16 of these patients (17 per cent) developed some degree of toxic nephropathy. In 6 instances the existence of a nephropathy was recognized early in the postoperative course, making it possible to pursue active studies of the disorder. In 10, recognition and association with methoxyflurane came about by a retrospective chart review. Information in this latter group was consequently incomplete, but occult disorders were identified, and flagrant disturbances of a previously perplexing and cryptogenic nature were clarified. A seventeenth case from our affiliated institution, the Mary Hitchcock Memorial Hospital, has also been included.*

Typically in such cases the immediate postoperative course was characterized by diuresis rather than antidiuresis. The urine was of a low, relatively fixed specific gravity, and its volume was equivalent to or in excess of the fluid intake, so that, in combination with gastrointestinal losses and insensible water loss, clinical dehydration and hypernatremia resulted. Weight loss was often pronounced, in confirmation of the negative fluid balance. A rising blood urea nitrogen level was part of the pattern in some but not all patients and often occurred in the presence of an increased fluid intake and urine volume. The diuresis lasted for only a few days in the majority of patients, but persisted in others for several weeks.

Some manifestations of the syndrome usually became apparent within 24 hours after the patients received methoxyflurane. This agent had not been used in this hospital prior to March 1964, and a similar clinical picture had never before been noted in spite of a keen interest on the part of the surgical staff in metabolic and fluid balance problems during the past 15 years.

Methods

The 17 cases were divided into 2 groups. Group I was composed of the 6 cases that were suspected of having a nephropathy while they were under observation. The 11 cases which were identified by a retrospective chart review make up Group II, which includes the single case from our affiliated hospital.

Fluid balances for each 24 hours were determined from the bedside intake and output

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* Courtesy of Dr. William T. Mosenthal.

TABLE 1. Salient Features of the 8 Patients Anesthetized with Halothane and Subjected to the Urine Osmolality Challenge Test During the Postoperative Period

Patient	Age	Post-operative Day	Diagnosis	Operation
A	49	7	Chr. pulmonary tbc. Cholelithiasis	Cholecystectomy
B	76	7	Abdominal aortic aneurysm BUN 28	Aortic aneurysmectomy and aorto-iliac graft
C	55	3	Sigmoid diverticulitis	Sigmoid resection
D	76	7	Hypertension Cholelithiasis BUN 22–25	Cholecystectomy
E	76	8	Abdominal aortic aneurysm	Aortic aneurysmectomy and aorto-iliac graft
F	59	5	Hepatic cirrhosis Raynaud's phenomenon	Bilateral transaxillary sympathectomy
G	65	7	Cholangitis Common duct stone Hypertension	Cholecystectomy and choledochostomy
H	64	10	Sepsis, cryptogenic Previous congestive heart failure Pancreatitis	Exploratory laparotomy and cholecystectomy

records maintained by the nursing staff, experienced and well indoctrinated in the importance of accurate fluid balance records. No allowances were made for insensible losses. Serum electrolytes and blood urea nitrogen determinations were done in the clinical laboratory. Urine and serum osmolality determinations were made on a Fiske osmometer.

In order to differentiate between a primary nephropathy and insufficient production of endogenous antidiuretic hormone (ADH) as the basis for the syndrome, a simple test was used in which urine osmolality was measured in response to fluid deprivation, rapid infusion and then the administration of exogenous ADH, vasopressin (Pitressin). When the test was first used, attention was directed toward determining the ability to respond to exogenous ADH of those patients exhibiting an unexplained diuresis and hypernatremia. They were already clinically dehydrated by several criteria; further stringent fluid deprivation seemed ill-advised, and the period was therefore limited to 6 to 8 hours. In subsequent tests, as these early patients were followed weeks and months later, and as other patients were tested who were not clinically dehydrated but were used as a basis for comparison, a more uniform procedure was evolved. After 11 to 13 hours without fluid, the bladder was emptied by catheter or spontaneous voiding and the urine discarded. Two hours later the initial urine specimen was collected, and an intravenous infusion of 1,000 ml. of 5 per cent dextrose in water was begun at a rate of 10 ml. per minute. Three more urine specimens were collected 30 minutes apart, and then, 90 minutes after beginning the infusion, 0.57 mU./kg. of Pitressin was injected into the infusion tubing near the needle.[1] Four more specimens were collected at 15-minute intervals to complete the "urine osmolality challenge test," as we refer to it. Eight patients who did not receive methoxyflurane were subjected to the challenge test in order to use their response as a basis for comparison. Salient features of these cases, in all of which halothane anesthesia was

used, are given in table 1. The individual results and a curve derived from the average values of the 8 tests are presented in figure 1.

A control group of 100 cases was analyzed for purposes of comparison of certain parameters. Extending retrogressively for the same period of time and beyond that during which methoxyflurane was used, a group of operations was selected which seemed comparable in nature and scope to the majority in which the nephropathy occurred. This group was composed of successive cases of biliary tract, gastric and colon operations in which agents other than methoxyflurane were used, primarily halothane. Fluid balance records of the study cases and controls were reviewed. For the first 4 days following operation, the 24-hour (midnight to midnight) intakes were averaged. Urine volumes were treated similarly. Gastrointestinal drainage was recorded, but for purposes of simplicity excluded from the fluid balance data presented on patients and controls except when illustrated in the figures or specifically mentioned in the case histories. The routine hospital records were the source of information regarding weights.

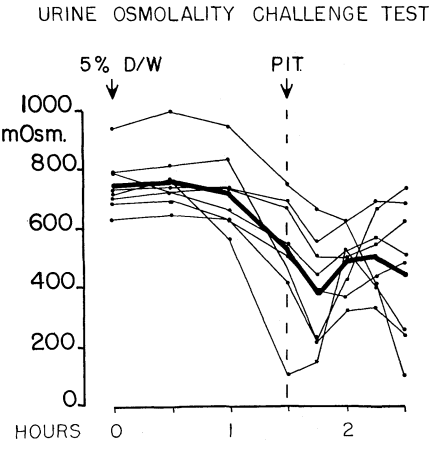


FIG. 1. Changes in the urine osmolality of 8 control patients in response to a challenge of fluid deprivation, rapid infusion and exogenous ADH (Pitressin) administration. See table 1 for further details.

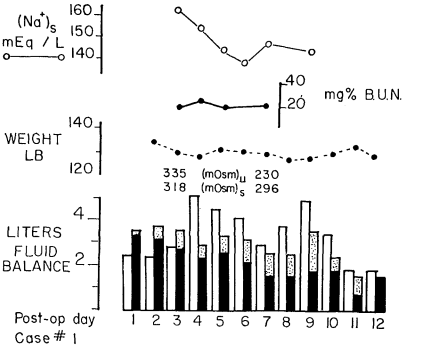


FIG. 2. Course of case 1 following transabdominal vagus section and pyloroplasty. Fluid balance symbols: clear bar represents volume of fluid intake; black, the volume of urine output, and shaded area the volume of gastrointestinal fluid drainage for 24 hours. (mOsm.) stands for milliosmols per kg. of water of serum (s) and urine (u).

Data from Case 17 (MHMH case) were not used in calculating average values for the group.

Case Histories

Unless otherwise stated, major surgical procedures used as a point of reference for the development of the nephropathy were carried out under methoxyflurane anesthesia administered according to standard anesthetic practices. Principles and techniques are described in further detail in Appendix B.

GROUP I

Case 1 (fig. 2). A 51 year old janitor with intractable duodenal ulcer of 14 years' duration was admitted on 1/1/65. There was nothing in the history to suggest renal disease, results of routine urinalysis were normal, and blood urea nitrogen (BUN) was 11 mg. per 100 ml. Cholecystography 1/11/65 by means of oral iopanoic acid (Telepaque) was normal. On 1/18/65 transabdominal vagus section and pyloroplasty were performed without untoward incident. On the day following operation the 24-hour urine volume (midnight to midnight) was 3,240 ml., gastric suction yielded 450 ml., and intravenous intake was 2,400 ml. of 5 per cent dextrose in 0.45 per cent saline solution. The unusually high urine output continued and was associated with severe thirst and evidence of dehydration. On 1/21/65

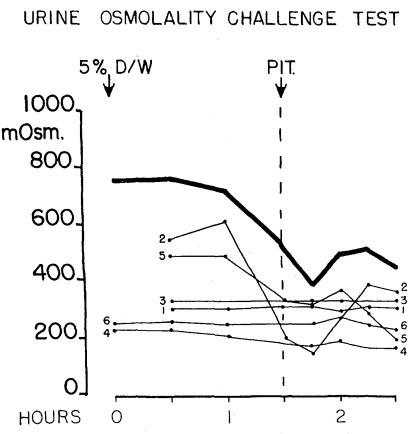


FIG. 3. The urine osmolality challenge test results for the 6 Group 1 cases plotted against a curve derived from the average values of the 8 patients from figure 1 and table 1.

serum sodium was 162 mEq., chloride 124 mEq., potassium 4.6 mEq. per liter. The BUN was 20 mg. per 100 ml. and serum osmolality 318 milliosmols per kg. of water.† Urinary constituents were as follows: sodium 32 mEq., potassium 28 mEq. per liter, urea nitrogen 500 mg. per 100 ml., and osmolality 335 milliosmols.

The high urine volume persisted for 8 more days. Fluid intake was increased accordingly, using serum sodium concentration as a guide. On 1/28/65, following 12 hours of fluid deprivation, urine osmolality reached a level of only 312 milliosmols, responded poorly to rapid infusion and not at all to intravenous Pitressin (fig. 3). Renal biopsy on 2/2/65 revealed minimal degenerative changes, nonspecific, of the proximal convoluted tubules. Convalescence was otherwise uneventful except that the patient thought that he drank and voided more fluid than he had done previously. Three months after operation a urine osmolality of 788 milliosmols, achieved after 11 hours of fluid deprivation, and a good response to rapid infusion and to intravenous Pitressin, indicated virtually full recovery of renal function as judged by these criteria.

Case 2. A 55 year old male school teacher with intermittent rectal bleeding over a period of 6 years was admitted on 1/7/65. There was no history suggestive of renal disease, and results of urinalysis were normal; specific gravity was 1.023. Sigmoid polyps were observed by sigmoidoscopy and barium enema. On 1/19/65 the sigmoid polyps were removed by excision, along with a Meckel's diverticulum unexpectedly encountered. The operation and immediate postoperative course were uneventful, but a urine volume of 4 liters was noted on both the first and second days. On 1/22/65 the following values were found: serum sodium 155 mEq., potassium 4.0 mEq., chloride 113 mEq., bicarbonate 23 mEq. per liter; BUN 12 mg. per 100 ml., serum osmolality 307 milliosmols. Urine concentrations were: osmolality 344 milliosmols, sodium 42 mEq., potassium 29 mEq. per liter, urea nitrogen 400 mg. per 100 ml.

The patient was treated vigorously with intravenous fluid until he achieved an adequately high oral fluid intake on 1/25/65. Urine output remained somewhat higher than usual through the tenth postoperative day, then average volumes were resumed. On 1/28/65 during a challenge test after 12 hours of fluid deprivation, he was able to concentrate to only 608 milliosmols but rose from 147 to 382 milliosmols in response to Pitressin (fig. 3). The test was interpreted as indicating definite moderate impairment of renal function. BUN was 17 mg. per 100 ml. Subsequent convalescence has been satisfactory.

Case 3. A 43 year old carpenter with a history of duodenal ulcer extending over 18 years was admitted on 3/22/65. There was no history of renal disease, routine urinalysis was normal, and BUN was 13 mg. per 100 ml. Vagus section and hemigastrectomy were accomplished uneventfully on 3/29/65. By midnight of the day of operation an increased urine volume was noted, and in the next 24 hours 3,650 ml. was voided, while he had an intravenous intake of 2,750 ml. Al-

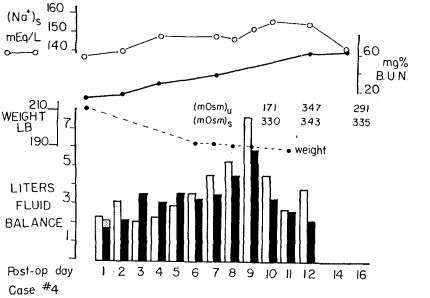


FIG. 4. Course of case 4 following cholecystectomy. Symbols as in figure 2.

† In our laboratory the mean normal serum osmolality is 290 milliosmols per kg. water, ± 2.6 (S.D.).

though fluid intake was increased, he developed a severe thirst, and water balance was negative.

On 3/31/65 the serum sodium was 143 mEq., potassium 4.9 mEq., chloride 111 mEq. and bicarbonate 21 mEq. per liter. Serum osmolality was 303 milliosmols, BUN 28 mg. per 100 ml. and urine urea nitrogen 488 mg. per 100 ml. On 4/1/65 during a challenge test after 7½ hours of fluid deprivation, serum osmolality was 320 milliosmols, but urine osmolality remained fixed at 333 to 334 milliosmols, completely unresponsive to Pitressin (fig. 3). On 4/5/65 serum sodium was 158 mEq. per liter.

When on the eighth day he was allowed liquids freely, he drank 5 liters of fluid both that day and the next. An infection of the subcutaneous portion of the wound prolonged hospitalization and permitted measurement of fluid balance for 3 weeks after operation. Voluntarily he consumed 3.5 to 5 liters of fluid daily, while the urine volume ranged from 3 to 4.2 liters per day. On 4/16/65 during a challenge test urine osmolality varied over a range of only 111 milliosmols, reaching only 232 after 11 hours of dehydration and rising from 173 to 247 under the influence of Pitressin, indicating persistent severe impairment of renal function. During a follow-up visit 9 months after operation a urine osmolality challenge test after 13 hours of fluid deprivation yielded a concentration of 793 milliosmols, a drop to 209 following rapid infusion and a rise to 602 milliosmols following Pitressin.

Case 4 (fig. 4). A 65 year old electrician with many years of fatty food intolerance was admitted to the hospital on 1/25/65. Urinalysis was normal, and the BUN was 13 mg. per 100 ml. Cholecystography on 1/28/65 revealed a functioning gallbladder with stones, but this test was followed by a recrudescence of symptoms for several days marked by pain and tenderness in the right upper quadrant along with mild fever and leukocytosis. Following subsidence of symptoms and further work-up which revealed no other signficant abnormalities, cholecystectomy with operative cholangiography was performed uneventfully on 2/8/65. Urine volumes for the first 2 postoperative days were approximately 2 liters per day, but from the third day through the next 8 days urine volume was in excess of 3 liters per day. He became thirsty and dry and had difficulty in raising thick, tenacious sputum. On 2/15/65 serum electrolytes were as follows: sodium 148 mEq., potassium 4.4 mEq., chloride 113 mEq. and bicarbonate 20 mEq. per liter. BUN was 37 mg. per 100 ml. On 2/18/65 a urine osmolality challenge test after 11 hours of fluid deprivation produced a flat curve ranging from 223 to 161 milliosmols without response to Pitressin (fig. 3). Prior to the infusion, serum sodium was 156 mEq., serum osmolality 330 milliosmols and urine urea nitrogen 137 mg. per 100 ml. On 2/20/65 the BUN was 60 mg. per 100 ml. By 3/1/65 the BUN had dropped to 35 mg. per 100 ml., and by 4/13/65 to 14 mg. per 100 ml. On 4/15/65, 9 weeks after operation, the urine osmolality challenge test after 11 hours of fluid deprivation produced a maximum concentration of 500 milliosmols, a dilution to 207 milliosmols but no change in urine osmolality in response to Pitressin, indicating some improvement but residual serious impairment of renal function.

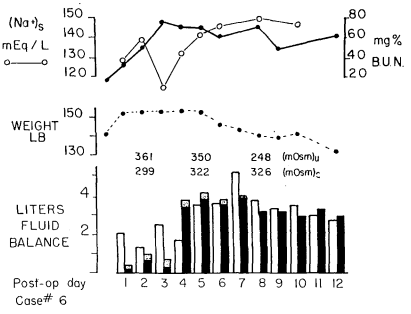


FIG. 5. Course of case 6 following colon resection for ulcerative colitis. Symbols as in figure 2.

Case 5. A 57 year old mechanic was admitted 1/27/65 with constipation, tenesmus, and rectal bleeding of 3 months' duration. Biopsy of a fungating mass low in the rectum revealed adenocarcinoma. Urinalysis was normal, BUN was 18 mg. per 100 ml., phenolsulfonphthalein excretion was 70 per cent, and intravenous pyelography on 1/29/65 was normal. An uneventful abdominoperineal resection of the rectum was accomplished on 2/3/65. An increased urinary volume was recorded from the second to the sixth day after operation, but was not unusually large thereafter. On 2/9/65 the challenge test was performed after only 7½ hours of fluid deprivation, but there was a pre-infusion serum sodium of 150 mEq. per liter and clinical evidence of dehydration. The highest urine osmolality was only 488 milliosmols, and response to Pitressin was minimal, from 327 to 362 milliosmols, indicative of serious renal damage (fig. 3).

Two and one-half months after operation the challenge test showed an improved but still somewhat impaired response after 11 hours of fluid

deprivation with a range of 702 to 100 milliosmols that included a rise from 156 to 372 under the influence of Pitressin. BUN was 11 mg. per 100 ml., and serum sodium was 140 mEq. per liter.

Case 6 (fig. 5). A 57 year old male caretaker was admitted 9/11/64 on transfer from another hospital because of intermittent rectal bleeding over the past year, and a draining rectal abscess with fever of 4 weeks' duration unresponsive to antibiotic therapy. Over the past 20 years certain joints had become intermittently swollen, stiff, tender and red, consistent with the clinical picture of rheumatoid arthritis. There was a draining sinus in the right wall of the rectum without a palpable abscess. He had brought from the other hospital films of a barium enema which showed diverticulitis of the sigmoid colon and of a lipiodol injection of the sinus tract which revealed a long extension up into the pelvis without connection with the colon. A presumptive diagnosis was made of diverticulitis with perforation and pelvic abscess with rupture into the rectum. Because of fever and a clinical picture of severe toxicity, a transverse colostomy was performed under halothane anesthesia on the day of admission. Convalescence was slow but gradual. Neomycin sulfate irrigations of the distal colon appeared helpful. Biopsy at sigmoidoscopy showed granulation tissue infiltrated with polymorphonuclear leukocytes, lymphocytes and plasma cells. He was discharged on 11/20/64 to follow-up clinic.

He was readmitted on 1/25/65 with weakness, anemia, and copious serosanguineous discharge from the rectum. Sigmoidoscopy revealed edematous, boggy mucosa with scattered areas of erythema. It appeared that he had ulcerative colitis in addition to diverticulitis. Urinalysis was normal with a specific gravity of 1.020; BUN was 16 mg. per 100 ml.

Resection of the colon from the transverse colostomy to the rectosigmoid was performed 2/10/65 under methoxyflurane anesthesia. Just prior to operation he was cystoscoped for bilateral intubation of the ureters. During the first 3½ hours of the operation he put out only 75 ml. of bloody urine. Intravenous mannitol was begun, and during the next 90 minutes he received 50 g., responding with 400 ml. of urine. Systolic blood pressure did not drop below 90 mm. of mercury throughout the operation. He received 3 units of blood as replacement for measured blood loss in addition to 4,000 ml. of electrolyte solution. The procedure was difficult and prolonged, but he was returned to the Recovery Room in good condition. During the next 20 hours only 34 ml. of urine was obtained. Blood urea nitrogen was 37 mg. and urine urea nitrogen 130 mg. per 100 ml. He remained in what appeared to be typical renal failure for the next 3 days. Suddenly, on the fourth day, diuresis began and persisted for the next 10 days. The oliguric phase was characterized by weight gain and hyponatremia, the diuretic phase by weight loss and hypernatremia. The BUN reached a peak of 77 mg. per 100 ml. on 2/13/65.

On 2/15/65 serum electrolytes were as follows: sodium 142 mEq., potassium 4.2 mEq., chloride 107 mEq. and bicarbonate 16.5 mEq. per liter, calcium 6 mg. and phosphorus 5.1 mg. per 100 ml. BUN was 67 mg. and urine urea nitrogen 350 mg. per 100 ml. Serum osmolality was 322 milliosmols, urine osmolality 350 milliosmols. Urine electrolytes were: sodium 59 mEq., potassium 15 mEq. and chloride 37 mEq. per liter. On 2/18/65 a urine osmolality challenge test showed a limited range, varying only between 273 and 228 milliosmols with a negligible response to Pitressin (fig. 3). Prior to infusion serum sodium was 149 mEq. per liter, BUN 71 mg. per 100 ml. Urine urea nitrogen was 131 mg. per 100 ml.

A subcutaneous infection required reopening of the laparotomy wound on 2/19/65. Subsequent convalescence was slow and gradual. He was discharged on 3/30/65, returning on 4/20/65 for reassessment. He was generally improved, but BUN remained elevated at 35 mg. per 100 ml. In response to the challenge test which followed 11 hours of dehydration, urine osmolality varied between 473 and 138 milliosmols and rose from 204 to 298 under the influence of Pitressin, still a very limited response 2½ months after operation. At a follow-up visit 8 months after operation BUN was still elevated at 32 mg. per 100 ml., and after 12 hours fluid deprivation urine concentration was only 709 milliosmols. A year after operation BUN was 28 mg. per 100 ml. Following 13 hours of fluid deprivation a level of 699 milliosmols was reached, and urine osmolality rose from 150 to 508 milliosmols in response to intravenous Pitressin.

Group II

The 11 cases in Group II are summarized in table 2. Each case is presented in more detail in Appendix A. Salient features of the group are as follows:

Their ages ranged from 35 to 73 years; 8 were aged 50 or less. All were male and were reason-

TABLE 2. Summary of Salient Features of the 11 Group II Cases

Case	Age	Date of Operation	Type of Procedure	Diuresis	[Na+] mEq./l.	BUN (mg./100 ml.)	Ratio UUN/BUN	Urine (mOsm.)	Serum (mOsm.)	Duration Weeks
7	69	5/25/64	Transcolonic polypectomy	+	156	47	5.5	294	317	Died
8	73	6/26/64	Cholecystectomy, common duct exploration	+ D* 48 hrs.	148	57	6	—	—	Died
9	35	7/7/64	Internal fixation fractured radius, iliac graft	+	—	—	—	—	—	½
10	48	7/14/64	Cholecystectomy, common duct exploration	+	158	135	2.4	—	—	70
11	69	7/22/64	Vagus section, gastroenterostomy	+	151	—	—	—	—	1½
12	49	9/8/64	Excision L-5 disc, fusion	+	—	—	—	—	—	1
13	42	10/7/64	Vagectomy, hiatus herniorrhaphy, pyloroplasty	+	—	19	—	275	303	1½
14	44	11/2/64	Vagus section, hemigastrectomy	+	—	—	—	—	—	1
15	48	11/9/64	Transthoracic hiatus herniorrhaphy, esophagotomy, excision web	+ D* 5 days	155	61	—	340	355	3
16	45	12/11/64	Vagectomy, hiatus herniorrhaphy, pyloroplasty	+	—	—	—	—	—	1
17	50	2/23/62	Rectosigmoid resection	+	153	—	—	—	—	
		2/28/62	Closure dehiscence	+	154	256	—	—	—	120

D* — Delay of onset of diuresis for stated time.

(+) indicates diuresis was present for at least 4 days. (−) indicates that the observation was not made. The highest recorded values for serum sodium and blood urea nitrogen are listed. Concomitant values for urine and blood urea nitrogen were used to calculate the UUN/BUN ratio; correlative values for urine and serum osmolality are given. The duration of the nephropathy as best judged by clinical symptoms or laboratory data is given in weeks.

ably good risks for elective major operations, of which 8 were abdominal, 1 thoracic and 2 orthopedic. Except for 1 patient who was slow to resume spontaneous respirations and another who required two re-explorations of his common duct when residual stones were found on cholangiography, the operations and anesthesia proceeded satisfactorily without prolonged hypotension or excessive blood loss necessitating numerous transfusions. Most cases were without postoperative complications other than the nephropathy, but when other complications did occur, the nephropathy was already manifest. All patients had unusually high urine volumes for several days and, when it was measured, a urine specific gravity usually in a narrow range of 1.006 to 1.012, often in spite of clinical or laboratory evidence of dehydration.

In all 7 patients in whom it was measured during the period of the diuresis, the serum sodium was elevated, and in 6 of the 7 it exceeded 150 mEq. per liter.

In 5 of the 6 patients in whom the BUN was measured it was distinctly elevated. In all 3 patients in whom the urine urea nitrogen/blood urea nitrogen ratio was determined, the value was in a range (less than 10) indicating severe renal damage.[2, 3] In the 3 patients in whom it was measured during a period of dehydration, the urine osmolality was inappropriately low, in fact lower than that of the serum. Two patients died from complications not directly ascribable to the nephropathy, but neither could the nephropathy be completely exonerated as a contributory factor.

Results

Comparison of the fluid balance data of the control group with that of those patients considered to have the nephropathy reveals a significant difference. The controls received an average of approximately 2,400 ml. of fluid a day, excreted about 1,500 ml. of urine daily for a positive balance (exclusive of other fluid losses, sensible and insensible) of 900 ml.

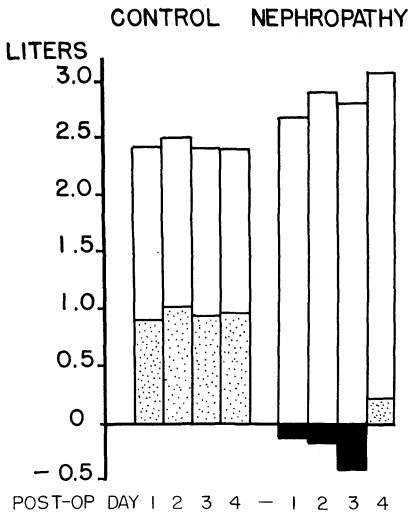


FIG. 6. Comparison, between control and nephropathy groups, of average 24-hour fluid intake and urine volume for first 4 days after operation. Combined intravenous and oral fluid intake is represented by the distance from the baseline to the top of the bar. From this point the urine volume is plotted downward. When the bar extends below the base line, in solid black, the balance is negative. Positive balance is indicated by a shaded area above the base line.

Patients with the nephropathy received somewhat more fluid on the average, 2,900 ml. but excreted approximately 3,000 ml. of urine to be in slightly negative balance (fig. 6).

Blood urea nitrogen values for the control patients and those with the nephropathy are plotted for comparison using data available from the charts (fig. 7). The nephropathy patients who did not have a rising blood urea nitrogen were, in general, either those who recovered quickly or those whose problem was recognized early and who therefore received a high fluid intake.

The comparison of serum sodium levels illustrates the numerous values which were above 145 mEq. per liter among the nephropathy patients, and the variability of the level among them as a group and as individuals is a reflection of the inability of the affected kidneys to maintain the constancy of the internal environment (fig. 8).

Discussion

According to the Council on Drugs of the American Medical Association, a toxic nephropathy is defined as "any adverse functional or structural change in the kidney due to the effect of a chemical or biological product which is inhaled, ingested, injected or absorbed, or which yields metabolites with an identifiable toxic effect on the kidneys." [4]

A most important renal function is that of maintaining the osmotic constancy of the external environment of the cells by excretion of appropriate amounts of solute or solvent. A time-honored measure of renal function is a test of the ability of the kidneys to concentrate or dilute. The limited fluid intake customarily imposed upon these patients during the postoperative period placed in sharp perspective the inability of the affected kidneys to conserve water. The relatively fixed urine specific gravity and osmolality further confirmed the existence of impaired renal function. That an increase in intake was not the primary cause of the diuresis is supported by the evidence in many patients of a continued rise in the concentration of the serum sodium and of the blood urea nitrogen with marked loss of weight in spite of an increased fluid intake.

Gullick and Raisz [5] have evaluated the concentrating ability of the kidney before, during and after major surgical procedures by measuring urine osmolality. Although they found concentrating ability markedly de-

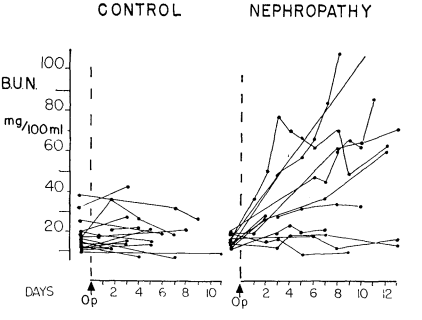


FIG. 7. Comparison of blood urea nitrogen values for individual control and nephropathy patients.

creased during operation, the impairment was transient and there was a return toward but not an attainment of preoperative values on the following day. Changes in concentrating ability were accompanied by parallel changes in endogenous creatinine clearance. Jacobson and his associates [6] found the urine osmolality concentration test to be a simple and reliable indicator of renal ability to concentrate urine.

Inability of the kidney to concentrate and dilute the urine in such a way as to maintain constancy of the solute to solvent ratio of the extracellular fluid has been construed as evidence of impairment of renal function. A review of the data in case 2 will illustrate the rationale of this assumption. The operation and immediate postoperative course were uneventful, but a large urine volume of 4 liters was noted on both the first and second days. On the third postoperative day the serum sodium was 155 mEq., serum osmolality 307 milliosmols, blood urea nitrogen 12 mg. and blood sugar 84 mg. per 100 ml.; the urine osmolality was 344 milliosmols. Homer Smith states,[7] "The evidence is clear that the steady state, the physiological desideratum around which water balance is coordinated, is the osmotic pressure of the plasma which in normal males is equivalent to 288 ± 3.5 milliosmols per kg. of water. The coefficient of variation of this value is only 1.2 per cent, possibly the smallest coefficient of variation among all known physiological variables." In association with a normal BUN and blood sugar, the measured serum osmolality of 307 milliosmols can be assumed not to be spurious and is 17 milliosmols above the normal value of 290, a variation of 5.8 per cent. The factor most closely related to the effective serum osmolality is the serum sodium concentration which, at 155 mEq. per liter, is 10 mEq. greater than the upper limit of normal, a variation of 6.9 per cent. Under such circumstances a very strong stimulus, about 5 times the normal, should be in effect favoring production of endogenous ADH to cause the kidney to conserve water and bring into proper balance the disturbed solvent to solute ratio. But in response to this presumably intense stimulus to the renal retention of water, the urine osmolality was only 344 milliosmols,

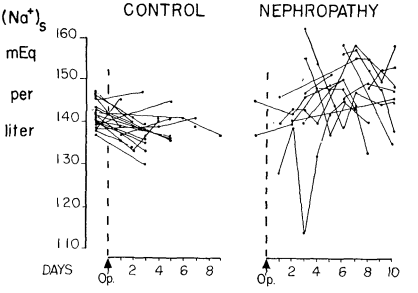


FIG. 8. Comparison of serum sodium values for individual control and nephropathy patients.

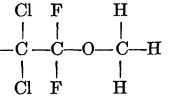
not much higher than that of the serum, so that the ratio of urine to serum osmolality ordinarily in the range of 3 to 4 under conditions of severe water deprivation is only slightly greater than 1, very strong evidence that the renal mechanisms are damaged at this time and unable to carry out their most important function, the conservation of water. By the ninth postoperative day the patient appeared to have recovered somewhat his ability to retain water under conditions of fluid deprivation by achieving a concentration of 608 milliosmols, which was still 150 milliosmols below the average for the 8 postoperative patients used as a basis for comparison.

To substantiate the evidence supporting the kidney as the fundamental site of the disorder and to rule out insufficient production of endogenous ADH as the cause, the concentrating and diluting functions of the kidney as measured by the urine osmolality were challenged by a program of fluid deprivation, rapid infusion of 5 per cent dextrose in water and then the administration of exogenous ADH (Pitressin). Normal values have not been established for this test, but 8 patients who underwent major surgical procedures under halothane anesthesia were selected and studied in the early postoperative period to serve as a basis for comparison. No nephropathy patient unresponsive to fluid deprivation responded significantly to Pitressin, evidence that primary renal dysfunction, not a deficiency of endogenous ADH, was the cause of the disorder.

Among the 94 patients at the Veterans Administration Hospital who received methoxyflurane, 41 underwent abdominal procedures, 3 thoracic, and the remaining 50 orthopedic, neurosurgical or urologic. Thirteen instances of nephropathy occurred among the 41 abdominal procedures, 1 among the 3 thoracic cases, and the other 2 followed orthopedic operations.

All patients received a large number of drugs in addition to methoxyflurane. A review of the case records with particular focus on iodinated compounds and antibiotics did not bring forth a significant association of any particular drug with the development of the lesion. Of 11 patients who had radiographic examination during the operation, 3 developed nephropathy, 8 did not. Among 35 patients who had preoperative studies involving iodides, 9 developed nephropathy, 26 did not. Of 32 patients who received antibiotics before or during operation, only 2 developed the nephropathy. Patients who received other anesthetic agents were meanwhile exposed to a similar range and variety of drugs.

Methoxyflurane is 2, 2-dichloro-1, 1-difluoroethyl methyl ether with the formula:



The metabolism and distribution of the drug has been studied recently by Van Dyke [8] with the aid of ^{36}Cl and ^{14}C. The ether linkage and carbon-chloride bond are cleaved by microsomal enzymes, enhancement occurring with prolonged exposure. Evidence of instability of the C-F bond was also obtained in rabbits chronically exposed to low concentrations. Hence, more biological transformation occurs than was realized from earlier studies. Over longer periods of exposure the agent is taken up by fat and slowly released with an increased opportunity for greater degradation. Most of the operations in which toxicity developed were moderately but not excessively long by modern standards—3 to 6 hours.

Contamination or modification of a particular lot of the product during manufacture, distribution or storage is a remote possibility. Another unlikely consideration is that an adverse change might have occurred from defective or improper equipment. There is no reason to suspect faulty technique of administration.

Case 17, which occurred at Mary Hitchcock Memorial Hospital, is thus of great importance because it antedated by over 2 years the use of methoxyflurane in the Veterans Administration Hospital. Furthermore, the agent was given by a different staff and with different equipment.

Nephrotoxicity in association with methoxyflurane anesthesia is not without precedent in the literature. In an early account of his experience with the agent in 100 cases Artusio [9] reported 4 deaths; none were attributed to anesthesia, but in 2 an element of renal failure was present. Diffuse carcinomatosis precludes evaluation of the effect of the agent in one case, but in the other the course was described as "progressive renal failure; death 5 days after second operation, electrolyte imbalance." At autopsy, "proximal convoluted tubules showed cloudy swelling and disruption and loss of nuclei." In a more recent communication Paddock [10] quotes Artusio as having described 3 patients in whom he noted an elevated urine output accompanied by rising blood urea nitrogen and plasma creatinine following methoxyflurane anesthesia. These changes resolved within 7 to 9 days.

In response to a recent inquiry, Artusio stated, "Several years ago we were concerned with the effects of methoxyflurane on renal function because of the development in several patients of high output azotemia. However, we have not seen any since then, although we have used methoxyflurane in many thousands of cases."

Paddock and his associates [10] observed the development of renal failure in 3 patients who had received methoxyflurane anesthesia. Two died in uremia, and the third survived with diminished renal function. The kidneys from both patients showed moderate arterial and arteriolar nephrosclerosis, and the tubules contained crystals composed of calcium oxalate. Minor degrees of tubular degeneration were present. These findings stimulated the authors to review kidney sections from 200

autopsies and to study renal function in 40 healthy males submitted to inguinal herniorrhaphy under methoxyflurane. Their study seemed to exonerate methoxyflurane as a cause of impaired renal function in healthy patients, but they deemed it advisable to investigate further the possibility that this conclusion might not hold true in seriously ill patients with previously existing renal disease.

Boba [11] conducted some acute experiments in dogs which demonstrated that methoxyflurane caused systemic hypotension, diminished renal blood flow and increased renal vascular resistance, effects potentially dangerous to renal parenchyma.

In a controlled study of 170 patients receiving methoxyflurane and 149 control patients receiving other agents, North and Stephen [12] found no instance of excessive diuresis. However, there was a significant increase in the incidence of elevation of the blood urea nitrogen among those receiving methoxyflurane. Further study was reported as under way.

The existence of impaired renal function associated with methoxyflurane is supported by the following line of reasoning:

(1) Ordinarily the course of patients following operation is characterized by antidiuresis and a fall in serum sodium concentration, presumably the result of a predominance of antidiuretic hormone activity with water retention in excess of sodium retention. In contradistinction the patients considered to have the nephropathy passed unusually large volumes of urine (fig. 6), and 13 out of 14 developed an elevated serum sodium (fig. 8). In all 8 patients in whom the serum and urine osmolality were measured concomitantly during the acute phase of the disorder, the serum osmolality was elevated, but the urine osmolality was below or only slightly higher than that of the serum, evidence that the kidneys were failing to accomplish their primary function, conservation of water.

(2) Not only were renal mechanisms unable to modify appropriately the solute to solvent ratio of the urine in the presence of clinical and laboratory evidence of dehydration, but in 5 of 6 cases tested in the early postoperative period there was inadequate response to intravenous Pitressin, indicating that the disorder was primarily renal in origin and not secondary to a deficiency of antidiuretic hormone.

(3) The blood urea nitrogen was elevated in 8 of the 13 patients in whom it was measured, reaching a value of 60 mg. per 100 ml. or higher in 5, indicative, in the presence of a large urine volume, of glomerular as well as tubular damage. In 5 of 8 patients in whom the urine urea nitrogen and blood urea nitrogen values were obtained on correlated specimens, the urine urea nitrogen to blood urea nitrogen ratio was less than 10 (2.3, 5, 5.5, 6, 2.4), indicative of severe renal damage.[2]

(4) In the majority of cases the diuresis began within 24 hours of an operation in which methoxyflurane was used as the anesthetic agent.

(5) Shock and blood loss with multiple transfusions were notably absent as antecedent factors thought developing later in 3 patients when polyuria was already present.

(6) The diuresis seemed not to be osmotic in nature since no osmotically active substance was identified in high concentration and the specific gravity and osmolality of the urine was at the approximate level of, or even below, that of the serum.

(7) The pharmacologic action of an unknown drug or the physiologic effect of some endogenous substance would appear an unlikely cause, for laboratory evidence or symptoms of impaired renal function have persisted in some patients for weeks and in 3 patients for a year or more.

(8) In all patients in whom the nephropathy was recognized, methoxyflurane was used as an anesthetic agent. No other common factor has yet been identified.

Summary and Conclusions

A disorder of renal function appears to have developed after operation in 17 patients. Evidence of impaired renal function was well defined in 13 (cases 1, 2, 3, 4, 5, 6, 7, 8, 10, 11, 13, 15, 17), circumstantial in 4 (cases 9, 12, 14, 16). The predominant characteristic of the nephropathy was an inappropriate diuresis producing dehydration, weight loss, and elevation of serum sodium, chloride and osmolality. Methoxyflurane was used as an anes-

thetic agent in all these cases; no other common factor has yet been identified. Until new evidence is brought to light, methoxyflurane must be considered the causal agent.

Appendix A

Case Histories

Group II

Case 7. A 69 year old retired government employee was admitted on 3/19/64 because of dyspnea. Work-up revealed anemia with hemoglobin of 8.9 g. per 100 ml. Stools were positive for occult blood, and polyps were present in the transverse colon. Results of routine urinalysis were normal, with a specific gravity of 1.020; BUN was 19 mg. per 100 ml. After a month on iron therapy at home, he returned with a hemoglobin of 14.3 g. per 100 ml.

He was prepared for transcolonic polypectomy on 5/25/64 by a low residue diet, cleansing enemas and 3 days of kanamycin sulfate per os. The operation was well tolerated and uneventful. On the 2nd day after operation an unusually high urine output was recorded and noted to continue through the 7th postoperative day. In spite of energetic efforts to maintain effective tracheobronchial toilet, he developed rales and a temperature of 104° F. on 5/29/64. He appeared very dry, and on 6/1/64 serum electrolytes were as follows: sodium 156 mEq., potassium 5.4 mEq., chloride 134 mEq., bicarbonate 18 mEq. per liter. The BUN was 47 mg. per 100 ml. The abdominal wound appeared infected; it was opened and packed.

On 6/2/64, the eighth postoperative day, the blood pressure fell to 100/60 mm. Hg, the pulse rose to 120 per minute, he had several bloody bowel movements, and urine volume dropped sharply from 3.8 to 1.3 liters per 24 hours. Prothrombin time was 40 per cent of normal. He was given a vitamin K preparation intravenously along with infusions of blood, albumin and electrolyte solutions. Vital signs improved, but he continued to pass currant jelly stools.

On 6/3/64 serum electrolyte values were: sodium 152 mEq., potassium 4.4 mEq., chloride 112 mEq.,. bicarbonate 19 mEq. per liter; calcium was 7.3 mg. and phosphorus 4.2 mg. per 100 ml.

On 6/4/64 the BUN was 66 mg. and urine urea nitrogen 363 mg. per 100 ml. Osmolality of the serum was 317 and of the urine 294 milliosmols. Further course was downhill with continued rectal bleeding, rising BUN, unstable vital signs and death on 6/8/64. Necropsy was not permitted.

Case 8. A 73 year old single retired blacksmith was admitted on 5/26/64 because of six episodes during the previous 2 years of colicky right upper quadrant pain associated with dark urine, chills, and fever. He appeared sprightly but slightly icteric. There was a firm nodule in the left lobe of the prostate, but the gland itself was not enlarged, and urinary tract symptoms were denied. Results of urinalysis were normal; BUN was 14 mg. per 100 ml. Biopsy of the prostate showed adenocarcinoma, and stilbestrol therapy was instituted. Serum bilirubin was 1.3 mg. per 100 ml., alkaline phosphatase was elevated, acid phosphatase was normal, and there was 22 per cent sulfobromophthalein sodium (BSP) retention. Visible dye excretion in the gallbladder or biliary tract was not accomplished by cholecystography with iopanoic acid (Telepaque) on 6/2/64, a double dose on 6/9/64, nor cholangiography with intravenous iodipamide sodium (Cholografin) on 6/23/64. While the patient was in the hospital, there were intermittent fever spikes from 101° to 104° F. with fluctuations in the severity of the jaundice and elevation of the serum bilirubin, which reached a peak of 4 mg. per 100 ml.

At exploration 6/26/64 an inflamed gallbladder and dilated common duct (3.0 cm. in diameter), both containing multiple stones, were found. Cholecystectomy and common duct exploration were carried out, but it was necessary to reexplore the common duct twice and perform a duodenotomy, as well as to use operative cholangiography three times, before the common duct was cleared completely of calculi. The patient appeared to tolerate this long and difficult procedure quite well and was without significant hypotension except for about 30 minutes following induction. He received 1 unit of compatible blood. Tetracycline hydrochloride 100 mg. intramuscularly every 6 hours was begun.

Urine output was below average for the first 2 days after operation, then above average for the next 2 days. On 6/29/64 the BUN was 48 mg. per 100 ml., serum sodium was 140 mEq., potassium 5.8 mEq. and bicarbonate 11.5 mEq. per liter. On 6/30/64 he appeared quite obtunded and apathetic. Arterial puncture revealed a *p*H of 7.30, P_{CO_2} of 28 mm. of mercury, and a base deficit of 11.8 mEq. per liter of blood by the Astrup method. Arterial oxygen saturation was 97 per cent on oxygen by nasal catheter. Tetracycline hydrochloride was discontinued and replaced by chloramphenicol 250 mg. intramuscularly every 6 hours.

On 7/1/64 the serum sodium was 148 mEq., potassium 6.0 mEq., chloride 115 mEq., and bicarbonate 10.5 mEq. per liter. The BUN was 57 mg., and the urine urea nitrogen 338 mg. per 100 ml. Copious flow of bile from the right upper quadrant drainage site was noted; it continued for the next 2 days. Injection of dye showed one limb of the T-tube displaced from the common duct. On 7/3/64 re-exploration, also under methoxyflurane anesthesia, disclosed disruption of the choledochotomy and leakage of the duodenotomy. Both were repaired and the pro-

cedure appeared to be well tolerated by the patient, but oliguria followed immediately and persisted for the next 26 hours, at which time he succumbed. Urine had been of fixed specific gravity, and the BUN had risen to 108 mg. per 100 ml. Postmortem examination revealed the precipitation of sheaf-like crystals in many tubules,[13] yet there was not much evidence of actual damage to or necrosis of the tubular epithelium. Occasional pyknotic cells or macrophages surrounded the crystals. Glomerular afferent arterioles were often thickened and hyalinized.

Case 9. A 35 year old heavy equipment operator was admitted on 6/26/64 in transfer from another hospital several hours after an automobile accident in which he had suffered fractures of both bones of the left forearm and contusion of the left leg. Attempts at closed reduction had not achieved satisfactory position. He had always been in good health, there were no symptoms of urinary tract disease, and results of urinalysis were normal.

On 7/7/64 internal fixation of the left radius with a right iliac crest bone graft was accomplished without untoward event. On the first 3 days after operation he coughed up purulent sputum and had a fever, but was much improved with tracheal toilet and penicillin therapy. However, on these same days, he passed 5 to 6 liters of urine a day, 3.8 liters in excess of his voluntary fluid intake. On the fourth postoperative day, when the intake and output record was discontinued, he had already passed 1.5 liters of urine by 6 A.M. Further convalescence was uneventful.

He returned by request for evaluation of renal function on 5/21/65, at which time urinalysis was normal and BUN 13 mg. per 100 ml. Urine osmolality responded to dehydration by reaching 968 milliosmols, a normal level.

Case 10. A 48 year old logger was admitted on 5/28/64 with a history of right upper quadrant pain of 5 days' duration. He was a muscular, well-nourished man with tenderness and a questionable mass below the right costal margin. Results of routine urinalysis were normal, and BUN was 15 mg. per 100 ml. Attempts to opacify portions of the biliary tract by intravenous cholangiography on 6/1/64 and oral cholecystography on 6/5/64 were unsuccessful. Symptoms subsided, and he was discharged on 6/10/64 on a low fat diet, to return in 6 weeks for re-evaluation.

Because of recurrent abdominal pain he was readmitted on 7/9/64. Oral cholecystography on 7/13/64 again showed no dye visible. Cholecystectomy, choledochotomy and cholangiography were performed on 7/14/64 with some technical difficulty, but the patient remained in good condition throughout the procedure. On the second and third days following operation urine volumes of over 3 liters per day were recorded. He was very dry, was troubled greatly by his nasogastric tube, and developed accumulative pneumonostasis for which he was exhorted vigorously to cough. On 7/19/64 there was disruption of the abdominal wound; it was repaired using 1 per cent procaine for regional infiltration. The following day serum electrolyte values were: sodium 158 mEq., potassium 5.5 mEq., chloride 115 mEq., bicarbonate 10.5 mEq. per liter. During the day urine output dropped sharply to 430 ml. per 24 hours, and for the next 3 days was 365, 675 and 225 ml. Although it increased the next day to 815 ml., urine volume remained less than a liter a day, with low specific gravity, for the next 11 days. On 7/24/64 the serum electrolyte values were: sodium 135 mEq., potassium 5.6 mEq., chloride 97 mEq., and bicarbonate 7.2 mEq. per liter. The following day the BUN was 135 mg. and urine nitrogen 325 mg. per 100 ml.

The lung infection, from which *Staphylococcus aureus* was the dominant organism, responded well to methicillin sodium (Staphcillin). Supportive therapy with lactate, bicarbonate and mannitol was employed to combat the low alkaline reserve, a condition presumably secondary to renal insufficiency. Urine culture on 8/6/64 showed scant growth of *E. coli* and *B. proteus,* but this finding was not considered significant because a bladder catheter had been employed for a week during the period of oliguria. Hypocalcemia developed, and the hematocrit dropped to 27 per cent without apparent blood loss. Urinalysis showed 20 to 50 white blood cells per high-power field and a fixed specific gravity. BUN remained elevated at 90 to 100 mg. until 9/20/64 when it was 58 mg. per 100 ml. On 8/28/64 a renal biopsy was performed and the findings reported as follows: "*Microscopic Examination:* Much damage is apparent. Tubules are often dilated and many of them contain shiny, birefringent crystals. Some crystalline material is also noted beneath tubular epithelium. The interstitial tissue contains many lymphocytes and plasma cells, and rarely there are small foci of polys, some of which are found in a tubular lumen. The glomeruli and blood vessels are not abnormal. The dilated tubules could have resulted from the crystals blocking the tubules, but other obstructive lesions should be considered."

The patient returned for a follow-up visit on 5/12/65, at which time the BUN was 24 mg. per 100 ml. In response to 10 hours of fluid deprivation urine osmolality reached only 519 milliosmols, an indication of continuing impairment of renal function. Following Pitressin it rose from 250 to 400 milliosmols.

The patient returned again 16 months after operation for repair of an incisional hernia. At that time serum sodium was 147 mEq. and chloride 107 mEq. per liter; serum creatinine was 2.7 mg. and BUN 30 mg. per 100 ml. In a concentration test after 12 hours of fluid deprivation urine osmolality was only 560 milliosmols.

Case 11. A 69 year old retired farm hand was admitted to the hospital for the seventh time on 7/3/64 because of exacerbation of intermittent epigastric distress and tarry stools of a weeks' duration. He had suffered from dyspepsia for many years, and a duodenal ulcer was demonstrated radiographically in 1954 for the first of many times. Symptoms and treatment had been sporadic. In 1963 he had undergone cholecystectomy for acute cholecystitis. During the past 5 years his urinary stream had diminished in size, and it had become necessary for him to void 2 to 3 times a night. The BUN concentration had always been below 20 mg. per 100 ml., and on 10/4/63 was 19 mg. per 100 ml.

Vital signs were within normal limits. Rectal examination revealed a slightly enlarged prostate, and dark stool was present. Results of urinalysis were normal except for a trace of albumin. Hemoglobin was 15 g. per 100 ml. of blood. On 7/9/64 the BUN was 23 mg. per 100 ml., and phenolsulfonphthalein excretion was 45 per cent in 2 hours. A gastrointestinal series demonstrated marked duodenal scarring with a small ulcer crater. On 7/21/64 a urine osmolality of 875 milliosmols was reached during a urine concentration test, and intravenous pyelography showed good dye excretion without evidence of bladder neck obstruction or enlargement of the prostate.

On 7/22/64 he underwent subdiaphragmatic vagus section with gastroenterostomy. Estimated blood loss was less than 200 ml., there was no hypotension, and he received 1,500 ml. of electrolyte solution intravenously. An unusually high urine output was noted immediately. On the day following operation he excreted 4.3 liters of urine, which, combined with his gastrointestinal fluid loss, created a negative sensible fluid balance of 3 liters. He continued to have a urine output that fluctuated at lower levels but was inappropriately high in volume and low in specific gravity in view of rather large gastric fluid losses and low intake. He lost 10 pounds in 4 days. On 7/27/64 serum electrolyte values were as follows: sodium 151 mEq., potassium 4.0 mEq., chloride 108 mEq., and bicarbonate 22 mEq. per liter. With resumption of an appreciable oral intake on 7/29/64 his condition rapidly improved. At discharge on 8/7/64 serum sodium was 140 mEq. per liter and BUN 13 mg. per 100 ml.

He returned for re-evaluation of his renal status on 5/20/65, at which time serum electrolytes and osmolality were entirely normal, and BUN was 12 mg. per 100 ml. During the challenge test, after 11 hours of fluid deprivation, a level of 845 milliosmols was reached, and urine osmolality rose from 414 to 480 in response to Pitressin.

Case 12. A 49 year old carpenter was admitted on 8/12/64 because of increasingly severe pain in the back and left flank during the past year. There were no specific urinary tract symptoms, results of urinalysis were normal, and the BUN was 9 mg. per 100 ml. Lumbar myelography on 8/21/64 showed anterior defects at L-4 and L-5 interspaces. On 9/8/64 exploration of the L-4 and L-5 interspaces with an S-1 to L-4 fusion utilizing a left iliac bone graft was performed. The estimated blood loss was 1,000 ml. for which he received 3 units of blood and a liter of 5 per cent dextrose in 0.2 per cent saline solution. He tolerated the procedure well but subsequently was unable to void spontaneously. Catheterization yielded 750 ml. at 2 A.M. of the first postoperative day and 900 ml. at 2 P.M., at which time a Foley urethral catheter was left in place. During the subsequent 4 days he passed 4 to 6 liters of urine a day, a total of 7 liters in excess of his fluid intake. Volumes of urine and intake gradually diminished. Convalescence was marred during the eighth week by thrombophlebitis of the left leg, which responded satisfactorily to anticoagulant therapy.

Renal function was evaluated 7 months following operation by a challenge test which followed 11 hours of fluid deprivation and produced a range of urine osmolality from 879 to 84 milliosmols. The BUN was 14 mg. per 100 ml.

Case 13. A 42 year old cook was admitted on 10/1/64 for intractable postprandial epigastric distress, and heartburn occurring at night. He had been troubled with symptoms of indigestion for many years and in 1945 was discharged from the Navy with a diagnosis of duodenal ulcer. In 1958 a sliding hiatal hernia was demonstrated which had enlarged and seemed increasingly symptomatic. He denied urinary tract symptoms, results of urinalysis were normal, and the BUN was 14 mg. per 100 ml. Studies of gastric secretion indicated very high acid values. Cholecystography on 10/6/64 demonstrated a normally functioning gallbladder.

Vagus nerve section, hiatal herniorrhaphy, and pyloroplasty with tube gastrostomy were accomplished uneventfully on 10/7/64. Operative blood loss was minimal. There was no hypotension, and he received 550 ml. of intravenous electrolyte solution during the procedure. On the first day after operation he voided 4 liters of urine and continued for the next 7 days to pass inappropriately large volumes with low specific gravity. On 10/13/64 serum osmolality was 303 and that of the urine was 275 milliosmols. The BUN was 19 mg. per 100 ml. On 10/20/64, after 13 hours of fluid deprivation, a urine osmolality of 444 milliosmols was achieved. Phenolsulfonphthalein excretion was 80 per cent in 2 hours on 10/22/64. He was discharged the next day.

Renal function was re-evaluated 6 months after operation, at which time the BUN was 14 mg. per 100 ml., and the urine osmolality test demonstrated a range from 873 to 97 milliosmols. There was a rise from 141 to 396 milliosmols under the influence of intravenous Pitressin.

Case 14. A 44 year old cook was admitted on 10/16/64 with an acute exacerbation of long-standing dyspeptic symptoms dating back to 1953 and attributed to duodenal ulcer. In 1958 a sliding hiatal hernia had been demonstrated radiographically, and it had continued to be symptomatic. He denied any urinary tract symptoms, results of urinalysis were normal, and the BUN was 18 mg. per 100 ml. Gastric analysis revealed very high acid values in response to betazole hydrochloride (Histalog) stimulation. Cholecystography on 10/28/64 demonstrated poor function of the gallbladder.

On 11/2/64 he underwent vagotomy and hemigastrectomy with Billroth I reconstruction. It was necessary to remove the spleen because of inadvertent injury. There was a period of hypotension for 30 minutes following induction. Estimated blood loss was 400 ml., and a transfusion of 1 unit of blood was administered. He also received intravenously 2,000 ml. of 5 per cent dextrose in 0.2 per cent saline solution. He tolerated the procedure well, though he had difficulty in voiding and required catheterization twice during the first 16 hours.

An unusually high urine volume was noted from the first day after operation. He voided from 2 to 3 liters each day for 8 days; the specific gravity was low and fixed. There were large gastric fluid losses so that sensible fluid balances were consistently negative, and he lost 18 pounds in 11 days. Serum electrolytes were within normal ranges on the first postoperative day and were not measured thereafter. Except for some accumulative pneumonostasis which responded well to tracheobronchial toilet and penicillin, convalescence was otherwise satisfactory and he was discharged on 11/14/64.

Six months later he returned for evaluation of his renal function. In response to the urine osmolality challenge test he achieved a range of 1,234 to 215 milliosmols, which included a rise of 350 milliosmols in response to intravenous Pitressin.

Case 15. A 48 year old unemployed house painter was admitted on 10/27/64 because of dysphagia which had become progressively worse over the past 2 years. He had been admitted 2½ years previously for upper abdominal pain and retching, which were attributed to a sliding hiatal hernia that was demonstrated radiographically. Nine months before he had been treated in the hospital for hypertension. Various studies including transfemoral aortography had not revealed a specific cause, and he was discharged on hydrochlorothiazide and reserpine with a favorable response. Urine at that time contained 20 to 30 white blood cell per high-power field. In the opinion of a consultant urologist, the pyuria was caused by chronic prostatitis. The BUN and electrolyte values were normal.

On 10/28/64 results of urinalysis were normal; serum electrolytes were normal except for a sodium of 146 mEq. per liter. The BUN was 19 mg. per 100 ml. A gastrointestinal series demonstrated a typical lower esophageal ring in addition to the hiatal hernia. Esophagoscopy on 11/4/64 was confirmatory and demonstrated esophagitis of the distal 6 to 8 cm. A level of 750 milliosmols was achieved on a urine concentration test.

On 11/9/64 transthoracic repair of the hiatal hernia with esophagotomy and excision of an esophageal web was carried out. The procedure was well tolerated without hypotension or undue blood loss, and the patient received 1,000 ml. of 5 per cent dextrose in 0.2 per cent saline solution. For the first 5 days his course was satisfactory, and fluid balance was not exceptional. On 11/15/64 there was rapid deterioration in his condition with the onset of tachycardia to 130–140 beats per minute and unstable low blood pressure. There was regurgitation and drainage of coffee-ground material. Urine volume increased to 5.2 liters, and there was a negative fluid balance of 3.5 liters accompanied by a weight loss of 9 lb. in 24 hours. On 11/16 hematocrit was 40 per cent, and serum electrolyte values were: sodium 155 mEq., potassium 4.8 mEq., chloride 118 mEq. and bicarbonate 11 mEq. per liter. Serum amylase was 600 Somogyi units on 11/17/64, hematocrit was 35 per cent, and the BUN was 61 mg. per 100 ml. Serum osmolality was 355 and urine osmolality 340 milliosmols. Analysis of a 12-hour urine specimen showed the concentration of sodium to be 30 mEq. and that of potassium 34 mEq. per liter.

For the next 6 days urine output continued inappropriately high at 2.7 to 3.9 liters per day with a relatively fixed specific gravity. Increased intake of "sodium-free" water, colloid, and blood helped to stabilize his vital signs, overcome his dehydration, and lower his serum sodium. However, vomiting and gastric drainage of blood continued intermittently, and aspiration of a sudden gush of blood on 11/21/64 necessitated emergency tracheostomy. Clinical evidence of esophageal obstruction developed, and an esophagram showed marked displacement of the esophagus to the right, presumably by a mediastinal abscess. Left transpleural mediastinal exploration under halothane anesthesia performed on 11/27/64 revealed multiple loculations of serosanguineous sterile fluid. Esophageal obstruction was relieved, good oral intake was quickly resumed, and subsequent recovery was rapid. On 12/3/64 serum electrolyte values were: sodium 144 mEq., potassium 4.6 mEq., chloride 101 mEq., and bicarbonate 27 mEq. per liter. The BUN was 14 mg. per 100 ml.

Three months later urine osmolality after 11 hours of fluid deprivation reached a level of 847 milliosmols.

Case 16. A 45 year old sign painter was admitted on 11/29/64 because of epigastric distress, retrosternal burning, and dysphagia, becoming worse since onset 20 years before. Hiatal hernia

had been demonstrated radiographically in 1958. Since an episode of urethritis 20 years earlier his urine had been slow to start and the stream of diminished force. Following a hemorrhoidectomy on 3/18/64 he had been unable to void spontaneously and required catheterization twice before being able to urinate by himself on the third day after operation. Catheterization had been readily accomplished with a no. 18 Fr. Foley, and the consultant urologist passed no. 18 and no. 20 Fr. sounds without undue difficulty on 4/1/64. There appeared to be no urinary sepsis, but a prophylactic antibiotic was to be continued for a week when he was discharged at that time. Admission urinalysis results were normal with a specific gravity of 1.018, BUN was 14 mg. per 100 ml., and urine culture showed no growth in 72 hours.

On 12/11/64 transabdominal hiatal herniorrhaphy, vagotomy, and pyloroplasty were performed. The procedure was well tolerated; estimated blood loss was 300 ml., and he received 600 ml. of 5 per cent dextrose in 0.2 per cent normal saline. However, on return to the Recovery Room there was delay in resumption of spontaneous respiration, with nail bed cyanosis and the development of hypotension to 90 mm. of mercury systolic which lasted about 2 hours. Because of the history of voiding difficulties a bladder catheter had been inserted during induction.

An increased urinary output was recorded for the first 4 days after operation, ranging from 2.4 to 4.2 liters per day and exceeding the fluid intake during this time by 3.7 liters. No clinical chemical tests were carried out in the immediate postoperative period.

He returned for evaluation of renal function 5 months later, at which time the BUN was 13 mg. per 100 ml.; the urine osmolality after 11 hours of fluid deprivation reached 791 milliosmols, responding to Pitressin with a rise from 78 to 317 milliosmols.

Case 17. A 50 year old laborer entered Mary Hitchcock Memorial Hospital on 2/18/62. Changing bowel habits and left lower quadrant cramps during recent weeks had caused him to go to the Hitchcock Clinic, where barium enema and sigmoidoscopy had established the existence of adenocarcinoma of the rectosigmoid. His general health had been good, he denied urinary tract symptoms, and urinalysis results were normal, as was an intravenous pyelogram. He was prepared for sigmoid resection by cleansing enemas and neomycin sulfate by mouth.

On 2/23/62 rectosigmoid resection with end-to-end anastomosis was satisfactorily accomplished. There was moderate blood loss, but he received 3 units of blood, and there was no hypotension. At the end of operation 50,000 units of bacitracin and 0.5 g. of streptomycin were left in the peritoneal cavity.

An unusually high urine volume was noted immediately and continued for the first 4 days following operation, during which time the urine volume exceeded fluid intake by 1.4 liters. Gastrointestinal fluid losses were not high, an additional 1.2 liters, but recorded weight loss was 21 pounds. He was very dry, and on 2/27/62 serum sodium was 153 mEq. per liter. On 2/28/62 wound dehiscence occurred, and closure was performed using methoxyflurane again for the anesthetic agent. The fluid balance record is incomplete for that day, but shows a continued high urine output for the next 4 days in the presence of a high daily fluid intake. On 3/1/62 serum sodium was 154 mEq. per liter, BUN 52 mg. per 100 ml. Vigorous therapy with "sodium-free" fluid lowered the serum sodium during the next 6 days to 128 mEq. per liter, but weight loss continued (6 pounds), and the BUN began to climb to a high of 256 mg. per 100 ml. on 3/14/62, the 20th day after the first operation. Urine sodium excretion was measured daily from 3/3 to 3/6 and varied from 9.5 to 16 mEq. per 24 hours.

On 3/10/62, a consultant nephrologist stated in the chart: "Severe renal failure as reflected by progressive BUN elevation and inorganic phosphate retention. . . . At any rate, the failure to concentrate the urine even with Pitressin, the low urinary sodium excretion, and the diuresis, all probably are best explained on the basis of a primary glomerular defect. One can only speculate whether the new anesthetic agent with which somewhat similar episodes apparently have been seen, or some catastrophic event such as renal infarction might be causative."

On 3/19/62, nearly a month after operation, the BUN remained elevated at 190 mg. per 100 ml., and urine volume remained a bit elevated at 2.1 to 2.6 liters per day. He had lost 36 pounds in weight.

On 3/29/62 the BUN was 42 mg. and on 4/4/62 22 mg. per 100 ml. On 7/25/64, 29 months after the original operation, the BUN was still slightly elevated at 22 mg. per 100 ml.

Appendix B

PRINCIPLES AND TECHNIQUE OF ANESTHESIA ‡

Indications for Selection of Methoxyflurane. At preoperative visits methoxyflurane was chosen as the agent in preference to halothane in cases which presented questionable liver function, a history of previous repeated or prolonged episodes of hemorrhagic shock, a history of previous repeated or prolonged procedures under halothane anesthesia, the prospect of prolonged surgical procedures (over 3 hours), the prospect of a biliary tract operation. In some cases a flammable anesthetic was precluded because of the use of radiologic apparatus or cautery.

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All patients received preoperative medication consisting of meperidine 50 to 75 mg. and atropine or scopolamine 0.2 to 0.4 mg. subcutaneously one hour before induction.

Induction was accomplished with sodium pentothal 200 to 375 mg. intravenously followed by succinylcholine 20 to 80 mg. intravenously. After ventilation with 40 per cent to 100 per cent oxygen for 2 to 4 minutes the tracheas were intubated with a cuffed endotracheal tube.

Variations in Maintenance Technique and Respiratory Support. Fifty-one anesthesias were conducted by one staff anesthesiologist with an Ohio Chemical Company Heidbrink machine with the Ohio No. 8 in-circuit vaporizer in a semiclosed circle absorber system using soda lime. Methoxyflurane was introduced at setting 2, gradually increasing to setting 8 to 10. After stabilization, the setting was reduced to maintain an appropriate depth of anesthesia at setting of 2 to 3. Nitrous oxide and oxygen flows were 5 to 10 liters per minute in a ratio of 60 per cent nitrous oxide to 40 per cent oxygen. Additional relaxation was obtained by 0.1 per cent succinylcholine in 0.9 per cent saline solution administered by micro-drip. Maximum dosage of succinylcholine (12-hour case) was 500 mg. With the exception of 2 patients who were transferred to the Bird Mark 4-8 respirator in the 5th hour of 10 to 12-hour procedures, all patients were maintained on manually assisted respiration with periodic controlled apnea when required.

Sixteen cases were conducted by a second staff anesthesiologist. After induction and intubation, maintenance was by means of the Ohio Heidbrink side-arm Vernitrol semiclosed circle absorber system with soda lime. Methoxyflurane was introduced in 0.5 per cent to 4 per cent concentration at a flow of 3.5 liters per minute with 100 per cent oxygen. In procedures lasting over 2 hours the patients were made apneic by divided doses of 20 mg. of succinylcholine, and maintained with controlled respiration by hyperventilation using a Bird Mark 4-8 respirator.

Eleven cases were conducted by nurse anesthetists using the Heidbrink no. 8 vaporizer and the Vernitrol interchangeably in a semiclosed circle absorber technique with either nitrous oxide-oxygen 60 per cent/40 per cent or 100 per cent oxygen at flows of 4 and 5 liters per minute.

Circulatory Support. All patients had blood pressure and pulse monitoring. In many patients where the conditions warranted, every effort was exerted to restore and maintain a satisfactory circulatory status by monitoring venous pressure. Where circumstances permitted, urinary flow was monitored by a Foley catheter throughout the operative procedure. Blood replacement was guided by sponge weights and, where possible, direct measurement of blood loss. Patients with low serum albumin and liver disease were given albumin or plasma as indicated by their vital signs. During any procedure lasting more than 3 hours it was the general policy to administer 2 liters of 5 per cent dextrose in 0.25 per cent saline. The use of intra-anesthetic vasopressors was sedulously avoided except on a few occasions when the nurse anesthetist administered methoxamine hydrochloride in varying amounts in response to low blood pressure readings or by direction of the surgeon.

Hypotensive episodes originating during anesthesia and attributable to the agent were minimal, and every effort was extended to maintain the patient's circulatory integrity in a preventive manner rather than by restorative measures.

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